

# Breast Cancer



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# Breast Cancer

## *Global Quality Care*

Second Edition

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## Preface

The second edition of the book *Breast Cancer: Global Quality Care* was the result of the worldwide success of the first edition, published in 2020. The publication was the start of a journey for fairer breast cancer care for all women worldwide, addressing the problem of cancer care delivery becoming unsustainable in many countries and indicating that assessing health-care value for the cost is becoming increasingly important. The book was highly appreciated by a lot of journals and organizations as ASCO (American Society of Clinical Oncology), ESO (European School of Oncology), and the Value-Based Healthcare Initiative. ASCO posted: 'Efforts like this one will help to ease the burden and suffering of women with breast cancer around the globe.' ASCO-Post highly recommended the book to their readers, calling it a monumental international effort. The interest in the subject was confirmed by the further publication of our work in many peer-reviewed journals such as *ESMO-open*, *European Journal of Cancer*, *European Journal of Breast Health*, and *The Oncologist*.

Not long after the first publication, five years ago, we had an ambition to create a new adapted second edition which would be 'open access', that is easily and freely available to all interested in global breast cancer care. The unconditional support of worldwide sponsors has made this initiative possible.

We thank the 'Oxford Breast Buddy Group' (OBBG), with Yvonne Walcott Yates and David Yates (as patrons): 'We are glad to contribute our support to clinicians and breast cancer services wherever they are in the world to achieve high standards of care to keep our mothers, daughters, and sisters safe from cancer—thank you for being there!' The OBBG is an Oxfordshire-based breast cancer charity, UK, run by people who've experienced breast cancer willing to support people and families affected by breast cancer. They bring vital support, including education, psychological assistance, a safe haven for sharing experience, opportunities to develop camaraderie, and a network for extending future support.

We would also like to express our gratitude to the 'Milburn Foundation', a United States-based philanthropic organization with an established history of supporting translational research and programmes involving Inflammatory Breast Cancer (IBC). The Milburn Foundation has structured multiple IBC-centric collaborations, resulting in published works and enhancements to a breast quality care platform with potential international reach. The Foundation takes pride in supporting the inclusion of IBC-specific information in this edition, while simultaneously championing the spirit of open access. More information about the Milburn Foundation is available at [www.themilburnfoundation.org](http://www.themilburnfoundation.org).

Lastly, we thank the 'FONDS ONCOLOGIE KLINA' for his support, especially Luk Leysen, former chairman of the executive board of the Antwerp hospital KLINA who always sympathized with our work for breast cancer patients with generous gifts. He sadly passed away in May 2024.

The production of the second edition was more exciting to work on than the first one. The group of experts has grown considerably, now forming a faculty of more than 140 experts from the five continents and more than 30 countries (Figure 1). We shared the progress of the project every three months during highly attended virtual meetings discussing advances

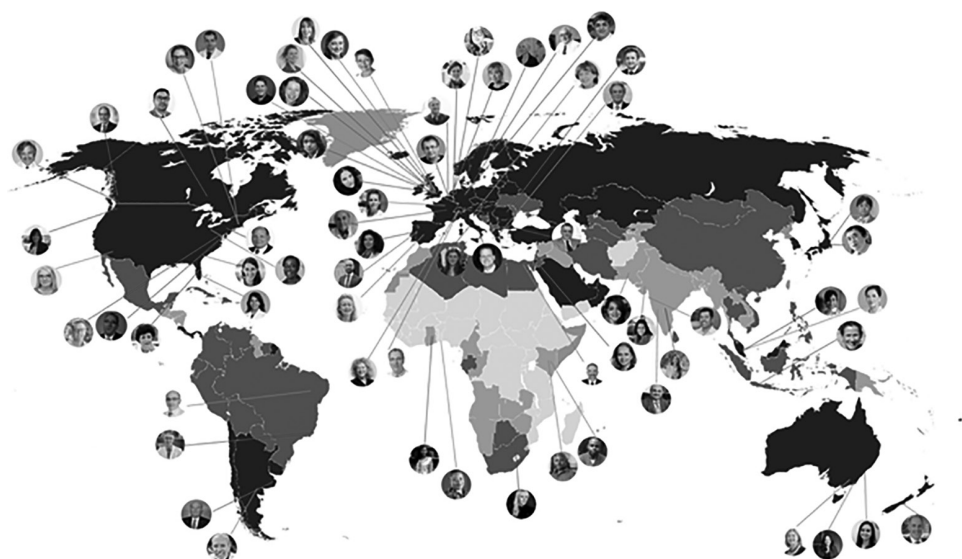


**Figure 1** A world-wide team, for fairer breast cancer care (leading experts depicted)

and challenges, trying to find a common perspective for HIC (high-income countries) as well as LMIC (low- and middle-income countries). We are delighted to have successfully engaged greater participation of experts from LMIC for this edition. We have focused on resource-specific issues in this issue with the participation and interaction of experts who have brought better insight to the complex problem of global health. The value of the book goes beyond this publication. The preparation has been instrumental in bringing together a broad cadre of skilled experts developing an international collaboration, not only building and promoting the book but also disseminating the values and concepts of value-based healthcare to grassroots levels with the final aim and hope for creating a 'butterfly effect'.

The active participation of the lead editor and many faculty members to the The Lancet Breast Cancer Commission (2021–2024) gave the project an actual perspective. Our shared mission is to highlight and identify hidden costs associated with suffering from breast cancer. Our vision offers a forward-looking and optimistic road map to address urgent challenges in breast cancer.

In addition, we participated in the Global Breast Cancer Initiative of the WHO, established in 2021 bringing together stakeholders from around the world and across sectors with the shared goal of reducing breast cancer by 2.5% per year, aiming to save 2.5 million lives over a 20-year period. These initiatives shared three key strategies: health promotion and detection, timely diagnosis, and comprehensive management.

Another exiting initiative has been the creation, with the support of eCANCER, of the GRAND ROUNDS: Breast Cancer Global Quality Care Webinar Series. This is a collaboration between leading partners of an educational programme with interacting webinars that are freely available (four times a year). The initiative provides a discussion forum, led by world-famous experts. The webinars are included in the e-book, easily available for the reader.

We believe our work has value for everyone working in the field of integrated breast cancer care, ranging from established breast cancer experts to non-experts working in the field and interested in the global vision.

The editors thank the faculty and all interested people around the globe for their advice, support, and contributions. We call upon all the readers to advocate for optimal breast cancer care and encourage open discussions about the topic.

The lead editor Didier Verhoeven would like to give special thanks for the outstanding secretarial support of Sofie Pauwels and Almedina Elkasovic; their expertise and contribution were essential for the success of the project. In addition, thanks go to Pascale Pollier-Green, Registered Medical Illustrator Artem Medicalis, for providing artistic illustrations <http://www.artem-medicalis.com>, past-Chair Medical Artists' Association of Great Britain and to her supporting colleague, Dr Ann Van de Velde.

Finally, the lead editor, Didier Verhoeven dedicates this second edition to his wife Jana, his supportive children Michaël and Sophie, and to the memory of his parents.

Didier Verhoeven, lead editor  
Cary S. Kaufman, Pankaj G. Roy, and Sabine Siesling



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# Abbreviations

|        |                                                                      |
|--------|----------------------------------------------------------------------|
| AAI    | African Access Initiative                                            |
| ABC    | Activity-based costing                                               |
| ABC    | Advanced breast cancer                                               |
| ABIM   | American Board of Internal Medicine                                  |
| ABS    | Association of Breast Surgery                                        |
| ABSI   | Association of Breast Surgery India                                  |
| ABUS   | Automated breast ultrasound                                          |
| ACOSOG | American College of Surgeons Oncology Group                          |
| ACP    | Advanced care planning                                               |
| ADC    | Antibody drug conjugates                                             |
| ADH    | Atypical ductal hyperplasia                                          |
| AFC    | Aesthetic flat closure                                               |
| AI     | Artificial intelligence                                              |
| ALND   | Axillary lymph node dissection                                       |
| ASCO   | American Society of Clinical Oncology                                |
| ASHA   | Accredited Social Health Activists                                   |
| BAPRAS | British Association of Plastic Reconstructive and Aesthetic Surgeons |
| BC     | Breast cancer                                                        |
| BCCC   | Breast Cancer Comprehensive Centre                                   |
| BCCE   | Breastcare Centre of Excellence                                      |
| BCH    | Breast Cancer Hub                                                    |
| BCRF   | Breast Cancer Research Foundation                                    |
| BCS    | breast-conserving surgery                                            |
| BCT    | Breast-conserving therapy                                            |
| BHGI   | Breast Health Global Initiative                                      |
| BIA    | Budget-impact analysis                                               |
| BQA    | Breast Quality Audit                                                 |
| BSE    | Breast self-examination                                              |
| BVGH   | BIO Ventures for Global Health                                       |
| CBE    | Clinical breast examination                                          |
| CCC    | Comprehensive Cancer Centres                                         |
| CCDSS  | Computerized clinical decision support systems                       |
| CDS    | Clinical decision support                                            |
| CEA    | Cost-effectiveness analysis                                          |
| CEU    | Clinical Effectiveness Unit                                          |
| CFO    | Chief financial officer                                              |
| CHW    | Community health workers                                             |
| CN     | Consultant nurse                                                     |
| CNB    | Core needle biopsies                                                 |
| CNS    | Clinical nurse specialist                                            |
| COI    | Cost-of-illness                                                      |
| CPG    | Clinical practice guidelines                                         |
| CQC    | Care Quality Commission                                              |

## xiv Abbreviations

|             |                                                               |
|-------------|---------------------------------------------------------------|
| CUA         | Cost-utility analysis                                         |
| CUP         | Cancer of unknown primary                                     |
| DALY        | Disability-adjusted life-years                                |
| DCIS        | Ductal carcinoma in situ                                      |
| DFS         | Disease-free survival                                         |
| DICA        | Dutch Institute for Clinical Auditing                         |
| DM          | Digital Mammography                                           |
| DNB         | Diplomate of National Board                                   |
| DP          | Digital pathology                                             |
| EAPC        | European Association of Palliative Care                       |
| EBCTCG      | Early Breast Cancer Trialists' Collaborative Group            |
| EBS         | Evidence-based surgery                                        |
| EC          | European Commission                                           |
| ECBIC       | European Commission Initiative on Breast Cancer               |
| EE          | Eastern Europe                                                |
| EEA         | European Economic Area                                        |
| EGFR        | Epidermal growth factor receptor                              |
| EHR         | Electronic health record                                      |
| EMA         | European Medicines Agency                                     |
| EML         | Essential Medicines List                                      |
| EMR         | Electronic medical records                                    |
| End-of-life |                                                               |
| EORTC       | European Organization for Research and Treatment of Cancer    |
| EPAAC       | European Partnership for Action Against Cancer                |
| ESMO        | European Society for Medical Oncology                         |
| ESO         | European School of Oncology                                   |
| ESSO        | European Society of Surgical Oncology                         |
| ESTRO       | European Society for Therapeutic Radiotherapy and Oncology    |
| EU          | European Union                                                |
| FDA         | Food and Drug Administration                                  |
| FNA         | Fine-needle aspirates                                         |
| FNAB        | Fine-needle aspiration biopsy                                 |
| FNAC        | Fine-needle aspiration cytology                               |
| FNR         | False-negative rate                                           |
| FTE         | Full-time equivalent                                          |
| GAHAR       | General Authority for Healthcare Accreditation and Regulation |
| GBCI        | Global Breast Cancer Initiative                               |
| GBCRI       | Global Breast Cancer Research Initiative                      |
| GDP         | Gross domestic product                                        |
| GIRFT       | Getting It Right First Time                                   |
| GoC         | Goals of care                                                 |
| GP          | General practitioner                                          |
| GROW        | Guidance for reporting oncology real-world                    |
| HBNI        | Homi Bhabha National Institute                                |
| HDI         | Human development index                                       |
| HEC         | Highly emetic chemotherapy                                    |
| HES         | Hospital Episode Statistics                                   |
| HIC         | High-income countries                                         |
| HIV         | Human immunodeficiency virus                                  |
| HQIP        | Healthcare Quality Improvement Partnership                    |

|        |                                                          |
|--------|----------------------------------------------------------|
| HRD    | Homologous recombination deficiency                      |
| HRQoL  | Health-related quality of life                           |
| IAEA   | International Atomic Energy Agency                       |
| IARC   | International Agency for Research on Cancer              |
| IBC    | Inflammatory breast cancer                               |
| IBCSG  | International Breast Cancer Study Group                  |
| IBTR   | Ipsilateral breast tumour recurrence                     |
| ICER   | Incremental cost-effectiveness ratio                     |
| ICG    | Indocyanine green                                        |
| ICGA   | Indian Cancer Genome Atlas                               |
| ICI    | Immune-checkpoint inhibitors                             |
| ICT    | Information and communication technology                 |
| IHI    | Institute for Healthcare Improvement                     |
| INSEMA | Intergroup Sentinel Mamma                                |
| IOM    | Institute of Medicine                                    |
| IPOS   | International Psycho-Oncology Society                    |
| IPU    | Integrated practice unit                                 |
| ISOPP  | International Society of Oncology Pharmacy Practitioners |
| IT     | Information technology                                   |
| JBCS   | Japanese Breast Cancer Society                           |
| JCST   | Joint Committee on Surgical Training                     |
| JRC    | Joint Research Centre                                    |
| KPI    | Key Performance Indicator                                |
| LABC   | Locally advanced breast cancer                           |
| LAS    | Low axillary sampling                                    |
| LLM    | Large language models                                    |
| LMIC   | Low- and middle-income countries                         |
| LN     | Lymph nodes                                              |
| MASCC  | Multinational Association of Supportive Care in Cancer   |
| MBC    | Male breast cancer                                       |
| MBC    | Metastatic breast cancer                                 |
| MBC    | Multidisciplinary breast conference                      |
| MBCU   | Multidisciplinary breast cancer units                    |
| MDT    | Multidisciplinary tumour decision teams                  |
| MEA    | Managed entry agreements                                 |
| MJC    | Multidisciplinary joint committee                        |
| ML     | Machine learning                                         |
| MOH    | Ministry of Health                                       |
| MRI    | Magnetic resonance imaging                               |
| MTB    | Molecular Tumour Board                                   |
| NABCOP | National Audit of Breast Cancer in Older Patients        |
| NABON  | National Breast Cancer Organisation Netherlands          |
| NAPBC  | National Accreditation Programme for Breast Centres      |
| NBCA   | NABON breast cancer audit                                |
| NCBC   | National Consortium of Breast Centres                    |
| NCCN   | National Comprehensive Cancer Network                    |
| NCCP   | National Cancer Control Plan                             |
| NCD    | Non-communicable diseases                                |
| NCG    | National Cancer Grid                                     |
| NCIP   | National Clinical Improvement Programme                  |

## xvi Abbreviations

|        |                                                      |
|--------|------------------------------------------------------|
| NCR    | Netherlands Cancer Registry                          |
| NCTN   | National Clinical Trials Network                     |
| NGO    | Non-governmental organization                        |
| NGS    | Next-generation sequencing                           |
| NHS    | National Health Service                              |
| NLP    | Natural language processing                          |
| NMC    | National Medical Commission                          |
| NP     | Nurse practitioners                                  |
| NST    | Neoadjuvant Systemic Therapy                         |
| OECD   | Organization of Economic Cooperation and Development |
| OEI    | Organization of European Cancer Institutes           |
| OS     | Overall survival                                     |
| PABC   | Pregnancy-associated breast cancer                   |
| PACS   | Picture archiving and communication system           |
| PACTR  | Pan African Clinical Trial Registry                  |
| PBI    | Partial breast irradiation                           |
| PC     | Palliative care                                      |
| PCCM   | Prashanti Cancer Care Mission                        |
| PCP    | Primary care physician                               |
| PHIN   | Private Healthcare Information Network               |
| PIWH   | Presidential Initiative for Women's Health           |
| PM     | Precision medicine                                   |
| PMJAY  | Pradhan Mantri Jan Arogya Yojana                     |
| PMRT   | Post-Mastectomy Radiation Therapy                    |
| PPI    | Patient and public involvement                       |
| PREM   | Patient-reported experience measures                 |
| PRO    | Patient-reported outcomes                            |
| PROCAS | Predicting-Risk-Of-Cancer-At-Screening               |
| PROM   | Patient-reported outcomes measures                   |
| PRS    | Polygenic risk score                                 |
| QA     | Quality assurance                                    |
| QALY   | Quality-adjusted life years                          |
| QI     | Quality indicators                                   |
| QoL    | Quality of life                                      |
| QOPI   | Quality Oncology Practice Initiative                 |
| R&D    | Research and development                             |
| RAS    | Robot-assisted surgery                               |
| RCB    | Residual cancer burden                               |
| RCC    | Regional Cancer Centres                              |
| RCT    | Randomized controlled trials                         |
| RFID   | Radiofrequency identification                        |
| ROB    | Risk of bias                                         |
| ROG    | Radiation Oncology Group                             |
| ROI    | Return on investment                                 |
| RSL    | Radioactive iodine seed localization                 |
| RT     | Radiation therapy                                    |
| SA     | South Africa                                         |
| SALAR  | Swedish Association of Local Authorities and Regions |
| SCP    | Survivorship care plan                               |
| SERD   | Selective oestrogen receptor degraders               |

|       |                                                       |
|-------|-------------------------------------------------------|
| SHS   | Serious health-related suffering                      |
| SLN   | Sentinel lymph nodes                                  |
| SLNB  | Sentinel lymph node biopsy                            |
| SOC   | Standard oncological care                             |
| SPICT | Supportive and Palliative Indicator Tool              |
| SSO   | Society for Surgical Oncology                         |
| STEEP | Standardized definitions for efficacy end points      |
| TAD   | Targeted axillary dissection                          |
| TCGA  | The Cancer Genome Atlas                               |
| TDABC | Time-driven activity-based costing                    |
| TFBDS | Turkish Federation of Breast Diseases Societies       |
| TIG   | Training Interface Group                              |
| TIL   | Tumour-infiltrating lymphocytes                       |
| TKI   | Tyrosine kinase inhibitors                            |
| TNBC  | Triple-negative breast cancer                         |
| TQA   | Technical quality assurance                           |
| TRIPS | Trade-Related Aspects of Intellectual Property Rights |
| UEA   | University of East Anglia                             |
| UEMS  | Union of European Medical Specialists                 |
| UICC  | Union for International Cancer Control                |
| UK    | United Kingdom                                        |
| VAB   | Vacuum-assisted biopsy                                |
| VBBC  | Value-based breast care                               |
| VUS   | Variants of unknown significance                      |
| WBRT  | Whole-brain radiation therapy                         |
| WE    | Western European                                      |
| WHO   | World Health Organization                             |
| WLE   | Wide local excision                                   |
| WTO   | World Trade Organization                              |



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**PART 1**  
**EPIDEMIOLOGY**





# 1

## Population-based cancer registries

*Sabine Siesling, Lien van Walle, Isabelle Soerjomataram, Otto Visser, Betsy Kohler, Ryan McCabe, Charles Wiggins, and Tomohiru Matsuda*

### Introduction

Cancer registry actions date back to the 1900s, when a German Committee for cancer research presented the first ‘Klinisches Jahrbuch’ describing the incidence, survival, prevalence, and mortality in Germany and Leiden, a city in the Netherlands (1). By 1946, cancer registries had been established in Hamburg in Germany, Connecticut, and New York in the USA, Denmark, Belgium, Saskatchewan in Canada, and England and Wales in the UK. Trying to obtain comparable cancer data, experts in clinical and experimental oncology, pathology, and cancer statistics met in September 1946 at the Danish cancer registry and decided that *systematic* data collection on cancer was required (2). Data from multiple data sources in defined coverage areas needed to be collected to cover and record cancer incidence of the whole population under their jurisdiction, which is distinct from pathology-based or hospital-based cancer registries that collect data only from one source. The international group stated that the information available based on point prevalence data, mortality statistics, and clinical observations was inadequate, and they prepared a formal recommendation to the Interim Commission of the World Health Organization (WHO) in collaboration with the Danish and British governments. This report outlined that (3):

1. great benefit would follow after collecting data about patients with cancer from as many different countries as possible;
2. data needed to be recorded on an agreed plan so as to be comparable;
3. each nation should have a central registry to arrange for the collection and recording of such data;
4. there should be an international body with the duty to correlate the data and statistics obtained in each country.

In 1964, the Union for International Cancer Control (UICC) set up a Committee on Cancer Incidence, which produced a Technical Report in 1966, the first volume of Cancer Incidence in Five Continents (CI5) (4). The International Association of Cancer Registries (IACR, <http://www.iacr.com.fr/>) was subsequently established with the aim of improving the quality and the comparability of data between cancer registries by standardizing methods of registration, definitions, and coding of a minimal data set (5). This minimal data set includes morphology of the tumour and primary site conforming to ICD-O

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coding and vital status. More recently, guidelines on the uniform gathering of supplementary items are given, such as stage and primary treatment have been published. The IACR is a non-governmental organization and professional society, aligned with the WHO since January 1979. The IACR is dedicated to fostering the aims and activities of cancer registries worldwide. The IACR convenes an annual scientific meeting that rotates through different continents to enable participation for all members. IACR works in close collaboration with the International Agency for Research on Cancer (IARC, <http://www.iarc.fr/en/about/>), which is the specialized cancer agency of the WHO. The objective of the IARC is to promote interdisciplinary international collaboration in cancer research and bring together skills in epidemiology, laboratory sciences, and biostatistics to identify the causes of cancer so that preventive measures may be implemented, and the burden of disease and associated suffering reduced. Key IARC publications related to cancer surveillance include the CI5-series (Figure 1.1), GLOBOCAN and the interactive web-based platform the Global Cancer Observatory (GCO, <http://gco.iarc.fr/>), presenting global cancer statistics. IARC also developed CanReg5, an open-source tool to input, store, check, and analyse cancer registry data. It has modules for data entry, quality control, consistency checks, and basic data analyses.

### **Cancer registries in low- and middle-income countries**

Many low- and middle-income countries (LMICs) lack quality cancer data. In response, the Global Initiative for Cancer Registry Development (GICR, <http://gicr.iarc.fr/>) was launched in 2012. Being the first worldwide strategy to improve cancer control through better data, the GICR is a partnership based on the commitment of leading cancer organizations to address inequities in underserved countries. Six IARC Regional Hubs for Cancer Registration have been established to provide technical support and training for Africa, Asia, the Caribbean, Latin America, and the Pacific Islands. Each IARC Hub acts as the main point of contact for countries within its catchment area to coordinate and deliver regional activities and strengthen capacity building. Recently, some of the Hubs/Centres of Expertise in Asia, Latin America, and Oceania are running high-quality population-based cancer registries (PBCRs) themselves and are providing reliable cancer statistics routinely.

### **Cancer registries in Europe**

The European Network of Cancer Registries (ENCR, <http://www.encr.eu/>) was established in 1990 within the framework of the Europe Against Cancer programme of the European Commission on the initiative of the IARC, the Association of Nordic Cancer Registries (ANCR), the IACR, and the Latin Language Registry Group (GRELL). In 2012, the two Directorate-Generals of the European Commission (DG SANTE and the DG JRC) entered a formal collaboration to address actions in support of the ENCR, paving the way towards further coordination and harmonization of cancer data in Europe. The ENCR secretariat is hosted at the European Commission's Joint Research Centre in Ispra, Italy. By 2024, more than 210 PBCRs are active in Europe.

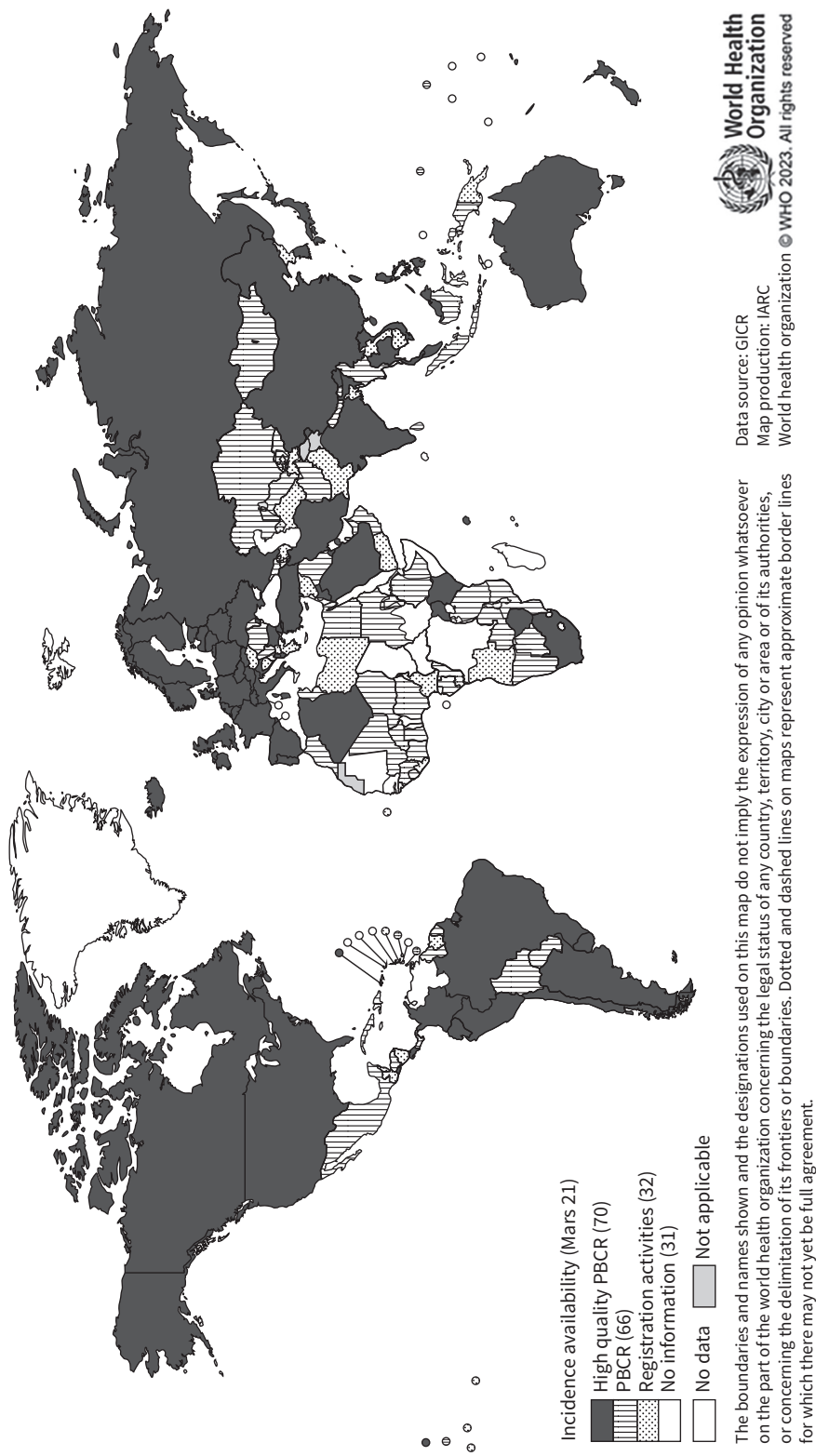


**Figure 1.1** Global overview of population-based cancer registries (PBCR).

Reproduced with permission from The global initiative for cancer registry development (GICR). Available at: <https://gicr.iarc.fr/>

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The Network has the following objectives:

- improve the quality, comparability, and availability of cancer incidence data;
- create a basis for monitoring cancer incidence and mortality in the European Union;
- provide regular information on the burden of cancer in Europe;
- promote the use of cancer registries in cancer control, healthcare planning, and research.

Standards and guidelines for cancer registration in Europe, the first ENCR recommendations, were published in the IARC Technical Publication No.40 in 2003, and afterwards by the ENCR in 2005. This European minimal cancer data set also included stage and initial treatment modality as essential variables, leading to an increase in use of the data (6). In 2024, the 2023 revised ENCR recommendations for the standard data set were published, promoting the collection of prognostic (tumour) factors and cancer recurrence/progression. In 2018, the European Cancer Information System (ECIS, <https://ecis.jrc.ec.europa.eu/>) was launched, a web application providing incidence, mortality, and survival estimates, designed to support research and public health decision-making in oncology in European countries.

The introduction of the General Data Protection Regulation (GDPR) 2016/679 of the European Union (EU) in 2018 raised concerns to the oncology community related to the performance of health research. The perception was urged that while fully protecting the privacy of patient data, the GDPR should not jeopardize clinical, translational, and epidemiological research in the EU. In particular for PBCRs, registries should be allowed to process data even without patient consent, provided that privacy-protecting safeguards are complied with. Although the GDPR recognizes the principle of 'one-time consent' for retrospective research and biobanking and the principle of 'no consent' for population-based registries, the challenge of unanimous interpretation and implementation of the GDPR across all EU countries persists.

## Cancer registries in the United States and Canada

Cancer surveillance in the United States (US) is primarily funded by two federal programmes, each established by an act of Congress. The National Cancer Act of 1971 directed the US National Cancer Institute to create an ongoing system of cancer surveillance that resulted in establishment of the Surveillance, Epidemiology and End Results (SEER) Programme in 1973. With the passage of the Cancer Registries Amendment Act in 1992, the National Programme of Cancer Registries was established within the Centres for Disease Control and Prevention, achieving a nationwide cancer surveillance system. Population-based cancer registries in each state are responsible for their respective areas of coverage.

In Canada, routine cancer surveillance is conducted by population-based provincial and territorial registries. Data from these registries are combined to create the nationwide Canadian Cancer Registry (CCR), which is administered by Statistics Canada. CCR is governed by the Canadian Council of Cancer Registries, a collaboration among the 13 provincial and territorial cancer registries and the Centre for Population Health Data of Statistics Canada. The CCR contains data on all cancers diagnosed in Canada since 1992.

Most population-based cancer registries in North America collect a common set of data items including information on patient demographics, anatomical site of primary tumour, tumour morphology, stage at diagnosis, first course of treatment, and follow-up for vital status. The registries collect data using common definitions and coding rules, as defined by funding agencies, and other standard setters. In recent years, information about molecular characterization of cancers and targeted therapies has increasingly become available to central cancer registries through record linkage techniques.

The North American Association of Central Cancer Registries (NAACCR) was founded in 1987 to enhance the quality and usage of cancer registry data. NAACCR develops and promotes uniform data standards for cancer registration in North America, provides education and training, certifies population-based registries meeting objective criteria for timeliness, accuracy, and completeness of data, aggregates and publishes data from central cancer registries, and promotes the use of cancer surveillance data and systems for cancer control and epidemiologic research, public health programmes, and patient care to reduce the burden of cancer in North America. NAACCR also combines data from state, provincial and territorial registries in North America to produce several analytic reports and datasets that are readily available to support public health surveillance for cancer and scientific research.

The National Cancer Database (NCDB), jointly sponsored by the American College of Surgeons and the American Cancer Society, collects approximately 200 data items for each of the 1.72 million newly diagnosed patient cases every year from 1,400 Commission on Cancer (CoC)-accredited hospitals in the US, covering 72% of newly diagnosed cancers and informing a historical research repository of over 40 million cancer cases. The NCDB is a *hospital-based* registry system and provides data-driven insight into the quality of patient care at the point of care. Participating hospitals are provided real time data-driven web-based tools regarding individual patient alerts for timing of therapy, quality measure compliance results, and performance comparisons with regional and national benchmarks. De-identified NCDB datasets are available for use by CoC member researchers.

Vital records are collected by individual states in the US and by individual provinces and territories in Canada. Death certificates are used to produce population-based cancer mortality statistics in both countries. Key data elements from death certificates are routinely integrated into PBCRs in both countries to allow for the accurate assessment of cancer survival.

## Cancer registries in Asia

Cancer registries in Asia have experienced significant advancements over the last decade, driven by GICR, promoted by the IARC. The central Hub, located in Mumbai, oversees this progress, supported by four countries—Japan, Korea, China, and Thailand—acting as Centres of Expertise. Numerous Asian nations have developed through this initiative, evident in the increasing Asian data in the CI5-series. In CI5XII, published in 2023, 14 Asian countries, and 230 registries have been adopted. In Vietnam, the first report of the national cancer registry was published in 2023. India and China, boasting huge populations, have not only expanded their cancer registry coverage but have also improved the quality of their respective registries. Notably, 157 out of the 230 registries listed in CI5XII are in China, 24 in India.

Despite this progress, LMICs in Southeast and South Asia face challenges in sustaining their registries, including budgetary constraints, inadequate human resources, inaccurate diagnosis due to lack of pathologists, and incomplete incidence rates caused by inadequacies in the health insurance systems and vital statistics. High-income countries (HICs), primarily in East Asia, are catching up with Nordic countries. For example, South Korea has consolidated all cancer information into a comprehensive big data centre. However, Asian HICs encounter obstacles such as limited progress in data utilization in research due to personal information protection, unsuccessful database linkage including genomic data, sluggish standardization of medical information, hindering direct data capture for timeliness.

## **(Future) Use of cancer registry data**

In addition to the data gathered for public health indicators on the burden of cancer, aetiology, and monitoring of screening programmes, more and more PBCRs gather supplementary data on tumour characteristics (molecular profiles), diagnostics, stage, treatment, and outcomes (cancer recurrence, patient-reported outcome/experience measures (PROEMs)). Additional data can be captured manually, by record linkage to other data sources (such as clinical audit/hospital-databases, general practitioner records, financial administrative sources, and screening programmes) or through distributed learning (federated analysis), thus leaving the data at the source. The latter might overcome privacy data protection regulation problems.

Many registries are currently developing technologies that will increase the efficiency of data collection and submission, expand the scope of disease-specific prognostic factor data, and enable the use of PROEMs and physician-based reporting. High-quality, curated source data offers great opportunities to registries for extended monitoring of cancer surveillance, providing insight into the actual delivered care, implementation of new recommendations, novel technologies, and treatment modalities, as well as allowing the monitoring of quality of care and the effect on the outcome without patient selection (real-world evidence). For example, data from cancer registries on breast cancer are being used extensively to support clinical auditing (see Chapter 8), and linkage to screening programmes (e.g. breast cancer) enables monitoring of the effectiveness of the screening.

Although research on outcomes based on cancer registry data can be prone to confounding, since the application of care is not random, it is complementary to trial outcomes. Close contact between cancer registry staff and the researchers analysing and interpreting the data is necessary and will improve the quality and ability to understand the significance of the findings. Awareness when analysing the data and interpreting results on outcomes and comparisons between groups is essential to support hypothesis generation for further research.

Cancer registries should be supported to routinely collect recurrence data to allow complete evaluation of metastatic breast cancer (MBC) and inform healthcare providers and researchers of the prognosis of both nonmetastatic and metastatic patients with breast cancer (7).

## Key messages

- Population-based cancer registries (PBCRs) provide insight into the burden of cancer in a specific population by systematically recording data on new (pre-)malignancies within a specific region, area, or treatment setting.
- PBCRs are an essential element in the planning and monitoring of cancer control strategies and for identifying priorities in public health.
- By collecting additional data on stage, treatments, molecular profiles and outcomes (such as recurrences and patient-reported outcome), PBCR data can be used more intensively for monitoring quality of care, guideline adherence, and outcomes research.
- Close contact between the PBCR, researchers, and caregivers will improve the quality and use of the data and enable understanding of the significance of the findings.

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## 2

# The global burden of malignant breast cancer in women

*Isabelle Soerjomataram, Didier Verhoeven, and Sabine Siesling*

## Introduction

The burden of cancer continues to increase as a result of both population ageing and growth, as well as changes in lifestyle and exposure to cancer risk factors (1). Today, breast cancer is the most frequently diagnosed cancer in women, and it is the most common cause of cancer death in women (2). Throughout this chapter, we present the most up-to-date population-based estimates of breast cancer incidence and mortality using data compiled by the International Agency for Research on Cancer (IARC) and World Health Organization (WHO). We only included primary, invasive breast cancer among women (International Classification of Diseases, 10th revision: C50), which we refer to as breast cancer. The national estimates for breast cancer incidence and mortality are dependent on the availability and accuracy of local data sources. Generally, there is a paucity of high-quality cancer registration and vital registration in low-resource and medium-resource areas, and, hence, interpretation of the estimates from these regions needs to be done with caution.

## Data sources and methods: incidence, prevalence, and mortality

### Cancer incidence

Cancer incidence is the frequency of occurrence of new cases of cancer in a defined area, for a specific population, and for a given period of time (3). It can be expressed as the absolute number of cases or as an incidence rate per unit time, where the number of incident cases is divided by the population at risk in a specified period of time. Comparisons of incidence rates can elucidate underlying risk factors, plan aid, and prioritize resources for cancer control, and monitor and evaluate the impact of specific primary prevention interventions (4). Cancer incidence data are collected and recorded in population-based cancer registries (PBCR, see Chapter 1), which are either national or regional in their coverage. Using these data, national cancer incidence is estimated within the GLOBOCAN project for 185 countries globally.



## Cancer mortality

Cancer mortality measures the average risk to the population of dying from a specific cancer and provides a measure of the outcome or impact of cancer (3). Similar to incidence, it is expressed as either the number of deaths occurring or as a mortality rate per unit time. Data are derived from vital registration systems, where a clinical practitioner usually certifies the fact and cause of death. The WHO mortality databank contains national cancer mortality data of ~100 countries, and, for many of these, over extended periods of time. Global mortality estimates by country are estimated at IARC and are available for 185 countries worldwide.

## Cancer prevalence

Prevalence is the number of persons in a defined population alive at a given time, who have had cancer diagnosed at some time in the past (3). It helps quantify the medical attention required by individuals that were affected by cancer. Prevalence is commonly presented as limited duration (partial) prevalence, which is the number of patients diagnosed with cancer within a fixed time in the past and is likely to be pertinent in estimating the needs for cancer services according to specific phases of cancer care (4). It can be directly estimated in PBCRs by counting the number of cases still alive at a certain time period, but this method requires long-term registration and follow-up. Alternatively, partial prevalence has been calculated as a product of incidence and time-specific survival.

## Global burden of breast cancer

### Incidence, prevalence, and mortality by world region

Breast cancer is the most common cancer in women in 158 of 185 countries (Figure 2.1) and is the most important cause of death from cancer. In 2022, breast cancer was responsible for an estimated 2,297,000 new cancer cases (23.8% of all cancers in women) and 666,000 deaths (15.4% of all cancer deaths in women); an estimated 8.2 million women were survivors living with a breast cancer diagnosed within the previous 5 years (partial prevalence) (5).

The risk of being diagnosed with breast cancer varies widely by world region (Figure 2.2). In Australia or New Zealand, the risk of getting breast cancer before the age of 70 years was 10.8%, meaning that 1 out of 10 women in the region will be diagnosed with breast cancer before the age of 70 years. This is followed by 10.3% and 9.8% among women in North America and in Northern Europe, respectively. The risk is lowest for women in Asia and sub-Saharan Africa, ranging from 2.9% to 3.2%. On the other hand, despite the diverse risks of getting breast cancer, the risk of dying from breast cancer is quite similar across the world region: on average, only 1.4% of all women aged <70 years are expected to die from breast cancer.

Due to differences in population size, and Asia being the most populated region with two-thirds of the total world population, the Asian continent reports the highest number of new cancer cases (42.9%, including 15.9% in China and 8.4% in India) followed by Europe (24.3%) and North America (13.3%). By contrast, better survival in the wealthier world regions leads

## Breast Cancer

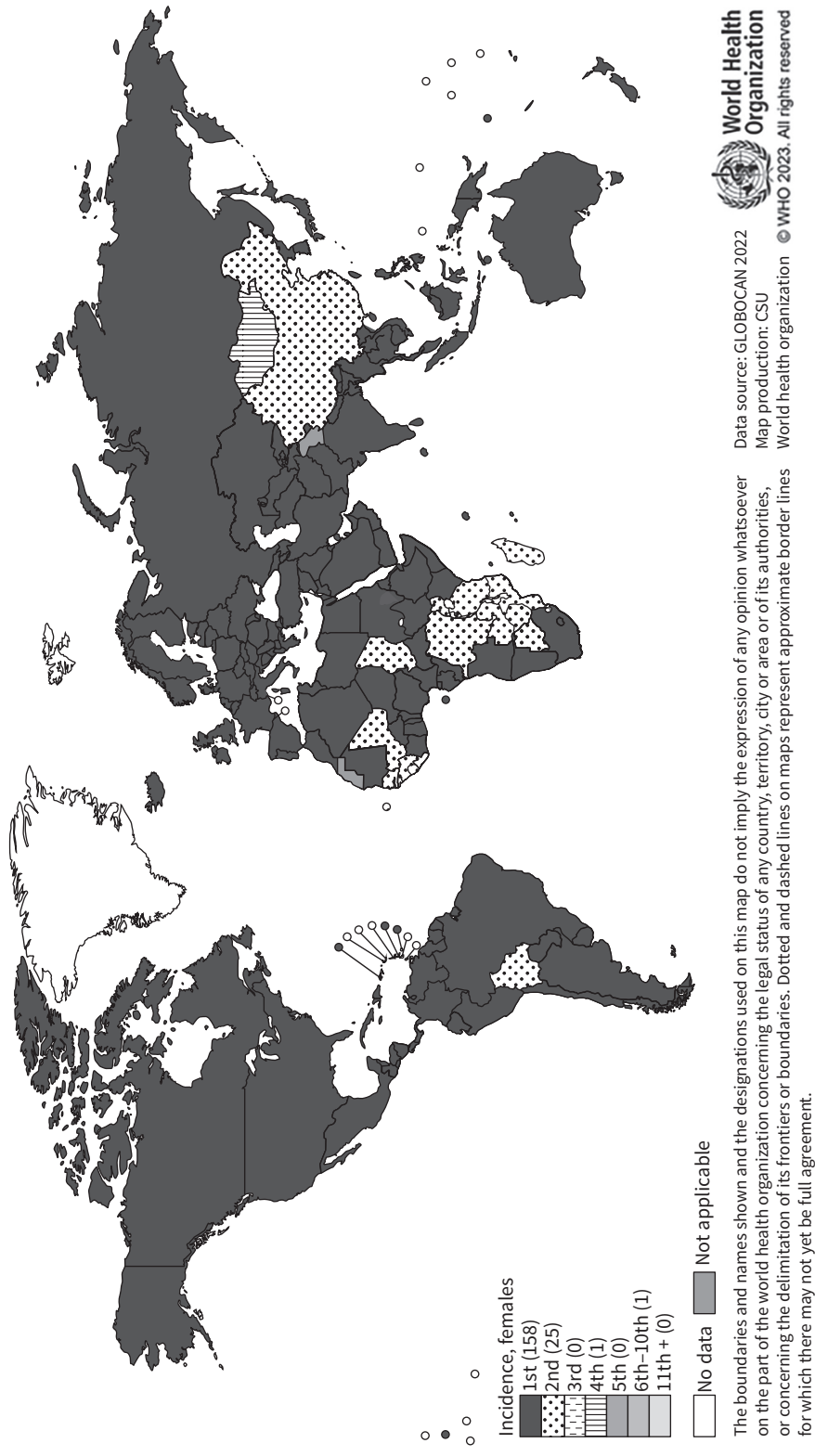


**Figure 2.1** Ranking of breast cancer among all cancer diagnosis in 2022 by country.

Data source: GLOBOCAN 2022. Reproduced with permission from Ferlay J, Ervik M, Lam F, et al. (2024). Global Cancer Observatory: Cancer Today (version 1.1). Lyon, France: International Agency for Research on Cancer. Available from: <https://gco.iarc.who.int/today>, accessed [10 June 2024]. Available from: <http://gco.iarc.fr>

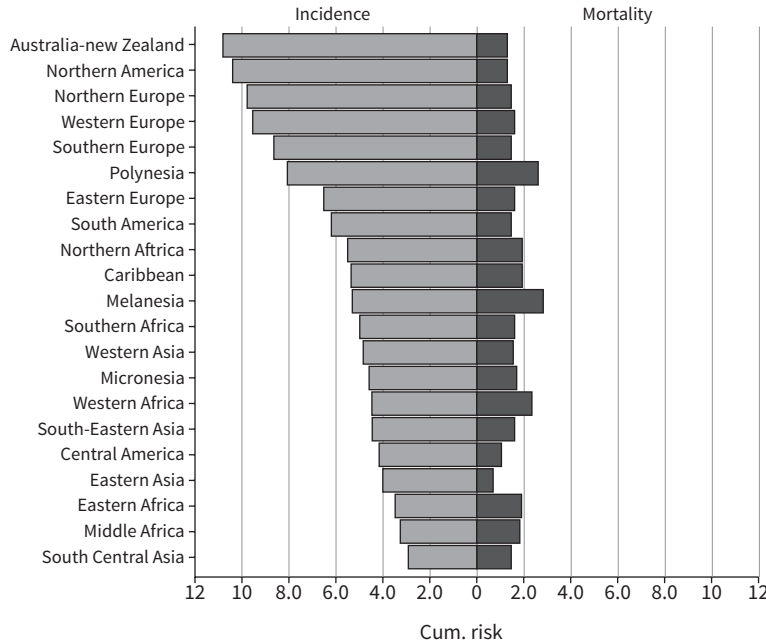


**Figure 2.2** Estimated cumulative risk of being diagnosed (left bars) and dying (right bars) from breast cancer among women before 70 by world region.

Data source: GLOBOCAN 2022. Reproduced with permission from Ferlay J, Ervik M, Lam F, et al. (2024). Global Cancer Observatory: Cancer Today (version 1.1). Lyon, France: International Agency for Research on Cancer. Available from: <https://gco.iarc.who.int/today>, accessed [10 June 2024]. Available from: <http://gco.iarc.fr>

to fewer deaths in these regions, and ultimately a higher number of survivors (prevalence) with Europe and North America showing the highest proportion of prevalent breast cancers, in addition to Asia linked to the large number of the population in the latter (Figure 2.3).

International variation in breast cancer incidence and mortality has been linked to differences in risk factors, early detection practices, and to the effectiveness of cancer treatment (2). Epidemiological studies have identified various modifiable risk factors for breast cancer in the general population. The consumption of alcoholic beverages, high body weight, lack of physical activity, and exposure to radiation are all factors that increase one's risk of breast cancer. About 40% of all breast cancers could have been prevented by reducing exposure to these factors, namely, alcohol consumption, adult weight gain, physical inactivity, and current postmenopausal hormone use (6). Global awareness about the link between alcohol and breast cancer continues to be low. Health professionals have the important task of increasing awareness, leading to reduced consumption. IARC data show nearly half (46%) of the world population consumes alcohol, with rates higher in men (54%) than women (38%). Breast cancer made up almost 1 in 4 of the new cases attributable to alcohol. Heavy drinking, defined as more than 60 g/day or about six daily drinks, accounts for 47% of the alcohol-attributable cancers. Risky drinking, between 20 and 60 g/day accounts for 29% while moderate drinking, less than 20 g/day or about two daily drinks, accounts for roughly 14% of alcohol-attributable cancers. The good news is that long-term trends show a decline in alcohol drinking in many countries, including wine-producing countries like France or Italy (6).

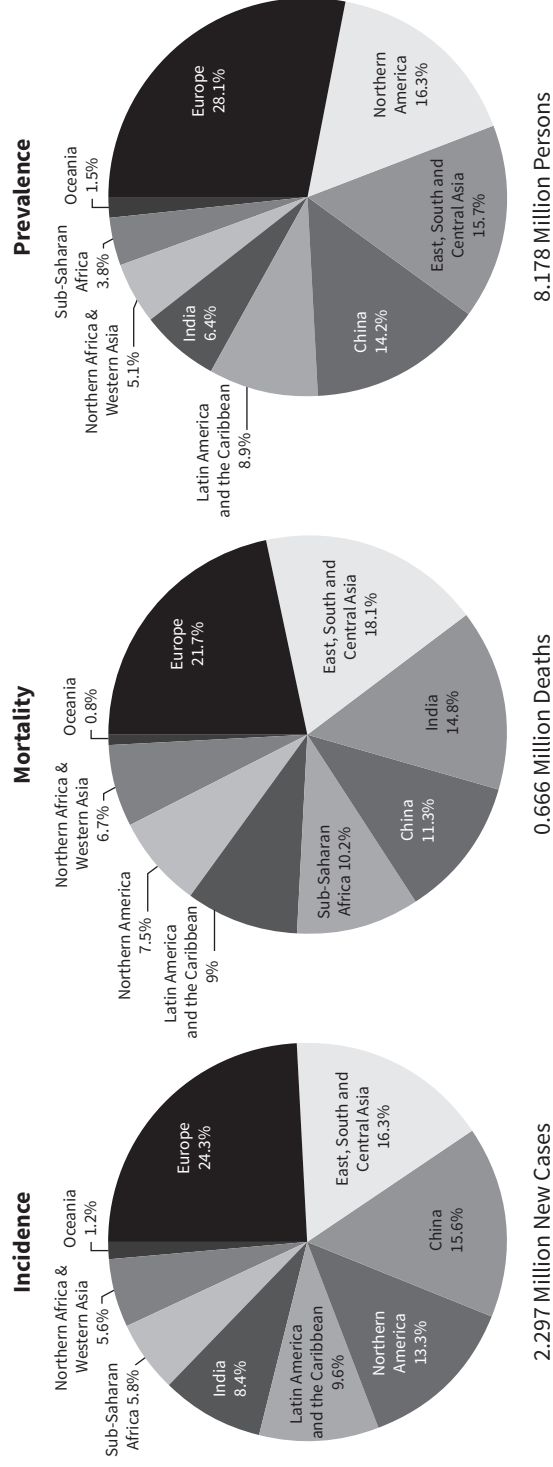


**Figure 2.3** Incidence (new cases), mortality (deaths) and 5-year prevalence (survivors) of breast cancer by world region in 2024. Data source: GLOBOCAN 2022. Reproduced with permission from Ferlay J, Ervik M, Lam F, et al. (2024). Global Cancer Observatory: Cancer Today (version 1.1). Lyon, France: International Agency for Research on Cancer. Available from: <https://gco.iarc.who.int/today>, accessed [10 June 2024]. Available from: <http://gco.iarc.fr>

Breast cancer is also highly related to various reproductive factors such as age at first child-birth and number of children. The contribution of such factors to the overall risk of breast cancer, which are generally considered as not modifiable (family history of breast cancer, personal history of benign breast disease, attained height, age at menarche, age at menopause, age at first birth, and parity), depends on the prevalence of these factors in a population and may be substantial. Nonetheless, a considerable proportion of breast cancers might be avoided by adopting a healthier lifestyle (7).

Further international differences in breast cancer burden, namely in incidence, mortality, and by extension survival, can be partly linked to variation in early detection programmes or breast cancer screening. In breast cancer screening, the primary target is to detect early invasive cancer, but *in-situ* carcinomas are also detected with up to one-fifth of the frequency of invasive cancer. Implementation of a breast cancer screening programme causes an increase in incidence because of the detection of the prevalence pool of breast cancer (that had been undetected and that would have remained undetected without the programme). Further, it has been estimated that biannual mammography screening in females aged 50–69 years improves survival and, consequently, reduces mortality from cancer by ~20% (8). As such, coverage, quality, and effectiveness of breast cancer screening programmes markedly affect the national burden of breast cancer.

## Trends in breast cancer incidence and mortality

### Trends in breast cancer incidence

High-quality cancer registry data provide some salient features for cancer incidence trends over time (9). Generally, we observed that breast cancer has been increasing in almost all countries and in all age groups. The increases seem to be larger in the youngest age groups, with an average yearly increase of 1.5% (<50 years) as compared to 0.8% among the oldest age group (70+ years). In several high-income countries, e.g. the USA, Australia, and Norway, we saw a stabilization or decline in the rate of breast cancer diagnoses for the older age groups, which seem to rise again after 2008. On the other hand, while the rates among the youngest age group seem to be increasing in these countries, in many countries classified as low and middle-income countries, we saw a stabilization or decline in rates of breast cancer (Figure 2.4).

These rising trends point to the westernization effect in countries, especially those in high- or medium-resource levels, which is likely linked to the increasing adoption of some reproductive, dietary, metabolic, and hormonal risk factors that are akin to those more commonly observed in the west (1). Increasing awareness of breast cancer and early detection (or screening) programmes have also been suggested to play a role in the rising rate of breast cancer, especially in the early stages and in ductal carcinoma *in situ* (a non-invasive type of breast cancer). On the other hand, decreased use of hormonal replacement therapy (HRT) following the announcement of its carcinogenic effects has largely impacted breast cancer incidence rates, particularly in countries such as the USA, where the consumption of HRT was high, and this may partly explain the observed decrease in incidence rates in such populations (10). Yet it seems that other breast cancer risk factors are dominating the most recent trends and driving the observed rising trends in this population.

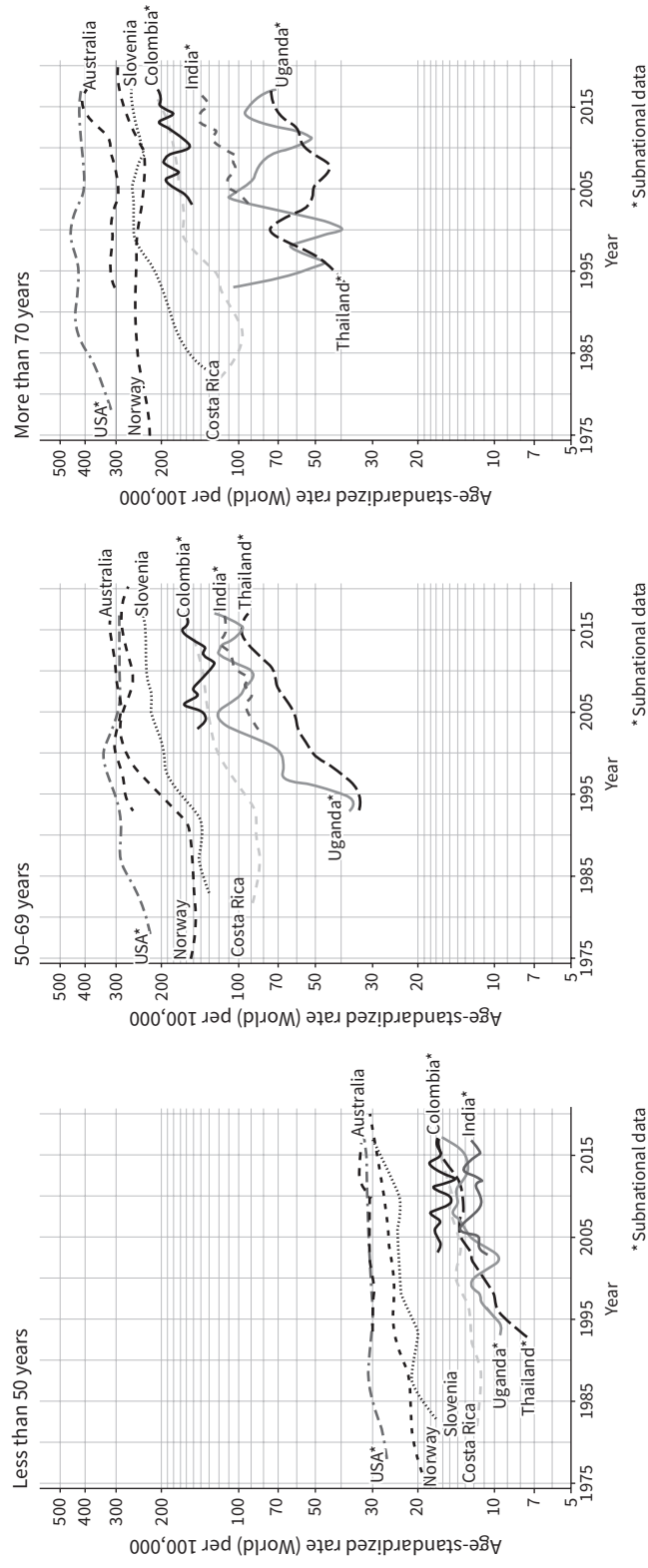


**Figure 2.4** Trends in breast cancer incidence rates according to age groups (<50, 50–69, ≥70 years) in a few representative countries.

Data source: Cancer Incidence in 5 Continents. Reproduced with permission from Bray F, Colombet M, Mery L, et al. (2021). Cancer Incidence in Five Continents, Vol. XI (electronic version). Lyon: International Agency for Research on Cancer. Available from: <http://gco.iarc.fr>

## Trends in breast cancer mortality

As for mortality rate, we observed a decreasing trend across countries overall and particularly in higher-income countries in Europe, North America, and Oceania as opposed to many Asian and sub-Saharan countries, where a rising trend of death from breast cancer was still seen (Figure 2.5). In higher-income countries, the observed declines in mortality rates were largest in the youngest age group (<50 years, on average, 3% yearly), and somewhat increasing in the oldest age group (>70 years, 1% change). In the US, the US Black and Hispanic white patients had the lowest rate of decrease in terms of mortality, as compared to non-Hispanic white patients, and the highest rise in the incidence of newly diagnosed breast cancer, as compared to white patients. This could partly be explained by differences in socio-economic status and overall more aggressive forms of breast cancer (11).

Cancer screening programmes and improvements in treatment are both major contributors to these observed favourable trends in mortality from breast cancer (11). The impact of breast cancer screening on mortality in the general population can best be seen in the age groups targeted by screening (50–69 years) and in countries where screening has been implemented since the late 1980s, such as in Sweden, the UK, and the Netherlands (12). Early declines in mortality, before the start of national screening programmes and in age groups outside of the screening coverage (<50 and >70 years), suggest that improved treatment, but also population awareness and hence earlier detection, have a major impact and explain this pattern.

Yet without adequate management of breast cancer, screening would have minor benefit, and treatment is also more likely to be effective if cancer is detected, and treated, at earlier stages. High-income countries have made remarkable progress in improving outcomes from breast cancer, whereas in many low- and medium-resource countries, breast cancer mortality is still rising. Part of this success originates from a better adherence to guidelines for surgery and radiotherapy, the introduction of more effective systemic treatment, namely adjuvant chemotherapy, especially among patients aged <50 years, and, particularly, hormonal and targeted therapies in those aged >50 years. Please refer to Chapter 1 on population-based cancer survival for an in-depth assessment of breast cancer survival and its determinants. By 2050, new cases and deaths will have increased by 38% and 68%, respectively, disproportionately impacting low-HDI countries (13).

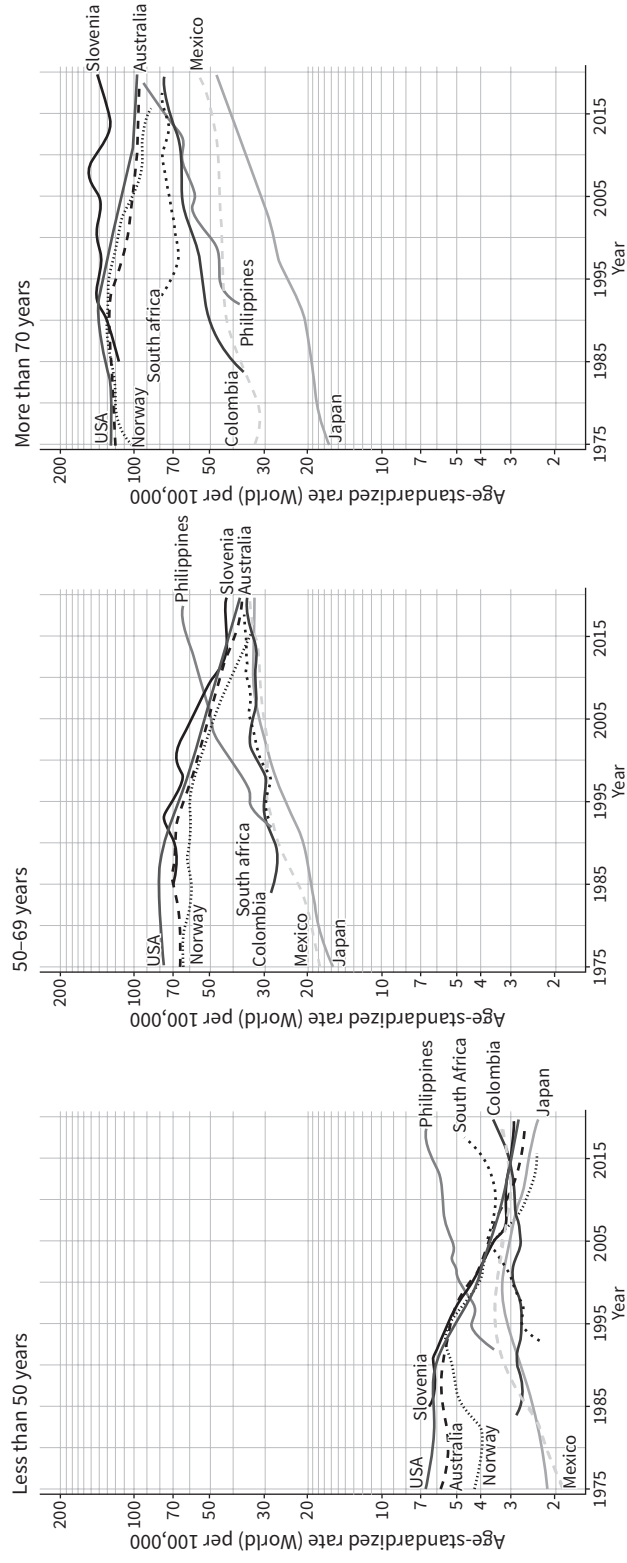


**Figure 2.5** Trends in breast cancer mortality rates according to age groups (<50, 50–69, ≥70 years) in a few representative countries.  
 Data source: WHO Mortality Database. Reproduced with permission from Bray F, Colombet M, Mery L, et al. (2021). Cancer Incidence in Five Continents, Vol. XI (electronic version). Lyon: International Agency for Research on Cancer. Available from: <http://gco.iarc.fr>



## Key messages

- The risk of being diagnosed with breast cancer varies widely by world region.
- Breast cancer is estimated to be the most common cancer in women in 158 of 184 countries.
- Breast cancer incidence has been increasing in almost all countries and in all age groups, and the number of women diagnosed each year is projected to reach 3.5 million by 2050.
- Epidemiological studies have identified several recommendations to modify risk factors such as adopting a healthy body weight, reducing alcohol consumption, and increasing physical activity.
- In 2022, an estimated 8.2 million women were survivors living with a breast cancer diagnosed within the previous five years.
- A decreasing trend in mortality in higher-income countries is observed, but there are striking worldwide differences.
- Early diagnosis and access to effective treatment are crucial in order to achieve further improvements in survival and, over the longer term, reductions in mortality.

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# 3

## Global trends in breast cancer survival in women

*Claudia Allemani, Lisa Montel, Pamela Minicozzi, Vesna Zadnik, and Veronica Di Carlo*

### Introduction

Survival from breast cancer in women has improved greatly over the last few decades, not only among women recruited to clinical trials, but also at the population level. The third cycle of the CONCORD programme (CONCORD-3) included individual data for over 6 million women diagnosed with breast cancer during 2000–2014 and followed up to 2014. It showed that age-standardized 5-year net survival increased steadily in most developed countries. For women diagnosed during 2010–2014, age-standardized 5-year net survival was 85% or more in 25 countries. Survival approached 90% in Australia and the US. However, international disparities remain very wide, with five-year survival estimates as low as 66% for women in India (1).

To date, these are the most recent estimates of robustly comparable breast cancer survival worldwide. They were obtained from real-world data collected by 298 population-based cancer registries in 66 countries.

Among the UN Sustainable Development Goals, the third goal is: ‘Ensure healthy lives and promote well-being for all at all ages’. A key target for 2030 is to: ‘reduce by one-third [the] premature mortality from noncommunicable diseases (NCD) through prevention and treatment’. Trends in cancer mortality inevitably reflect the joint impact of past trends in cancer incidence and cancer survival (2). To reduce cancer mortality, it is necessary both to reduce incidence (prevention) and to improve survival (early detection, optimal treatment). Prevention is crucial, but long-term. The most effective way of reducing cancer mortality rates in the medium term (by 2030) will be to improve survival. Therefore, monitoring trends in cancer survival is imperative.

### Population-based survival

Population-based survival is estimated from individual data on newly diagnosed patients, followed up indefinitely for their vital status. It is a key measure of the overall effectiveness of the health system in managing cancer in a given country or region (3). The data are provided by population-based cancer registries (see Chapter 1). These survival estimates provide a sharp contrast with survival estimates derived from randomized clinical trials. Trials are

designed to determine the highest achievable survival in patients who are usually selected based on age, stage of disease, and lack of comorbidity. Short-term outcomes are compared between patients randomized to receive either the best-known treatment to date or the latest proposed improvement. However, clinical trials typically involve less than 10% of adult cancer patients (4).

By contrast, population-based survival is a measure of the average survival achieved by all cancer patients, young and old, rich and poor, with and without comorbidity, and with early or advanced disease at diagnosis. These patients are treated in a wide range of health-care facilities, reflecting different levels of rigour in the application of clinical protocols and guidelines, a wide range of treatments, and equipment of dissimilar quality. Some patients may withdraw from treatment due to out-of-pocket costs, the length of travel to the clinic, or side effects of treatment. For these reasons, population-based survival reflects the overall outcome of cancer care in a country or region, and it is used to inform strategies for cancer control.

Generally, population-based survival is presented as net survival, which is the probability for cancer patients to survive their cancer after controlling for the risks of dying from competing causes of death (background mortality), which are higher in the elderly (5).

With a few rare exceptions (6–8), robust international comparisons of cancer survival are comparatively recent. The earliest example was a comparison of survival in the USA (Connecticut) with that in six European countries in the 1950s (6). More recently, the EURO CARE studies have provided a systematic series of survival estimates for patients diagnosed since 1978: EURO CARE-5 included data from 107 cancer registries on patients diagnosed in 29 European countries during all or part of 2000–2007 and followed up to 2008 (9). Since the early 2000s, several international studies have compared cancer survival in selected geographical areas (10–13).

## The CONCORD programme

The CONCORD programme was designed to compare survival in five continents. Robust comparison of trends in cancer survival requires data collection according to a detailed common protocol (preferably translated from English into the most common languages), centralized data quality control following a strict set of rules, and analyses using the most up-to-date statistical methodology, including construction of complete life tables of all-cause background mortality by age, sex, and calendar year to correct for competing risks of death (1, 14–16).

CONCORD is an ambitious research programme for the long-term surveillance of cancer survival worldwide. It has been developed since 2000 to inform national and global policy for cancer control (17). In 2015, CONCORD established global surveillance of trends in cancer survival for the first time (15). In 2018, CONCORD-3 updated global surveillance of cancer survival trends with data on 37.5 million patients diagnosed with one of 18 cancers, including over 6 million women diagnosed with breast cancer during the 15 years, 2000–2014 (1). Data were provided by 322 registries in 71 countries. CONCORD-4, now in progress, will examine long-term trends in survival for adults diagnosed with one of 22 cancers during the 32 years, 1990–2021. It will also monitor progress towards the target set by the World Health Organization's Global Initiative for Childhood Cancer, to increase five-year survival

for all children with cancer combined to 60% by 2030 (18). By August 2024, CONCORD-4 had received anonymized individual records for over 85 million adult patients, including 12 million women with breast cancer.

Survival estimates from the CONCORD programme have become the *de facto* standard for international survival comparisons, as a metric of health systems performance, cancer policy, and improvement in outcomes. The Organisation for Economic Co-operation and Development has been in partnership with CONCORD since 2017 and has included survival estimates from 48 countries in its regular *Health at a Glance* publications.

The CONCORD programme now involves 600 collaborators.

## Data available in cancer registries

Among the non-communicable diseases, cancer is unique in that population-based cancer registries in many countries capture the basic details of the person, the pathology of the tumour, and the final outcome for every person diagnosed with cancer in the resident population of the territory that they cover (see Chapter 1). Some registries, mainly in high-income countries, also collect data on the stage at diagnosis and the treatment. Cancer registries provide direct evidence of trends in cancer incidence, which guide the priorities for prevention. Many registries also capture data on the death of all registered patients, regardless of the cause of death. This enables direct monitoring of trends in cancer survival.

## Global trends in five-year survival from breast cancer

In CONCORD-3, 6,422,553 anonymized individual tumour records were provided by 298 population-based cancer registries in 66 countries on women diagnosed with breast cancer during 2000–2014. The range of survival estimates was very wide in each continent, apart from North America and Oceania. In Figure 3.1, each box plot shows the range of survival estimates in each continent among all cancer registries for which reliable estimates could be obtained for patients diagnosed in each calendar period. Survival estimates considered less reliable are not included, but most estimates were considered reliable. The vertical line inside each box represents the median survival estimate among all contributing registries.

In most countries in Central and South America, East and West Asia, and in all of Europe, 5-year net survival continued to increase up to 2010–2014. Yet, survival remained lower in Eastern Europe than in Northern, Western, or Southern Europe. In North America and Oceania, 5-year net survival approached 90% (1).

## Worldwide distribution of stage at diagnosis and stage-specific survival

The stage of disease at diagnosis is a key determinant of long-term survival for almost all malignancies, including breast cancer. Differences in cancer survival between population subgroups, e.g. over time, or by socioeconomic status or ethnicity within a country, or between countries, may be explained, at least in part, by differences in the stage of disease at diagnosis

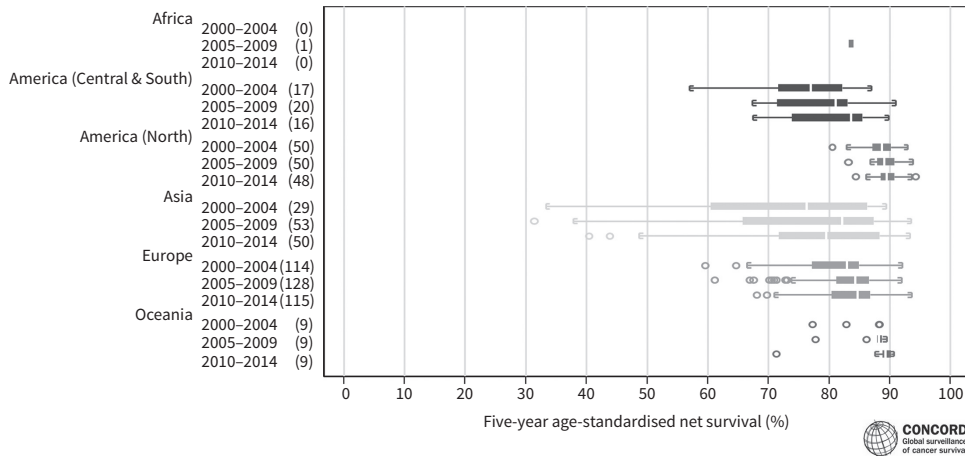


**Figure 3.1** Global range of age-standardized 5-year net survival estimates for breast cancer, among 298 cancer registries in 66 countries, by continent and calendar period of diagnosis.

Reproduced with permission from Allemani C, Matsuda T, Di Carlo V, CONCORD Working Group et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet*. 2018 Mar 17;391(10125):1023–1075. This figure is not covered by the Creative Commons licence terms of this publication. For permission to reuse please contact the rights holder.

Each box plot shows the range of survival estimates among all cancer registries for which suitable estimates could be obtained for patients diagnosed in each calendar period, in each continent.

Survival estimates considered less reliable are not included. The vertical line inside each box represents the median survival estimate among all contributing registries (the central value in the range, or 50th centile). The box covers the IQR between the lower and upper quartiles (25th and 75th centiles). Where there are only a few widely scattered estimates, the median might be close to the lower or upper quartile. The extreme limits of the box plot are  $1.5 \times \text{IQR}$  below the lower quartile and  $1.5 \times \text{IQR}$  above the upper quartile. Open circles indicate outlier values, outside this range.

in the cancer patient populations being compared. The survival of all women with breast cancer may be lower in one country than another because women in that country are generally diagnosed with more advanced disease that is less susceptible to treatment of curative intent. Alternatively, their survival may be poorer at each stage of disease, which may imply that optimal treatment is not available, particularly for early-stage tumours. Thus, more advanced disease and lower survival at each stage of disease at diagnosis may both play a role in international differences in survival.

In CONCORD-3, registries were asked to submit data on stage at diagnosis, using one of three stage classifications: the Tumour Node Metastasis (TNM) classification (19), SEER Summary Stage 2000 (20), or condensed TNM (21). CONCORD-3 also collected data on the tumour size, in millimetres, and on the number of lymph nodes removed at lymphadenectomy, as well as the number of lymph nodes that were positive, showing evidence of infiltration. Stage at diagnosis was then classified as node-negative (T1–3N0M0), node-positive (T1–3N1–3M0), locally advanced or metastatic (T4M0 or M1), using a complex stage algorithm to summarize all the available data on stage for each patient. Registries were only included in survival analyses by stage at diagnosis if data on stage were available for at least 70% of women.

The distribution of stage at diagnosis for women diagnosed with breast cancer during 2009–2014 is shown in Figure 3.2. Countries are ranked in alphabetical order within each

## 24 3 Global trends in breast cancer survival in women

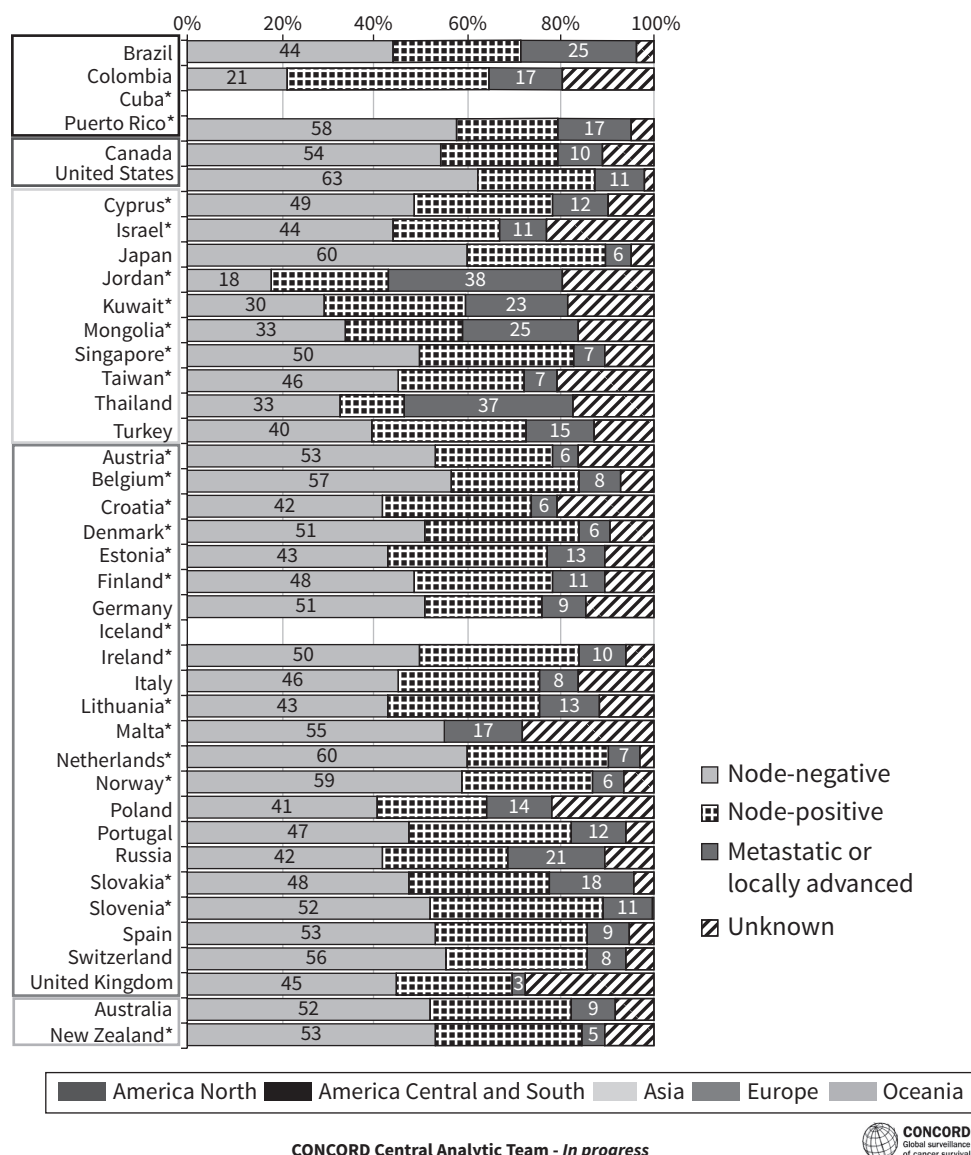


**Figure 3.2** Breast cancer stage at diagnosis (%), 2009–2014.

continent. The availability of data on stage varied widely. Stage was known for over 99% of women in Slovenia, but for less than 75% in Malta and Northern Ireland. Data on stage at diagnosis were not available for any participating African registry.

Overall, the stage distribution in low- and middle-income countries was much less favourable than in high-income countries. In Japan, the Netherlands, and the United States, 60% or more of women with breast cancer were diagnosed with a node-negative tumour. The corresponding proportion was 30% or less in Colombia, Jordan, and Kuwait.

The proportion of node-positive breast cancer diagnoses ranged from 13% in Thailand to over 40% in Colombia. The proportion of metastatic or locally advanced disease ranged

between 3% and 11% in North America, in Oceania, and in most Nordic and Western European countries. Countries in Eastern Europe continued to show a higher proportion of more advanced disease than the rest of Europe, ranging from 14% in Poland to 21% in the Russian Federation. Wide differences were also observed in Asia, with the proportion of women diagnosed with metastatic or locally advanced breast cancer ranging from 6% to 7% in Japan, Singapore, and Taiwan, and up to 37–38% in Thailand and Jordan.

Since the 1980s, most European countries have begun to adopt population-based mammography screening programmes to improve early detection (22). This has contributed to a gradual increase in the overall proportion of women diagnosed at an early stage in Europe.

In Asia, only Israel, Japan, Singapore, South Korea, and Taiwan had a population-based national breast cancer screening programme in place before 2010 (23). All screening programmes in Central and South America are currently opportunistic, except for Cuba, where a national population-based screening programme is available. Very often, low- and middle-income countries lack the necessary resources and an efficient healthcare infrastructure required to conduct population-based screening for cancer control. This leads to a less favourable stage distribution than in high-income countries.

Figure 3.3 shows the global distribution of age-standardized 5-year net survival for women diagnosed with node-negative and metastatic or locally advanced breast cancer during

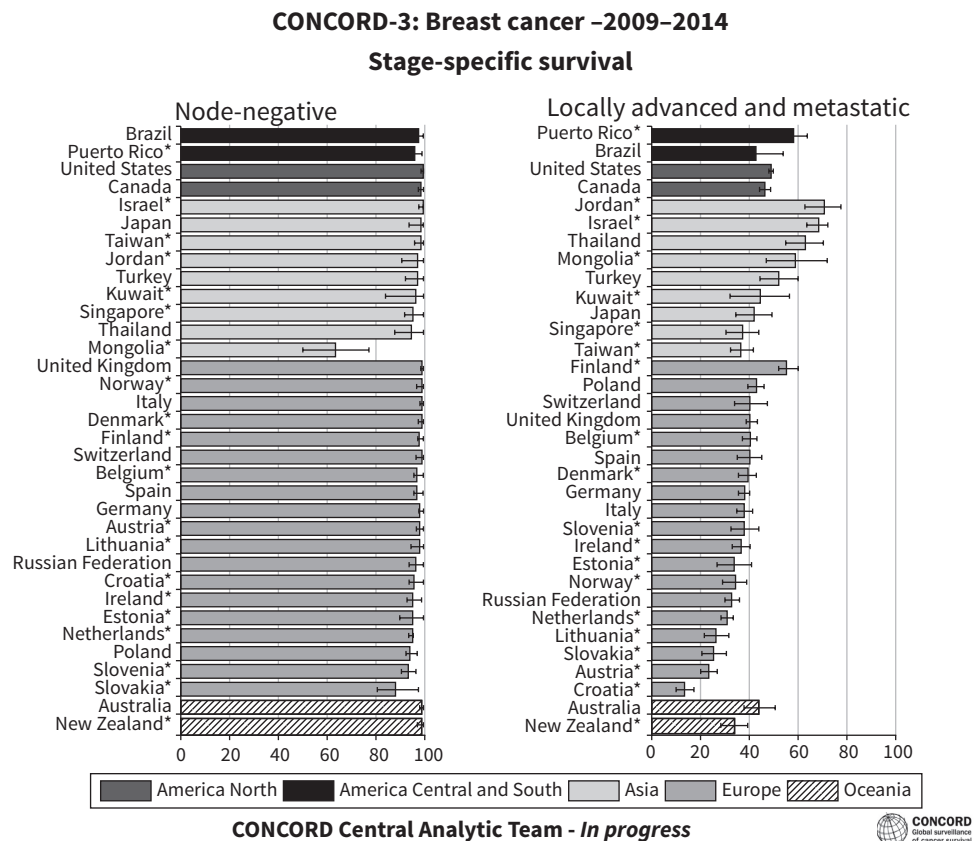


**Figure 3.3** Age-standardised 5-year net survival for breast cancer, by stage and country, 2009–2014.



2009–2014. Within each stage category, survival estimates for each country are ranked from highest to lowest within each continent.

Five-year net survival for node-negative breast cancer was excellent and stable throughout 2000–2014 in most countries worldwide. In 2009–2014, age-standardized 5-year net survival for women diagnosed with node-negative disease was higher than 90% in 32 of 34 countries included in CONCORD-3, and approached 99% in Australia, Denmark, Finland, Israel, Italy, New Zealand, Northern Ireland, Norway, Switzerland, and the US. Five-year net survival for node-negative breast cancer was only 63% (95% CI 49.9–76.5%) in Mongolia.

For most countries, an improvement in 5-year net survival was observed for women diagnosed with node-positive breast cancer, particularly in Slovenia (from 78.6% during 2000–2004 to 85.1% during 2009–2014), Spain (from 80.3% to 87.1%), Estonia (from 73.0% to 78.1%), Lithuania (from 66.8% to 74.9%), Norway (from 79.7% to 86.6%), UK (from 73.9% to 88.3%), and New Zealand (from 78.2% to 85.7%).

By contrast, 5-year net survival for metastatic or locally advanced disease varied widely. During 2009–2014, five-year net survival in Europe ranged between 13.4% (9.9–16.9%) in Croatia to 55.6% (52.0–59.3%) in Finland. In Asia, survival ranged between 36.1% (31.5–40.7%) in Taiwan to 67.6% (63.7–71.6%) in Israel. In Australia, Canada, and the US, 5-year survival was over 40%. Little or no improvement was observed in survival from metastatic or locally advanced disease over the 15-year period, 2000–2014.

## Survival by the availability of radiotherapy

Radiation therapy is essential in the treatment of early-stage breast cancer. It is also crucial in the palliative treatment of advanced-stage breast cancer. A report from the International Atomic Energy Agency (IAEA) showed dramatic discrepancies in the ability of cancer patients to access life-saving radiotherapy across countries and regions of the world. Access to radiation therapy facilities is especially poor in sub-Saharan Africa, where only 24.4% of the population can access facilities within two hours of travel by road (24).

The IAEA Advisory Group on Increasing Access to Radiotherapy Technology (AGaRT) in LMICs has set a minimum threshold of at least 1 radiotherapy machine per 500,000 population. In high-income countries, one radiotherapy machine (LINAC or cobalt) is available for every 120,000 people. In middle-income countries, one machine serves over 1 million people. In low-income countries, about 5 million people may rely upon a single radiotherapy machine, and in some countries, no radiotherapy machine is available.

Figure 3.4 shows the association between 5-year net survival for women diagnosed with breast cancer during 2010–2014 (CONCORD-3) and the number of radiotherapy machines in 48 countries included in the analyses.

Five-year survival was higher in countries where the number of radiotherapy machines per 1,000,000 population in 2013 or the nearest year was at least as high as the threshold set by the IAEA. The median five-year survival among the 41 countries for which the availability of radiotherapy equipment was at least as high as the IAEA threshold was 85%, compared with 76% for the seven countries with a lower level of availability.

In 2007–2013 and still today, radiation therapy equipment was lacking in many low- and middle-income countries (LMICs). IAEA estimates that 50% of all cancer patients need radiation therapy. Based on the proportion of optimal radiotherapy utilization and the



**CONCORD-3: Breast cancer –2010–2014**  
**Five-year net survival by availability of radiotherapy equipment as**  
**per minimum international standard**

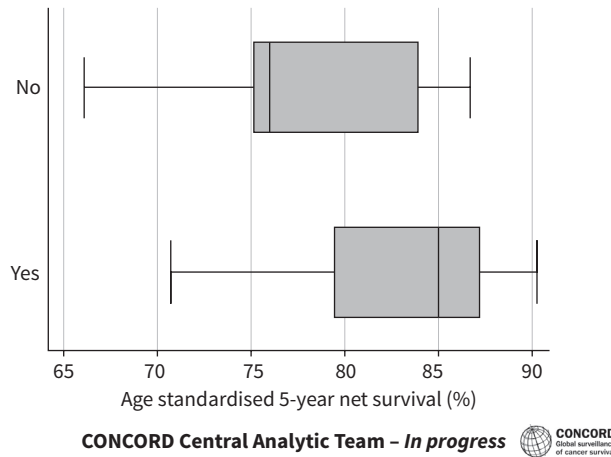


**Figure 3.4** Five-year net survival by availability of radiotherapy equipment as per the minimum international standard, 2010–2014.

Adapted from Montel-Riffaud LM. (PhD thesis) Assessing the implementation of the right to health through indicators: an interdisciplinary effort applied to breast cancer. 2024. Cancer Survival Group, Department of Non-communicable Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine. University of London. PP 141.

availability of radiation therapy equipment in 2007–2013, IAEA estimates that only 25.3% of radiation therapy needs were covered in Africa, and 26.4% in Southeast Asia. In at least 70% of LMICs, more than 50% of radiation therapy needs could not be met, due to a lack of or underprovision of machines. Even where radiation therapy equipment is available, it may not be used optimally, due to a lack of training or the costs of maintaining the machines. Patients also face accessibility barriers, such as affordability and lengthy travelling distances in LMICs, as well as long waiting times in both LMICs and high-income countries.

The VENUSCANCER project on women's cancers (25), embedded in the CONCORD programme, aims to examine why worldwide differences in survival for breast, cervical, and ovarian cancer still persist, and whether they could be explained by international differences in the biological characteristics of the cancers, or in the healthcare that women receive, or in broader aspects of society, such as women's socioeconomic status or level of education. The overall aim is to provide actionable evidence for health policies to reduce the burden of women's cancers worldwide.

The VENUSCANCER high-resolution study (26) showed that for women diagnosed during 2015–2018 early, node-negative cancers (T1N0M0) comprised over 40% of breast cancers in high-income countries (HIC), but the proportion was generally below 20% in LMIC, and higher in Cuba (30%, breast).

During 2015–2018, consistency with international clinical guidelines (ESMO, ASCO, NCCN) for surgery in early-stage breast cancer was very variable. The proportion of women with early-stage breast cancer who were treated with breast conserving surgery and radiotherapy ranged from 13% in Georgia to 82% in France. Mastectomy was the only surgical option in South Africa (Eastern Cape) and Mongolia (26). Most women in Thailand and in Palestine were treated with mastectomy, either due to the lack of radiotherapy facilities, or to

the belief that a more radical surgery offers a better chance of cure (27). Some type of cancer surgery, at least for T1N0M0 tumours, has become more accessible in LMIC. However, unfortunately, the proportion of these women was still far too low. Mastectomy was also common in the US, Canada, Estonia, the Netherlands, and Portugal (26). A study in the USA based on more recent data has highlighted an inappropriate denial of radiotherapy services within the Medicare Advantage plans, which could explain the choice of mastectomy for women older than 65 years (28).

Consistency with systemic treatment guidelines for node-positive (N+) breast cancer showed less variation. The proportion of women with N+ breast cancer who were treated with chemotherapy was in the range 50–70% in most HIC, but, despite the high cost, this treatment was also a very frequent option in LMIC, reaching over 90% in Cuba and Palestine and 77% in Uganda and South Africa. Endocrine treatment was offered to 80% of women with oestrogen-receptor-positive (ER+) tumours in most countries worldwide, reaching over 90% in Italy, the UK, and Estonia. Data on targeted treatment were limited, but our study showed that in spite of the high proportion of HER-2+ breast cancers in Thailand, anti-HER-2+ treatment was offered to only 26% of women with these tumours, probably due to insufficient resources. By contrast, anti-HER-2+ treatment was widely offered in South Africa (Eastern Cape; 67% of eligible women) (26).

The median time to treatment for women with an early-stage cancer was generally less than one month in several HIC, but as long as four months to one year in some LMIC, leading to more advanced stages and sub-optimal treatment (26).

Several major initiatives and commissions on breast cancer have been published within the last five years. It remains to be seen how effectively they are implemented and their longer-term impact on prevention, early diagnosis, treatment, and survival. These include WHO's Global Initiative on Breast Cancer (29) and *The Lancet* Breast Cancer Commission (30, 31).

The CONCORD-*Lancet* Global Commission on Cancer (32) was announced in May 2024, in collaboration with scientists, cancer survivors, and policymakers. It aims to illustrate the value of long-term, global, collaborative science for effective policy-making, and how population-based cancer registries can continue to provide actionable evidence for shaping cancer control strategy.

## Recommendations

- Support continuous monitoring of trends in population-based breast cancer survival, which are crucial for policymakers to improve cancer control.
- Reduce the persistent disparities in breast cancer survival between low- and middle-income and high-income countries through leveraged policies.
- Promote early detection of breast cancer through education.
- Increase availability and accessibility of optimal treatment, including radiotherapy in LMIC, but also for ethnic minorities in HIC.
- Advocate for the importance of statutory cancer registration to obtain timely data on incidence, stage at diagnosis, treatment, survival, and possibly recurrence.
- Involve cancer patients in the design of research projects.

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**PART 2**

**QUALITY MANAGEMENT  
OF BREAST CANCER**



## 4

# Tackling the value crisis in breast cancer care

*Didier Verhoeven, Matthew Hickey, Sabine Siesling, and F. Lee Tucker*

## Introduction

Defining and achieving the best quality of care is a complex process and can only be achieved through proficient quality assessment and management. This requires the use of a combination of tools such as guidelines, protocols, care pathways, registries, evaluation and monitoring, and improvement projects.

Progressive quality management follows the principle of Observe → Learn → Optimize → Repeat ([www.theHVA.com](http://www.theHVA.com)). Similarly, Deming provides a continuing process model of Plan → Do → Check → Act, in which all phases influence one another, and where all stakeholders of the patient pathway should be closely involved. These stakeholders include both intra- and extramural caregivers, governments, clinical scientific associations, cancer societies, patient coalitions, and health insurers.

The five Deming principles to improve healthcare ([www.deming.org](http://www.deming.org))

- Quality improvement is the science of process management;
- If you cannot measure it, you cannot improve it;
- Managed care means managing the processes of care;
- The right data at the right time in the right hands;
- Engage the smart cogs of healthcare.

The history of health quality in the US was published in the *New England Journal of Medicine* (1). This highlighted the beginning of the twentieth century: self-regulations, court recognitions, and standardization programmes. After the Second World War, the Joint Commission on Accreditation was created. In the early 1980s, evidence-based guidelines were becoming more popular. As the decade passed, the foundations of quality evolved, focusing more on adverse events and medical errors. In the last two decades, quality has become a major component in the development of new reimbursement models by payers seeking to financially incentivise (or penalize) care service providers for quality. Models include the CMS Oncology Care Model (OCM) <https://www.cms.gov/priorities/innovation/innovation-models/oncology-care>, the more recent Enhancing Oncology Model (EOM) <https://www.cms.gov/priorities/innovation/innovation-models/enhancing-oncology-model>, ICHOM (see Chapter 8) and the ESMO Magnitude of Benefit Scale <https://www.esmo.org/guidelines/esmo-mcbs>. A recent model, the Health Value Alliance's cancer performance indicator (CPI) was co-designed by

providers, clinicians, payers, and patients from the UK, Europe, and North America. HVA's CPI model provides a holistic and multistakeholder model for the multidimensional assessment and monitoring of cancer performance, i.e. quality, outcomes, and value (<https://www.theHVA.com>).

## Value crisis in cancer care

Value is the summation of quality, cost, operational aspects, outcome, and patient preference relative to the resources available. The fight against breast cancer must focus on ensuring that those diagnosed with cancer achieve the very best outcomes that matter to them, no matter where they live and at a cost that is affordable to all.

Globally, cancer is reaching epidemic levels, with 35 million new cancer cases predicted in 2050, a 77% increase from the estimated 20 million cases in 2020 (see Chapter 2). Consequently, the global cost of cancer is expected to increase 60% to \$2.25 trillion across the same period (2).

OECD Projections of Health Expenditure can be found on their website: <https://www.oecd-ilibrary.org/docserver/3d1e710c-en.pdf?expires=1717686587&id=id&accname=guest&checksum=E002D5DCAD9A2E986E3E32FA1B7B0431>

The current conundrum is, in part, due to there being a lack of a 'value' synergy or partnership between stakeholders. Without this, a value imbalance is created between stakeholders, where one stakeholder may derive value from the ecosystem to the detriment of another. This can cause outcomes to be skewed and funds to get overloaded. As a result, reimbursement models get reformed, investment slows, innovation and access are hampered, and the industry's value proposition is diluted. In this scenario, the patient is always the ultimate loser.

A true value-based cancer care ecosystem establishes value equity as a foundation, which fosters collaboration between stakeholders to establish synergy, where equitable, sustainable improvement in value is achieved, for all. However, to realize a model of value synergy, cross-sector leadership to transition the ecosystem from a reactive sick care model to a proactive healthcare system is needed. However, to achieve this, an independent, non-biased central source of truth is needed. This will provide the necessary transparency to support the development of trust in the model and between stakeholders. Using this approach, stakeholders can then commit to reducing risk for all, and true value synergy can then be achieved. This scenario creates win:win for the stakeholders, where the patient is the ultimate beneficiary (3).

## Measuring quality of care: quality indicators

Implementation of quality management tools can be accomplished with the definition of evidence-based quality indicators. These must be designed in a way that provides timely, relevant, and non-biased insight into the quality of the provided care. Furthermore, it highlights the effect quality has on outcomes and value, as perceived by other stakeholders, e.g. patients, payers, medtech/pharma, hospitals, etc. Ultimately, better-quality care should translate to improved quality of life for patients, which in turn results in a number of benefits for other stakeholders.



Donabedian divided quality indicators into three categories: structure, process, and outcome indicators, with love for the patient and understanding the medical care process as core requirements (4).

- **Structure indicators** are related to the organization of the healthcare system.
- **Process indicators** are related to the way care is given and measure what is done, often in comparison with (local) guidelines.
- **Outcome indicators** measure the results of the given care.

Both process and outcome indicators are often expressed as a ratio of the numerator (patients who received a certain treatment) divided by the denominator (all patients eligible for the treatment). Also, medians can be used, such as the median time between diagnoses and the first treatment, or the time between two interventions.

Outcome indicators are the most difficult to define and interpret because of the difficulties in identifying the essential factors influencing the achieved value of the indicator. In case a long time between the given care and the measured outcome, e.g. in case of a good prognosis, it is difficult to distinguish the effect of care and many other things that influence the outcome which occur meanwhile. Moreover, outcome indicators are not easy to register, since the events of interest often take place long after treatment is complete and when the patient is no longer engaged in hospital care. Furthermore, the outcomes measure(s) are often stakeholder-specific, and the desired outcome of one stakeholder could conflict with another, e.g. reduced cost of care to a payer versus revenue generation by a commercial care provider.

Some examples of outcome indicators are recurrence-free survival and overall survival. However, these outcomes must also be put into context. For example, overall survival is a common performance indicator. But, if achieving overall survival comes at the cost of patient quality of life and/or results in significant or disproportionate resource use and cost, then survival as an outcome measure alone could mask the effect achieving survival has on patient preferred outcome and/or the viability of a care fund. Furthermore, indicators that are time-lapse-based might reflect performance that has resulted from technology and resources that were available in the past, but which may not be relevant in today's context, rendering the results of the outcome indicator less valuable for a current situation.

In recent years, there has been a movement to add patient-centred/patient-reported measures to conventional quality measures. This involves the routine and longitudinal collection of patient-reported outcomes measures (PROMs) and patient-reported experience measures (PREMs). PROMs are a structured methodology for measuring the health status e.g. symptoms, functional capacity, and quality of life, of a patient, from their point of view. Whereas, PREMs enable the measurement of how a patient perceived their experience while receiving care and subsequent experiences. PREMs also address the patients perspective of practical/service-related issues such as waiting times, available facilities, follow-up, and the experience of shared decision-making (see Chapter 8).

Fundamentally, these indicators provide a formal and structured approach for the assessment of the outcome and quality of received care, as seen from the patient's perspective. Ultimately, these measures serve to place the patient at the centre of the healthcare ecosystem and provide a crucial reminder that the ecosystem is ultimately designed to serve them (5).

## Criteria for developing quality indicators

While it is clear that quality indicators should meet specific criteria, there is still much space for improvement. Indicators must be reliable, not sensitive to chance, be evidence-based, timely, contextual, and therefore valid. Moreover, indicators must be defined in a way that the calculation and interpretation of the results is easy and therefore supports better real-world applications. Existing QI do not always meet these criteria and there is still much space for improvement (6).

Quality indicators should measure what they are supposed to measure without selection or measurement bias, or be confounding. Indicators should also be able to be adjusted to enable differentiation between circumstance, for example enabling case-mix adjustment, differentiation between research and real-world care, and consideration of sociodemographic and socioeconomic differences in the population(s) being assessed. Comparison of more homogenous groups can also be achieved by stratification of the patient groups, which can improve valid comparisons. Moreover, QI should be able to differentiate between research and real-world care.

An appropriate volume of subjects and data is also vital to reveal meaningful and statistically robust differences between hospitals. In order to be relevant, indicators must be contextual, have a high level of evidence, be available in a timely manner and be presented in a manner that is understandable to the end user. Moreover, they should be designed to facilitate action; fundamentally, if the insights derived from the indicators (including understanding the underlying factors) do not support meaningful and measurable change, then the indicators lose their value. Finally, indicators must be developed with all stakeholders in mind and provide a balanced view. Insights reports that encompass operational, clinical, quality of life, and costs indicators provide a broader context and correlation than a single indicator, as was illustrated with overall survival in this chapter.

When designing indicators, it is important to co-create them together with the end user and be mindful of the purpose of the insights derived from the indicators. Patients might want to use the indicators to help them choose the care that best fits their personal situation. However, indicators should always be interpreted cautiously and should ideally be presented as part of a complete set of indicators. Where necessary, interpretation should be provided to show how one indicator might be influenced by another. This will help ensure that insights are not misinterpreted and a balanced, informed decision can be made from the data.

Furthermore, to minimize resource burden and increase the likelihood of adoption, the data needed for the indicators must be easy and reliable to collect and in a cost-effective way, preferably reusing already gathered data, as e.g. cancer registries do.

Use of, or the inclusion of, existing outcomes measure sets and models, e.g. the International Consortium on Health Outcome Measures (ICHOM) (see Chapter 8), can help ensure consistency between service entities and their quality measurement, and use of evidence-based and internationally recognized methods for measuring outcomes.

Finally, the use of an independent third party, e.g. a cancer registry, for the design, collection, and reporting of data can help ensure objectivity, prevent bias, provide crucial context and prevent manipulation and fraudulent reporting (see Chapter 1) (7).

## Development of quality indicators

Developing and defining quality indicators is a key service the medical community provides to society. For optimal design, the participation of multiple stakeholders such as recognized experts in the multidisciplinary breast cancer field, as well as patients, patients' families, and advocates, is required (8). Knowledge and experience in the process of care, the existing guidelines, changeability, the wider cancer care ecosystem, the relevant political and legal landscape and the potential challenges associated with obtaining data and the reporting and use of the indicators are also required (Box 4.1).

### Box 4.1 Core considerations when developing quality indicators

- **Timeliness:** Are the indicators delivered within a time and about a period that is relevant to the user?
- **Relevance:** Do the indicators align with the goals and objectives of the user and are they relevant to the system or process being assessed?
- **Validity:** Do the indicators accurately measure and represent the quality dimensions they are supposed to assess?
- **Context:** Does the indicator context provide the necessary background and framework for interpreting and understanding the data it generates?
- **Reliability:** Do the indicators provide consistent insights when repeatedly applied to the same population, system, or process? (Reliability ensures that variations in measurement are due to actual changes in quality rather than inconsistencies in the measurement tool.)
- **Sensitivity:** Are the indicators sufficiently sensitive to enable the detection of improvements and declines in quality/performance changes over time?
- **Specificity:** Are the indicators sufficiently specific to provide clear insights into what aspects of quality are performing well and where improvements are needed, and also support root cause analysis?
- **Feasibility:** Is it practical and feasible to collect the indicators within the constraints of available resources, including time, budget, and data availability, and to ensure sustainable measurement over time?
- **Measurability:** Are the indicators quantifiable or observable, allowing for consistency and standardization of measurement to ensure accurate, consistent interpretation, and comparison of results?
- **Benchmarking:** Can the indicators be used as comparative measures?
- **Action ability:** Will the indicators provide actionable insights, inform decision-making and drive improvements, and support stakeholders to identify, design, implement, and monitor the impact of insight-driven strategies?
- **Stakeholder involvement:** Are relevant stakeholders involved in the selection or design of the selection of the indicators to ensure relevance and acceptance of the indicators?

One structured method of developing indicators involves the use of the Delphi method (<https://www.thehealthcompass.org>). Here, an initial list of indicators is defined based on the identification of a core question or problem. Next, a comprehensive literature review is performed, which helps to define themes, indicators and relevance and context and support the design of stakeholder interviews and/or questionnaires. Stakeholder perspectives are then collected, resulting in the indicators being rated by means of pre-defined inclusion criteria. Ultimately, this process results in a limited set of indicators (9).

Adoption of existing evidence-based indicator definitions or a standardized taxonomy can prevent unique data collections and ease data aggregation. By standardizing the definitions of numerator and denominator, it becomes easier to compare performance measures across institutions, regions, and countries.

## Quality management with indicators in daily practice

The aim of quality management is to transform the distribution function of the outcome for a number of patients from a curve with a broad flat distribution to one with a taller and narrower distribution and a better average outcome (10). This must be done while taking the financial challenge of cancer care into account, i.e. accounting for more expensive care options with a limited budget. However, many indicators do not lend themselves to a narrower bell-curve (Gaussian distribution). Examples are the ‘wait time for screening mammogram appointment in days’ or ‘the % of patients biopsied with guided needle biopsy as opposed to open surgical excision’. In these examples, the goal of quality management is to shift, but not narrow, the curve (and its mean or median) towards a benchmark value (along the x-axis) (11). Moreover, often QI are expressed in funnel plots, having the (volume of) individual hospitals on the x-axis against the outcome of the QI (expressed in a ratio) on the y-axis. The funnel plot expresses the 95% CI around the average of all hospitals together.

Furthermore, only in cases where the definitions of numerator and denominator are exactly the same and reliable data gathering has been performed can indicators be compared between hospitals (the so-called benchmark). Large interhospital variations may reflect variability in the quality of data, differences in underlying patient populations, lack of evidence, lack of consensus regarding scientific evidence or guidelines, or, ultimately, true differences in quality of care. Possible differences in underlying patient populations can be considered with case-mix corrections of the indicators, e.g. age or socioeconomic status or overcome by stratification to achieve more heterogeneous patient groups.

Performance, as measured by quality and value indicators, reflects the given care influenced by the available evidence for treatment, the patient’s and doctor’s preferences (ideally as a shared decision with the patient), the healthcare system, and the resources available within that system.

Indicators should not be used by the breast care team to monitor the delivered practice in isolation, but rather should also consider the whole care delivery system these indicators are influenced by. Regular discussion of the results of the indicators within the relevant teams, e.g. administration, operational, and the multidisciplinary team will support a consistent Plan-Do-Check-Act or Observe—Learn—Optimize—Repeat cycle and support continual quality improvement. Moreover, indicators can be discussed in regional or national networks, not only to benchmark but also to debate about the differences and

learn from each other. Finally, ensuring indicators are collected and reviewed regularly, and not only when they must be sent to the inspectorate, health insurers, or auditors, will promote a proactive and learning and quality improvement environment, as opposed to a reactive environment changing only when forced to do so by a higher authority (12).

### An example: the cancer performance indicator (CPI)

To make transparent, consistent, and multidimensional analysis of outcomes and value-based oncology a reality, the Health Value Alliance created the cancer performance indicator (CPI) (Figure 4.1).

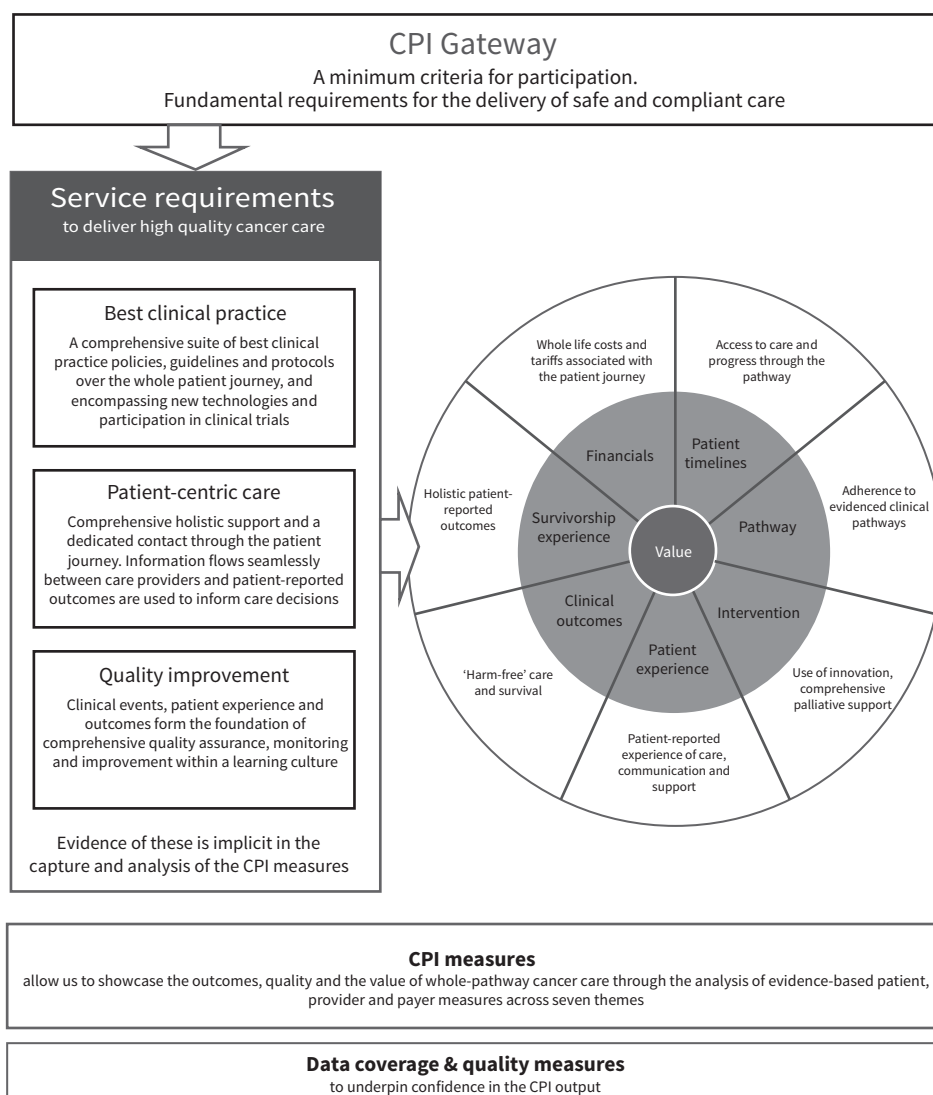


**Figure 4.1** The Health Value Alliance Cancer Performance Indicator Value Model.

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The CPI provides a standardized, evidence-based, non-biased platform for decision makers to use to assess, monitor, and report on cancer service, innovation, and funding performance, i.e. quality, outcomes, and cost. Importantly, the CPI provides a standard data model that incorporates other international measure set models, e.g. ICHOM (see Chapter 8), against which stakeholders can submit. The CPI then analyses these data for volume and quality to ensure results are based on the highest quality data only. Correlating clinical and patient-reported outcomes with financial metrics provides insights into the relationship between PROMs, PREMs, and total cost of care at varying time points. The CPI can also illustrate the multitude of pathways a patient may take through their cancer journey and showcase the outcomes associated with varying pathways.

The comparison of ourselves to others is a powerful tool to help us understand what we might improve and who to learn from (12). Therefore, a fundamental principle of the CPI is to ensure data and perspectives of the different stakeholders are represented in the CPI performance reports. The CPI can also be used to establish a foundation of value equity and drive value synergy while always maintaining patient-centricity.

Use of the CPI by different stakeholders includes:

For **clinical care providers**, the CPI can support the consistent evaluation and improvement of clinical quality, operational efficiency, and patient-centred effectiveness.

For **payers**, the CPI support provider and innovation quality and value assessment, directionality, and cost/risk exposure.

For **accreditation agencies**, the CPI brings further dimensions to accreditation, covering clinical, patient-reported and value performance and enables dynamic/more agile accreditation cycles.

For **pharmaceutical, medtech research** the CPI supports evaluation of innovation safety, effectiveness, adoption, and cost-efficacy, which in turn supports access and return-on-investment.

For **policy designers**, the CPI supports consistent policy effectiveness evaluation and the informed evolution of policy.

Crucially, use of the CPI in the above scenarios ultimately leads to improved patient benefits.

## **A holistic vision on breast cancer care: Determinant of the final outcome**

A holistic vision of breast cancer care encompasses a comprehensive approach that considers all aspects of care and maintains an unwavering focus on addressing the diverse needs of patients throughout the continuum of diagnosis, treatment, survivorship, and end-of-life care (Figure 4.2).

Several key determinants contribute to achieving optimal outcomes in breast cancer care, including: early detection and diagnosis, multidisciplinary care teams, comprehensive and novel treatment options, holistic needs assessments during and beyond treatment, shared decision-making, patient access to supportive care services, continued research and innovation.

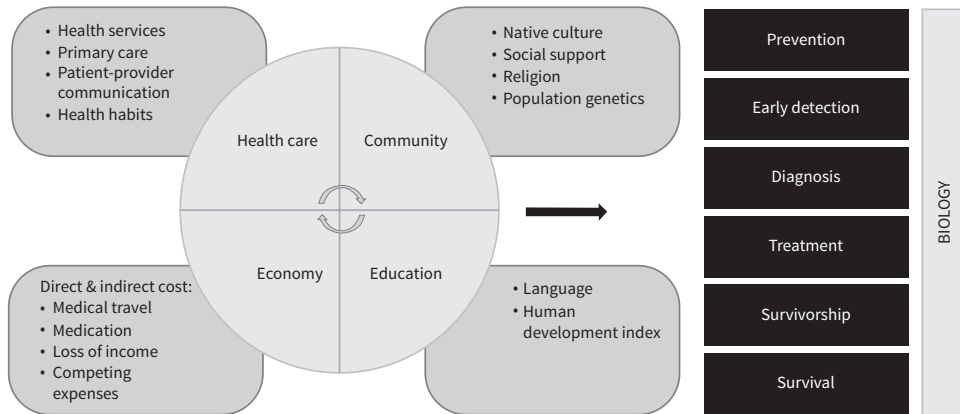


**Figure 4.2** Holistic vision on breast cancer care.

Additional key factors in achieving optimal outcomes include the organization of the healthcare system, the economic reality, the local community with the specific population genetics and lastly the education status with the human development index (13).

By addressing these determinants within a holistic framework and monitoring the effects of the framework by using models like the Health Value Alliance's Cancer Performance Indicator, healthcare providers can optimize breast cancer care outcomes and improve the quality of life for individuals affected by breast cancer (14).

In addition, the built environment influences health and cancer outcomes through multi-level social and structural mechanisms. Geospatial genomics uses geospatial analytical tools to extend the applicability of multilevel frameworks to understand how a neighbourhood's location may affect germline and tumour genomics, epigenomics, transcriptomics, and ultimately cancer outcome. This creates great opportunities to reduce cancer health disparities and improve health equity, taking into account gene–person–place relationships (15).

## Key messages

- The fight against breast cancer must focus on ensuring that those diagnosed with cancer achieve the very best outcomes that matter to them, no matter where they live and at a cost that is affordable to all.
- Quality inequity is a major driver of value erosion in breast cancer care, driving inequity, inefficiency, poorer outcomes, and increased costs.
- Defining and achieving the best quality of care is a complex process, but can be achieved through the use of an evidence-based quality management framework and tools like the HVA CPI that enables consistent evaluation and improvement.
- Developing and defining quality indicators requires the participation of stakeholders from across the cancer care ecosystem.
- Quality indicators should meet specific criteria and be defined in such a way that the interpretation and calculation are easy and the insights non-biased, timely, and relevant.
- Implementation of quality management tools can be accomplished with the adoption of standardized and evidence-based quality indicators.

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## 5

# Defining quality breast cancer care in Europe

*Lorenza Marotti and Isabel T. Rubio*

## Introduction

EUSOMA is the European multidisciplinary society of health professionals dealing with breast cancer care. The society aims at fostering the implementation of Breast Centre, improving and harmonizing the standard of breast cancer care (1).

## Defining quality

Quality is a multifactorial concept that can be fully achieved only if all elements are taken into account. With regard to breast cancer care, the main factors are: organization, training, and expertise, dedication, evidence-based guidelines/recommendations, multidisciplinary cooperation and liaison, data collection, and quality assurance.

All these elements need to fit together as the pieces of a puzzle to get the desired outcome.

EUSOMA, in its commitment to improve breast cancer care, has worked and is working on these factors to support those involved in breast cancer care to reach the objective of offering the best possible quality care to breast cancer patients.

For EUSOMA, the main pillars to work on this have been: recommendations, quality control, training, and research.

## Breast centre requirements

In the year 2000, EUSOMA published its milestone paper on the requirements of a specialist breast unit (2), nowadays better known as Breast Centre, aimed at underlining the concept that specialists of the different disciplines contribute to building up a breast centre in an organized manner with all the necessary equipment and services. Since then, the paper has been updated regularly to keep pace with the new developments and changes in breast cancer care. The last 2020 update has been endorsed by ECO (European Cancer Organisation), with representatives in the working group of the different European organ-related societies and ESMO (European Society of Medical Oncology) (3).

The paper guides health professionals, hospital management, and decision-makers on how to set up a breast centre and what is needed to work with a multidisciplinary approach

aimed at having them all over Europe, breast cancer treated only in Breast Centres. In terms of staff, the Breast Centre has a core team made up of those specialists who are always involved in the management of a breast cancer patients, such as radiologists, pathologists, surgeons, medical oncologists, radiation oncologists, breast care nurses, radiographers, and data managers. Moreover, there must be an extended team made up by the professionals that are involved in the treatment of specific group of patients, such as the geriatrician for elderly patients or the palliative expert for advanced, metastatic patients. Other specialists may be needed for consultation during the patient pathway, the so-called allied professionals, such as fertility preservation experts, neurosurgeons, etc.

An important aspect to underline is that the Breast Centre has to take care of all breast cancer patients independently from the stage of the tumour, which includes early, advanced, recurrent, metastatic tumours, from diagnosis to follow-up and end of life.

For EUSOMA the challenge was and is to see the requirements implemented in real life in the different countries, to demonstrate the efficacy and reproducibility of such a model and to show the benefit for breast cancer patients. A great challenge.

The requirements had a capillary diffusion among health professionals, and thanks also to the support of advocacy, were well received at a political level and by decision-makers. In 2003 and 2006, the European Parliament included the urgent need to establish BCs in the Breast Cancer Resolutions (4, 5).

The EU declaration 2015 (6) called on member states to ensure, by 2016, access to treatment in breast units set up in accordance with the 'European guidelines for quality assurance in breast cancer screening and diagnosis' (7), which included the EUSOMA requirements.

This has been fundamental to see in some countries the definition of national regulation stating that breast cancer has to be treated only in a breast centre with reference to EUSOMA requirements (8).

The multidisciplinary approach started growing little by little with the introduction of the multidisciplinary meeting (MDM), previously used only for early breast cancer patients and more recently also in the metastatic setting, to discuss and define, as a team, the treatment strategy to propose to the patient. This has been a change, moving from the *one specialist patient approach* to the *patient-centred approach among a multidisciplinary team*, with all the specialists working together on the best treatment.

MDM is a guarantee for shared decisions, increases the possibility to include patients in ongoing clinical trials, is educational both for trainees but also essential for any team member to be updated on the other disciplines, and also helps in creating a cohesive team. And most importantly, increases survival (9).

Breast care nurses and breast centre data managers emerged in many countries as part of the multidisciplinary team, as in the EUSOMA requirements they are indicated as part of the core team, fostering supportive care and quality assurance, respectively.

Through the development of a detailed patient pathway based on national and international evidence-based guidelines, including also the expected timing to perform each step, together with monitoring timing, recommendations/indicators have helped Breast Centre to keep up with the best timing, pushing for constantly decreasing any delay and identifying any bottleneck.

Another milestone paper has been the one on quality indicators (QIs) in breast cancer care that described QIs, for the non-metastatic setting, based on the patient pathway, to be monitored within the breast centre to evaluate the performance. The first publication was in 2013

(10). This paper has been regularly updated (11). In 2017, EUSOMA updated these QIs to incorporate new scientific knowledge in the field, as well as to reflect the experience acquired in more than 80,000 primary cases treated in European EUSOMA breast centres undergoing certification procedures.

The last update, published in 2024, encompasses QIs on the variety of evidence-based treatment and those that already entered clinical practice but still cannot be considered standard of care (12). To complete the set of quality indicators, EUSOMA—in collaboration with ABC Global Alliance—has also published those evaluating the care of metastatic breast cancer patients (13). The process of updating these QIs has involved a panel of European experts in the core team specialties of BC management, considering the clinical evidence, feasibility of measurement, and potential impact on BC patients.

## Certification of breast centres and real-world data

In 2006, to support Breast Centres in its important activities relating to quality assurance, benchmarking, auditing, and developing research projects, EUSOMA created a central data warehouse (EusomaDB) that includes over 200,000 cases from breast centres in 13 different European countries. EusomaDB collects individual pseudonymized patient data from breast centres undertaking the voluntary breast centre certification based on the EUSOMA requirement and QIs.

The EUSOMA data centre produces a yearly report for each breast centre on their performance towards EUSOMA QIs and interacts with data managers and clinical supervisors through this process.

Through its data warehouse, EUSOMA supports the breast centres in improving the quality assurance activity at a local level, addressing any need to implement actions to improve completeness, adherence to QIs.

Following the publication of the papers on breast centre requirements and QIs, a voluntary certification process based on the EUSOMA requirements has been developed (14) to provide health professionals with the opportunity to measure against such European requirements. The certification procedure is focused on the whole patient pathway, is based on real-world data, and is a support for breast centres in the process of taking all necessary actions to comply with the requirements. Last but not least, certification helps women in finding breast centres following EUSOMA recommendations as a guarantee of quality care.

Real-world data are nowadays an essential tool, as they represent the state of the art of the care given to the patients and can provide the answer to questions such as applicability and compliance with clinical guidelines. They act as signals for any item or procedure that needs to be discussed or re-modulated within the scientific community; they inspire research topics and future progress.

The quality of data is essential, i.e. solid and complete data allow a robust analysis to be performed that can represent a state-of-the-art picture. Thanks to the reliability of these data, necessary projects or actions can be developed to improve the situation or, vice versa, they represent important tools to show the efficacy of a specific item.

EUSOMA has created a European network of breast centres that includes all certified breast centres. This has allowed the development of research projects with real-world data, to help clinicians in measuring the efficacy of the provided care, highlighting areas in which

interventions for improvement are needed, and helping hospital management and decision-makers in better understanding the level of care offered and the importance of keeping all the steps of the patients' pathway monitored for the sake of best care to be offered to the patients.

In recent years, EUSOMA has produced several manuscripts using these real-world data from its breast centres' network. For example, one of these focused on the impact of SARS-CoV on the quality of care in the EUSOMA breast centres (15). The analysis showed that neoadjuvant treatment was used safely to delay surgery, and there was no reported underuse of various treatment modalities resulting in normal breast cancer quality of care standards in the entire breast cancer population treated in EUSOMA centres.

The conclusion was reassuring, as the paper concludes by saying that the quality of breast cancer care was well-maintained in EUSOMA-certified breast centres during the first wave of the COVID-19 pandemic.

## Other recommendations

Over the years, EUSOMA developed a set of recommendations on controversial issues to support breast centres in taking the most appropriate decision for patient care. Some have been developed in collaboration with other societies, such as the recommendations for the management of elderly patients produced with SIOG (16) and those on the management of breast lesions with uncertain malignant potential (B3 lesions) in collaboration with EUSOBI, ESSO, and ESP (BWG) (17).

With regard to elderly patients, its paper concludes that the management of breast cancer in this population is challenging because the disease is highly heterogeneous and there is insufficient evidence specific to older adults. Decision-making should not be driven by age alone but should involve geriatric assessments and close interaction with members of the multidisciplinary team, plus careful consideration of life expectancy, competing risks of mortality, and patient preferences.

For the management of B3 lesions, in the paper, experts conclude that the diagnosis and management of B3 lesions have changed due to improvements in radiological imaging and more adequate image-guided sampling. Further evaluation and potential interventions based on each lesion are better managed by a multidisciplinary team that will ensure a comprehensive evaluation and individualized care depending on the patient's risks, wishes, and characteristics of the lesion. Adequate communication with the patient is necessary for shared decision-making as an essential aspect of managing B3 lesions.

## Conclusions

Quality in breast cancer care is a continuous challenge that needs the collaboration and effort of all those involved at different level and competencies: health professionals, stakeholders, decision-makers, patients' associations and governments to agree on the best policies, to understand the priorities, to make the system effective and to facilitate the implementation of what defined by the health professionals both for the clinical and research aspects.

Interaction with the advocacy groups is an essential part of this process in order to highlight and include all those aspects related to communication, information, social and familial aspects, working issues, and unmet needs that must be integrated in the process of care.

## Key messages

- Quality in breast cancer care is a continuous challenge that needs the collaboration and effort at different levels: health professionals, stakeholders, decision-makers, patients' associations, and governments.
- Quality in breast cancer care needs to be measured by QIs to evaluate the patient's care pathway and to improve outcomes.
- Agreement on the best policies makes the system effective and facilitates the implementation of clinical and research aspects.
- Interaction with the advocacy groups is an essential part, including all those aspects related to communication, information, social, and familial aspects, working issues, and unmet needs that must be integrated in the process of care.

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## 6

# Defining quality breast cancer care in the US

*Cary S. Kaufman and Terry Sarantou*

## Breast centre definitions

Since breast cancer is the most common cancer in women around most of the globe, the organized approach to diagnosis and treatment should be easily defined. Breast centres and breast units populate all major cities and countries, yet a unified definition of a breast centre or unit has not been universally accepted. We have several definitions from major organizations that can be noted as follows:

- EUSOMA definition (1): ‘The Breast Centre is made up by a cohesive group of dedicated breast cancer specialists working together as a multidisciplinary team with access to all the facilities required to deliver high-quality care throughout the breast cancer pathway from genetics and prevention, through the treatment of the primary tumour, to care of advanced disease, palliation, and survivorship.’
- NAPBC definition (2): ‘A breast centre provides comprehensive care that has met or exceeds quality standards established by the National Accreditation Programme for Breast Centres.’
- NQMBC definition (3): ‘The definition of a breast centre is a physical setting where breast healthcare services are provided. The management of breast diseases requires the interaction of multiple specialist surgeons, medical oncology, radiation oncology, radiology, pathology, plastic surgery, physical therapy, behavioural medicine, and nursing. Quality care means providing the patient with accurate evaluation and appropriate services provided with compassion in a technically competent and timely manner, with good communication and shared decision-making in a culturally sensitive fashion.’
- ECIBC definition (4): Rather than a definition of a breast centre, the European Commission Initiative on Breast Cancer established a comprehensive manual of quality and safety requirements for breast cancer services across diverse healthcare settings. It offers a person-centred quality assurance scheme alongside the European evidence-based guidelines.
- SIS definition (5): Rather than a definition of a breast unit, the Senologic International Society have developed an accreditation process whose goals are stated. ‘Universality: quality processes in the diagnosis and treatment of breast cancer should be accessible to all women regardless of the geographical location of their homes. Uniformity: The quality indicators required must be equal for all Breast Centres.’

The common threads noted in all these statements define the building blocks of quality breast care. Breast centres should have the following essential components to provide multidisciplinary care. These components will be expanded throughout this book. Each centre must have the administrative and organizational components of a breast centre as well as the operational performance components reviewed by their effort to self-scrutinize their results. The building blocks to provide quality breast care are described as follows (see Table 6.1)

In the US, the National Accreditation Programme for Breast Centres (NAPBC) has established a set of foundation standards that embody these components for breast centres (2, 6). The first three mandatory requirements include 1) the leadership team with authority, 2) multidisciplinary provider care, and 3) regularly scheduled multidisciplinary meetings to recommend and coordinate care. These components are the central hub of the breast centre. These foster multidisciplinary care and communication between the disciplines, with the authority to make decisions. All breast centres must have these three components. Recently, the NAPBC has updated their standards.

In addition, the National Quality Measures for Breast Centres (NQMBC), a quality programme from the National Consortium of Breast Centres, evaluates breast centre quality performance using an online set of performance measures (3). The NQMBC assumes all the components of Table 6.1 are in place and then asks to calculate the level of performance of

**Table 6.1** Components of a quality breast centre

|                                                  |                                                                                                                                                                                            |
|--------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Breast programme leadership with local authority | A small leadership team of the breast centre with authority to direct actions and direction of the breast centre                                                                           |
| Multidisciplinary providers of care              | A team of dedicated clinical professionals with specialty expertise with regards to breast disorders                                                                                       |
| Regular multidisciplinary breast conferences     | Regularly scheduled multidisciplinary meetings of the breast centre clinical team with pre-treatment discussion of all patients                                                            |
| Set of approved treatment guidelines             | An agreed-upon set of standards, guidelines, or treatment schemes that guide the initial approach for each unique clinical situation                                                       |
| Concurrent database management                   | Ongoing real-time monitoring of clinical care facilitated by maintaining a database on all patients                                                                                        |
| Maintained equipment for diagnosis and treatment | A fully equipped breast centre with up-to-date supplies and functioning equipment within the practical restrictions of the region                                                          |
| Quality improvement programmes                   | Regular quality improvement projects initiated and completed by the multidisciplinary team and reported to the breast centre leadership. This may often include clinical research projects |
| Clinical research opportunities                  | Provide patients with opportunities to participate in clinical research                                                                                                                    |
| Community outreach and awareness programmes      | Outreach efforts to provide and inform the local community of the need for screening as defined by your region                                                                             |
| Genetics and high-risk assessment                | Identifying those at high risk for breast cancer or genetic mutations. Assessing and/or testing diagnosed patients for gene mutations                                                      |
| Survivorship                                     | After completion of treatment, providing a resource to manage the effects of local and systemic treatment and associated side effects                                                      |
| Palliative care                                  | For those patients who fail therapy, connections with specialists in palliative care                                                                                                       |



over 40 quality measures. A centre can then compare its performance with similar breast centres. These comparison findings may stimulate internal processes to improve care.

### **A leadership team with authority (mandatory requirement)**

A designated leadership team of the breast centre should have the authority to initiate actions and modify the direction of the breast centre. Since breast centres may reside within larger medical facilities, it is important that there is some ability for self-control of the actions of the breast centre. Without such authority, many breast centres fail in their ability to provide optimal care. Although a single individual may be identified as the leader, often it will be a small team of specialists who make strategic decisions for the breast centre to confirm the centre stays on a course of optimal quality care for their patients. Further discussion on this topic may be found in Chapters 5 (EUSOMA) and 7 (rest of the world).

### **Multidisciplinary care (mandatory requirement)**

The breast centre engages a team of dedicated professionals to provide quality breast care. For any woman with a breast cancer diagnosis, a team of clinicians is required to provide optimal care. The team includes a central core of providers including a breast imager, a pathologist, a breast surgeon, a medical oncologist, a radiation oncologist, a plastic surgeon, a breast care nurse (navigator), a genetics professional, and a psycho-oncologist. Beyond that core team are administrators, technologists, mammographers, physical therapists, rehabilitation specialists, psychologists/therapists, and social workers. Even beyond those clinicians are other supportive individuals. The key ingredients are that each provider of care is dedicated, competent, experienced, and maintains their competence with ongoing education. Current education activities should be monitored. Individual sites and countries may provide their own definitions of these criteria of professional competence based on local or regional standards. Yet, the constant theme must be proficiency and experience in their discipline as it relates to breast cancer diagnosis and quality treatment. Ideally, common requirements will be applied to all breast centres in each region. Further discussion on this topic may be found in Chapters 5 (EUSOMA), 7 (rest of the world), and 11 (multidisciplinary meeting).

### **Multidisciplinary meetings (mandatory requirement)**

No one provider should work alone without the benefit of other clinical views from other disciplines. Perhaps the most important aspect of a breast centre is the agreement to approach each patient in a multidisciplinary fashion. Multidisciplinary meetings of the breast centre team are scheduled regularly. Each patient should receive the benefit of all the breast care specialties by having their case presented to the multidisciplinary meeting/conference. At each meeting, attendance is taken to document that all specialties and all active breast centre participants attend the meeting to provide a healthy discussion on each new patient. It is essential that these discussions should take place before major treatment has

occurred. Many centres will have patients discussed after initial diagnosis (e.g. needle core biopsy), and then again at a second conference after initial treatment (e.g. surgery). Further discussion on this topic may be found in Chapter 11 (multidisciplinary meeting), and 25 (tele-oncology)

## **Evidence-based guidelines**

A set of standards, protocols, guidelines, or treatment schemes that guide the initial approach to care for each unique clinical situation should be available. Since no single set of guidelines can provide the answers to all situations, the set of documents noted here is used to initiate discussion and approach to varied clinical situations. Thereafter, with discussion and the joint experience of the multidisciplinary group, decisions of care can be generated from the outlines provided by this set of standard approaches. When the team of professionals are gathered in meetings, a mutually agreed-upon set of guidelines promotes uniformity of care within the breast centre. Ongoing monitoring of treatment results using a database is a vital part of providing comprehensive breast cancer care. All patients should be entered into the breast centre database for long-term assessment of quality. The database may be used to demonstrate conformity of breast cancer management with agreed-upon guidelines. Further discussion on this topic may be found in Chapter 10 (role of guidelines).

## **Equipment**

Breast Centre equipment must be up to date and current within the practical limits of the region. Breast cancer is the most common cancer in women around the globe. Since it affects all areas, regional financial support for breast centres will, to some degree, determine the spectrum of equipment available to each breast centre. With that in mind, there are some pieces of equipment that are vital to the success of any breast centre. Equipment is not limited to imaging machines or breast MRI but also includes the spectrum of pathology laboratory equipment needed to examine each patient's findings. Further discussion on this topic may be found in Chapters 12 (imaging), 13 (pathology), 16 (radiation therapy), and 17 (systemic therapy).

## **Clinical database management**

Ongoing monitoring of quality care requires a concurrent database as well as quality management with continuous quality-of-care monitoring. Changes in breast cancer care may occur at a rapid pace, and breast centres must continually assess whether they are providing state-of-the-art quality care. A database should be available to enter all patients treated at the breast centre. The database should be searchable, and regularly report outcomes based on database content. These reports should be shared with all the clinical providers and reviewed for quality improvement. In addition, specific quality measures and programmes should be integrated into the care of all breast cancer patients. These quality measures may be sourced

from programmes like the NAPBC, NQ MBC, EUSOMA, SIS, ECIBC, and other regional quality programmes. For example, the German Cancer Society (DKG) found improved survival by their certified breast units compared to non-certified (6, 7). Further discussion on this topic may be found in Chapter 1 (cancer registries).

## **Quality improvement and research**

Regularly scheduled quality improvement projects should be initiated and completed by the multidisciplinary team and reported to the breast centre participants. During administrative meetings or multidisciplinary meetings, areas for quality improvement may become apparent. Resources should be dedicated to investigating those areas and considering options for improvement. The real-time clinical database will be helpful in gathering data on specific quality questions to achieve valid answers. Each year, several focused quality questions should be initiated and researched. Some quality improvement comparisons may be found when centres use the National Quality Measures for Breast Centres (<https://www.nqmbc.org>). This may often include specific research projects. A breast centre should provide patients with information on the availability of applicable clinical trials and offer patients the opportunity to participate in the advancement of evidence-based medicine. Some individual countries have successfully instituted quality management for their breast centres and have shown benefits of participation (7, 8). Further discussion on this topic may be found in Chapters 5 (EUSOMA), 7 (rest of world), and 26 (clinical research).

## **Community outreach and high-risk programmes**

Outreach efforts provide and inform the local community of the need for screening as defined by your region. Regardless of the country, some patients arrive too late to benefit from modern treatment. Increasing breast health awareness to the community near the breast centre should be an obligation of each breast centre. A competent and fully equipped breast centre without any patients is an unfortunate situation. Methods of ongoing outreach should be developed and maintained to ensure that those who will benefit from a high-quality breast centre are made aware and seek care. As genetic assessment becomes more available, both in cost and complexity, high-risk programmes and genetic testing will become a more significant aspect of outreach and education by breast centres. Further discussion on this topic may be found in Chapters 18 (primary care), and 23 (genetics).

## **Combine all components**

This list of breast centre components helps define the optimal quality breast centre. This list also helps develop breast centres ensure comprehensive care for their patients by attending to the list of standards and components. Utilizing a web-based collection and assessment tool quality measurements are available to compare a participating breast centre with similar centres across the nation (9, 10).

## Key messages

- Quality breast centres require the integration and coordination of a focused group of clinical providers.
- Breast Centres require defined leadership with authority over the centre.
- All breast centres should have multidisciplinary providers who meet on a regular basis to discuss the management of patients.
- A maintained database is essential to assess breast centre performance and quality.
- Focused retrospective quality assessments are vital to maintaining a high-quality breast centre.
- Outreach to their local community is a responsibility of each breast centre.
- Assessment of high-risk and genetic mutation carriers will become an important component of breast centres.
- Organizations supportive of the initiative to improve quality breast care include the NAPBC, NQ MBC, EUSOMA, SIS, ECIBC, and others.

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## Defining quality breast cancer care around the globe

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### Introduction

In several countries throughout the world, national quality programmes aim to standardize and improve the quality of care for breast cancer patients. These programmes have the potential to stimulate the development of clinical practice guidelines, foster implementation in multidisciplinary breast cancer units, and monitor implementation through quality indicators (QIs).

National quality programmes vary in strategies for obtaining optimal quality of breast cancer care, encompassing approaches from auditing to certification and accreditation. Maes-Carballo et al. performed a systematic review to compare quality programmes and focused on quality indicators in European and North American countries (1). The outcomes confirmed the variability in programmes, and specifically highlighted high variability in QIs between countries. Additionally, more than half of the countries included in the review lack an implemented programme.

This chapter will explore various international perspectives (Figure 7.1) on the regulation of quality programmes. We will highlight key aspects of breast cancer care accreditation, including guidelines, centre definitions, quality monitoring methods, defined QIs, benchmarking, data usage, public accessibility, and patient perspectives. Furthermore, we will provide insights into the future perspectives of different countries and regions.

### The Dutch perspective

In the Netherlands, the National Breast Cancer Organisation Netherlands (NABON) is a nationwide multidisciplinary working group. Members are all healthcare professionals working in the breast cancer care organized in regional breast cancer care networks. The goal of the NABON is to improve quality in breast cancer care with different initiatives, including the distribution and adaptation of national guidelines, standardization of data registration in the



**Figure 7.1** World map indicating countries with quality programmes discussed in this chapter.

electronic medical records (EMR), patient education, implementation of patient-reported outcome measurements (PROMs) and development of QIs and performing audits.

## Quality monitoring by the NABON Breast Cancer Audit (NBCA)

In 2011, the multidisciplinary NABON Breast Cancer Audit (NBCA) was developed as part of the Dutch Institute for Clinical Auditing (DICA; <http://www.dica.nl>) to measure the quality of care in non-metastasized, surgically treated Dutch breast cancer patients (2). The primary goal is nationwide monitoring of quality of breast cancer care, and the provision of feedback to individual hospitals on their results in relation to 'real-time' national benchmark information.

For the gathering and reporting of data, a collaboration between DICA and the Netherlands Comprehensive Cancer Organisation (IKNL; <http://www.iknl.nl>), responsible for the Netherlands Cancer Registry (NCR), was established. Hospitals have the option to either self-register data through DICA's web-based system or have IKNL registrars that perform the registration as part of the NCR. A data dictionary is available to secure uniform data acquisition. When data are registered by IKNL, which is in practice in about 75% of the 72 hospitals, hospitals can check the data at patient level for inconsistencies before the data are transferred to the (national) DICA system, the indicators are calculated and partly become transparent. Patient data is anonymized before data transfer.

Participation in the NBCA is obligatory for all 72 hospitals delivering breast cancer care. Other conditions that must be achieved for breast centres are defined in the SONCOS (Oncological Collaboration Foundation) standardization report (3). The scientific committee of the NBCA consists of mandated members of all medical associations involved in breast cancer care (radiology, pathology, surgery, medical oncology, radiotherapy, plastic surgery, and clinical genetics), the breast cancer patient's association and a representative

of the Dutch healthcare insurances. They define and annually evaluate the QIs based on their validity. They discuss if indicators enhance transparency, and which indicators may be adapted or removed when considered appropriate (2). DICA ensures the calculation of the indicators. A selection of indicators is publicly available on <https://zorginzicht.nl/kwaliteitsinstrumenten/mammacarcinoom>.

Individual hospitals have continuous insight into their own performance on the QIs along with other baseline information such as patient-, tumour-, and treatment characteristics; these are regularly updated on a secured website. The QIs are nationally benchmarked against the other (anonymously presented) hospitals using funnel plots showing the 95% confidence interval in conjunction with the benchmark results. The NABON sets up audit visits to the hospitals together with the scientific societies of the specialists. Moreover, regional breast cancer working groups, supported by IKNL, discuss the breast cancer care including the NBCA indicators on a regular basis. In the last ten years, improvements were seen in nearly all QIs. As examples, pre- and postoperative patients nowadays are almost all discussed in multidisciplinary meetings, and more MRIs (magnetic resonance imaging) are performed prior to Neoadjuvant Systemic Therapy (NST) and for patients with lobular breast cancer (Figure 7.2).

In the context of the NBCA, there is an annual assessment based on the expert opinion of the QI set by the scientific committee. Internal and external indicators will be critically assessed based on the criteria of relevance, validity, reliability, and feasibility, which can lead to changes in the QI set (2). For example, the external indicator ‘if a patient is discussed in multidisciplinary team’ has been removed from the QI set, as the QI consistently scored 100% in the last years, leaving no room for improvement. Internal indicators are evaluated to determine if they should be transitioned to external indicators (publicly available). Furthermore, new QIs can be introduced as, first, internal indicators based on new insights and/or guideline revisions.

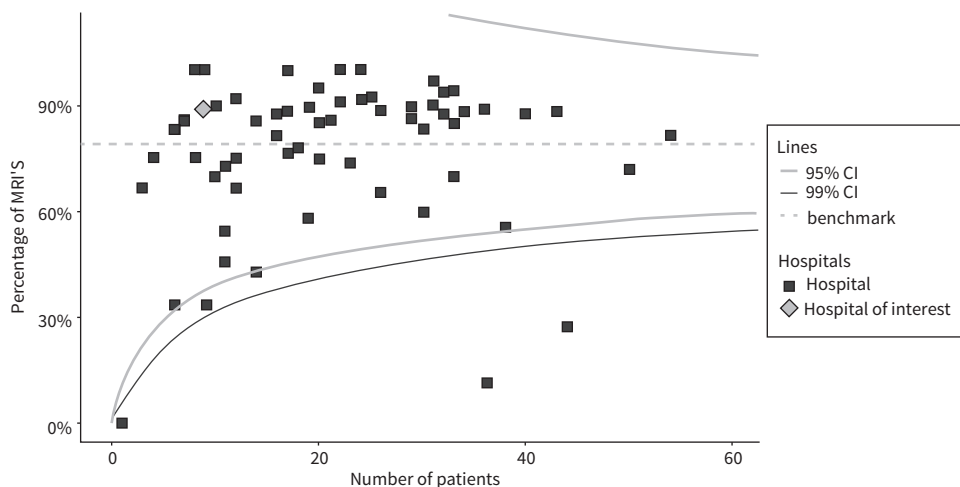


**Figure 7.2** Quality indicators are displayed in funnel plots, providing short-term feedback. This funnel plot shows the percentage of MRI scans conducted before breast cancer surgery for patients with lobular breast cancer. Each square presents a hospital. The hospital of interest is presented as a diamond (now randomly selected), allowing to assess their performance relative to others. The dashed line represents the Dutch benchmark (mean of all hospitals), while the grey lines indicate the 95% and 99% confidence intervals.

## Future perspective

To align with the report ‘Outcome-oriented care for breast cancer’ of the Dutch ministry, the focus will be more and more on the outcome indicators ‘quality of life’ and ‘shared decision-making’ (4). Moreover, QIs for patients with metastatic cancer are discussed upon and whether a separate registry should be set up. The NCR gathers up to now only the synchronic metastatic breast cancer patients (through notification by the pathology archive PALGA) and will expand the registration to metachronic metastasis by notification through the Dutch Hospital Data. To decrease the registration burden, linking the NBCA with various databases and closer collaboration between DICA and IKNL are being explored. Furthermore, the care will, in the near future, be organized in regional networks in which hospitals work together. This will potentially lead to the calculation of QIs at the network level. In terms of harmonization and standardization, international alignment will be increased, e.g. to the European Commission Initiative on Breast Cancer recommendations (<https://cancer-screening-and-care.jrc.ec.europa.eu/en/ecibc>).

## The United Kingdom perspective

In the United Kingdom (UK), the healthcare systems differ slightly between England and the devolved nations, however all four nations are keen to focus on enhancing healthcare quality and improving cancer care. In this section some of the systems, initiatives, and organizations at the forefront of improving the quality of Breast Cancer care especially in England are highlighted.

In the UK, integrated Breast units are responsible for diagnosing and treating BC within a multidisciplinary setting. There are regional plastic surgical units (hubs) for tertiary referral for complex cases and free flap surgery. Regional cancer alliances are responsible for standardizing care in their region.

## Quality monitoring and improvement programmes

Getting It Right First Time (GIRFT) Programme, National Clinical Improvement Programme (NCIP) and The Model Health System (Model Hospital): The GIRFT Programme is a ground-breaking multidisciplinary clinically led programme that performed an in-depth review of breast surgery services across National Health Service England (NHS). All 129 breast surgery teams in England were visited by a senior clinician, their data was presented, and discussions about current practices, challenges, variations in practice, and priorities for change were had with each team. The annual report was published in 2021 containing recommendations to improve patient care ([https://gettingitrightfirsttime.co.uk/surgical\\_specialties/breast-surgery](https://gettingitrightfirsttime.co.uk/surgical_specialties/breast-surgery)). The senior clinical advisor is a committee member of the Association of Breast Surgery Clinical Standards and Practice Committee (ABS CPSC) and feeds back themes to the national committee. There are now over 100 breast-specific metrics on Model



Hospital—a centralized secure online portal—allowing providers to compare their performance with their peers or others in their system. The data is automatically and centrally captured from the Hospital Episode Statistics (HES), which includes all care performed in the NHS. NCIP will serve as a valuable resource for surgical quality improvement and consultant learning and development.

To improve the quality of care for older individuals (aged over 70), the National Audit of Breast Cancer in Older Patients (NABCOP) was set up in NHS hospitals across England and Wales (<https://www.nabcop.org.uk>). It was launched in 2016 through collaboration between the Association of Breast Surgery (ABS) and the Clinical Effectiveness Unit (CEU) of the Royal College of Surgeons of England (RCS). NABCOP, commissioned by the Healthcare Quality Improvement Partnership (HQIP), evaluated age-related disparities in breast cancer care. The 2021 audit revealed comparable 5-year survival rates for older patients undergoing surgery as their initial treatment, emphasizing the importance of identifying fit older patients using established frailty tests. The datasets were supplied by the national cancer registration services.

The National Cancer Audit Collaborating Centre (NATCAN), also managed by the CEU, is the new cancer audit. Building on the lessons learned from NABCOP, NATCAN is conducting two breast cancer audits: NAOpri, focusing on primary breast cancer (stages 0 to 3) and NAOme, addressing metastatic breast cancer (MBC; <https://www.natcan.org.uk/professionals/reports-2/>). Key features of all CEU audit projects include close clinical-methodological collaboration, the utilization of national linked datasets whenever possible, and strong collaboration with data providers in England (National Disease Registration Service [NDRS], NHS Digital [NHSD]) and Wales (Wales Cancer Network [WCN], Public Health Wales [PHW]). This audit incorporates additional data sources compared to the NABCOP. The data is not automatically updated. Embracing a clinical epidemiological approach, these audits will uphold NATCAN's commitment to the three 'Rs', ensuring clinical relevance, methodological robustness, and technical rigour in all activities. Commissioned by the HQIP, NaoPri, and NAOme provide valuable insights into the total breast cancer care, supported by surgeons, oncologists, breast nurses, and patient advocates. In the coming years QI will be defined.

Private Healthcare Information Network (PHIN) offers comprehensive, unbiased information about private hospitals and consultants, promoting transparency through a rigorous data verification process. Patient feedback remains unedited, fostering transparency, and encouraging continuous improvement in services.

The Care Quality Commission (CQC) serves as the independent regulator for health and adult social care in England, ensuring that these services deliver safe, effective, compassionate, and high-quality care. Through monitoring, inspecting, and regulating services, the CQC aims to protect individuals from harm and ensure they receive care that aligns with established standards. The Association of Breast Surgery (ABS) along with the British Association of Plastic Reconstructive and Aesthetic Surgeons (BAPRAS) have drawn up breast metrics for the CQC who are moving to specialty specific inspections. The CQC works to drive improvement in services that have fallen below acceptable levels of care, holding care providers and managers accountable for any shortcomings in the delivery of care.

## Future perspective

Released in January 2019, the NHS Long Term Plan (LTP) outlines significant goals to enhance cancer outcomes and services in England over the next ten years. The plan aspires to achieve, by 2028, an annual increase of 55,000 individuals surviving cancer for five years or more and to diagnose 75% of cases at early stages (stage one or two). These objectives not only focus on quantitative targets but also emphasize the improvement of quality of life and patient experience. Additionally, the plan aims to reduce variation in healthcare delivery and address existing inequalities in cancer care.

## The Swedish perspective

### Introduction

The Swedish six Regional Cancer Centres (RCC) are responsible for cancer care quality register operation and support and assemble data on a common national web-based platform. The Swedish Association of Local Authorities and Regions (SALAR) represents and advocates local government in Sweden and is responsible for the confederation of RCC in Sweden for quality management and finances the quality registers through yearly grants.

The National Quality Register for Breast Cancer (NKBC) was functioning in 2008 and to date includes information on over 140,000 cases (<https://statistik.incanet.se/brostcancer>). It contains data on lead times, diagnostics, tumour characteristics, breast and axillary surgery (including oncoplastic surgery and primary reconstruction), oncological treatment, and follow-up, collected through six different forms; notification, preoperative oncological treatment, surgery, oncoplastic surgery, and primary reconstruction, adjuvant treatment, and follow-up. Since 2020, also PROMs are collected through a web form (measuring baseline symptoms, as well as symptoms at follow-up at 6, 12, and 36 months).

The NKBC steering committee, with regional multidisciplinary and multiprofessional representatives and patient representatives, has overall responsibility for the register's design, use, and development. An executive management group consisting of five members handles the tasks of the registry in close cooperation with the national support team from the RCC.

All Swedish hospitals engaged in the diagnostic and therapeutic process of breast cancer care report data on cancer cases to the RCC web-based platform and the reported data is handled by the NKBC support group at the Regional Cancer Centre in Stockholm. Patient information is not anonymized but protected within the secure national database. Participation into any national quality registry is managed by an opt-out procedure. In 2023 NKBC had a 99% coverage using the Swedish National Cancer Register (to which reporting is mandatory by law for all healthcare professionals) as golden standard.

Breast cancer care units are defined as units that offer the full range of health provision. To date, 33 units report to NKBC of which 28 report >150 cases per unit/year.

## Quality monitoring

Quality monitoring is achieved by the NKBC support team. Quality indicators are developed by the steering group and updated regularly according to national guidelines. Relevant indicators are selected that mirror the process and outcome of Swedish breast cancer patients. The Ministry of Health and Welfare recommend certain key indicators for cancer care, for example multidisciplinary team meetings, contact nurses, and a documented care plan for all patients. The data items for the calculation of the indicators are centralized, and calculation of the indicators takes place by the support team of NKBC. Reported data can be viewed real-time behind a log in. Selected data are fully available for the public on the NKBC website and are updated twice yearly. Differences on regional, municipality, and hospital levels are displayed as is county of residence and notifying hospital. The website with the interactive report exists in an English version (<https://cancercentrum.se/samverkan/cancerdiagnoser/brost/kvalitetsregister>). The data dictionary is set up within the multidisciplinary working group, the executive management team of NKBC that assembles monthly.

A validity assessment of the quality indicators was published in 2019 and repeated in 2022 (5). The register maintains high validity, but PROM reporting has been lagging and outcome data is only reported in aggregated form. Adjustments and updates of all variables are done based on the validation report and on updated national and international guidelines. The register data is a source of scientific publications with more than 400 cited publications.

## Future perspective

As manual registration of data is resource demanding, much effort is made to achieve automated transfer from clinical charts, pathology reports, and image results. Because several systems for data storage (clinical and lab data) exist, this constitutes a major challenge

## The Romanian (Eastern Europe) perspective

In Romania, much as in most other countries in Eastern Europe, the responsibility for quality assurance of breast cancer care is shared between various healthcare organizations and regulatory bodies that regulate and finance cancer care. There is no specific national quality assurance system for breast cancer. The different players' roles will be described next, but as a result of incomplete harmonization among them, there is no standardization of measurements, or development of QIs, which leads to variation in care across the country/region.

## Quality monitoring

The Ministry of Health is responsible for setting healthcare policies, regulations, and standards, which indirectly influence the quality of breast cancer care in the country; it also develops the National Cancer Control Plan (NCCP). The most recent version (2023:

<https://ms.ro/en/of-public-interest/news/planul-na%C8%9Bional-de-combatere-%C8%99i-control-al-cancerului-pncc/>) focused on prevention and screening, supporting the evolution of the regional screening pilot project to become a national breast cancer screening programme, and it supports the introduction of certification schemes for screening services in accordance with the guidelines of the European Commission Initiative for Breast Cancer (<https://cancer-screening-and-care.jrc.ec.europa.eu/en/ecibc>), adapted to national capacities. However, there is no mention on the development of breast units.

The National Health Insurance House healthcare financing and reimbursement policies, which can impact access to quality breast cancer care, including screening, diagnosis, and treatment. Access to innovative and expensive medicines has improved substantially over the years. The quality of care is regulated through reimbursement protocols that define eligible patients, but it does not allow the assessment of outcome indicators.

The National Authority for Quality Management in Health (<https://anmcs.gov.ro/web/>) is a specialized body of the central public administration in the field of quality management in health, which functions under the government and the coordination of the Prime Minister, that is responsible for accreditation of health units. It maintains lists of standards and QIs, mainly in relation to the ISO standard, but again nonspecific for breast cancer care.

Professional medical associations play a role in establishing guidelines and standards of care for breast cancer diagnosis and treatment. European and international clinical guidelines are replicated in national recommendations or institutional protocols, multidisciplinary discussions are mandatory, but adherence is quite heterogeneous and there is no system in place to check for deviations.

Non-profit organizations and patient advocacy groups also advocate for improved access to quality breast cancer care and provide support and resources to patients and their families, but with limited impact. Due to lack of publicly available data on the performance of the different hospitals treating breast cancer, patients are often disoriented and lack information on how to navigate the health system when needed.

Therefore, for the moment, individual cancer centres and hospitals are responsible for implementing guidelines, protocols, and quality improvement initiatives to ensure the delivery of high-quality breast cancer care to patients; due to lack of regulated national priority, it is up to the enthusiasm and initiative of centres to implement quality assurance programmes to pave the way toward certified breast care. Some centres have understood the need and are applying individually for international accreditation if their breast unit, such as the Cancer Institute Ion Chiricuta in Cluj-Napoca, which is in the process of obtaining accreditation from the German Cancer Society (DKG, Deutsche Krebsgesellschaft), thus becoming the first internationally certified breast cancer unit in Romania.

## Future perspectives

Overall, ensuring quality assurance in breast cancer care in Romania will require the prioritization at the national level of the necessity of developing a network of certified breast units. This will more extensive collaboration among various stakeholders, including government agencies, healthcare providers, professional associations, accreditation bodies, and patient advocacy groups. Adherence to the European Commission Initiative on Breast Cancer recommendations (<https://cancer-screening-and-care.jrc.ec.europa.eu/en/ecibc>) can facilitate

and ensure the success of this process, for the benefit of breast cancer patients and their families.

## The Brazil perspective

In Latin America, the absence of national cancer control programmes in most countries significantly contributes to disparities in access to care. These programmes are crucial for coordinating prevention, detection, and treatment efforts. Without them, equitable access to care and improvements in quality are lacking. Nevertheless, it's crucial to recognize the existence of treatment guidelines, offering evidence-based recommendations for cancer prevention, diagnosis, and treatment. In this section, we highlight Brazil, a country from Latin America that does have a programme. Information about Argentina can be found in Chapter 37.

## Quality monitoring

Brazil has a universal health system (SUS) that includes high complexity. Cancer control is carried out by the National Cancer Institute (INCA). Around 80% of the population uses this system. Around 60% of tumours are self-detected, 35% of which are advanced cases. The priority is early detection of symptomatic patients in primary units and training teams to create new secondary units for integrated diagnosis and reduction of treatment time. The public system adopted opportunistic mammographic screening from 50 to 70 years of age. Although there are more than 5,000 mammographs in the Public System of Brazil, they are underused mainly in the north and northeast regions and there are difficulties in performing stereotaxic biopsies. Mammography screening rates vary from 43% in the north and northeast to 65% in the south and southeast. Radiotherapy availability aligns with this distribution, showing lower access in the north and northeast regions.

In the supplementary or private health system, there is quality control for Hospitals and Clinics by the Brazilian Societies of Gynaecology, Radiology, and Mastology. The programme includes mammographic screening from the age of 40 and the protocols are same of ASCO guidelines (American Society of Clinical Oncology). Around 20% of tumours are *in situ*, 50% in stage I and only 10% advanced. One obstacle is the delay to incorporation of new drugs by Ministry of Health.

In May 2013, a federal law was passed in Brazil, the 60-Day Law (12.732/12), which mandates that patients with cancer begin treatment in the public system of health within 60 days of a confirmed breast cancer diagnosis. Despite the law, some regions of the north and northeast of Brazil don't have trained teams or infrastructure for diagnosis and poor integration with oncological hospitals. Consequently only 65% of the patients are treated before 60 days (6, 7).

The experience of the One-Stop Clinic with integrated diagnostic centre (radiologist, gynaecologist, pathologist nurses and oncologist) with biopsy in the first consultation in the Women's Reference Centre in São Paulo, Brazil was an important outpatient model to reduce the time for diagnosis and treatment. They observed downstage with reduction of 30% of advanced disease (8).

The National Cancer Institute (DATASUS) annually has statistical data in each state of the country with the number of new cases, age, number of mammograms performed, staging, type of surgery (mastectomy and breast-conserving surgery), chemotherapy sessions, hormone therapy, and survival in 5 and 10 years. The Institute follows an oncological treatment protocol aligned with the Brazilian oncology and mastology societies, centralizing basic information from all Brazilian cities in its database. However, there is no comparison made between different reference hospitals (public and private) to evaluate the quality of oncology treatment.

## Future perspectives

Telemedicine and navigation programmes for patients in small cities and rural areas are being implemented together with public-private partnerships to increase the number and improve the quality of mammograms, reduce the time for pathological diagnosis with immunohistochemistry, initiation of treatment before 60 days (federal law) and improvement of genetic evaluation in different regions of Brazil. Secondary references with resolute diagnosis with integrated oncological hospitals to start the treatment, are essentials for downstage and reduction of mortality in populations with access and transportation difficulties in big cities and rural areas (8, 9).

## The sub-Saharan perspective

In Botswana, Africa, the non-communicable diseases department of the Ministry of Health (MOH) is responsible for monitoring breast cancer, from early detection to palliative care. The main activity is to register incidences, disseminate guidelines and guide initiatives or implementation programmes (e.g. on Navigation) that improve breast health.

There is no set definition of a breast cancer care centre, but in practice, the four breast cancer units located in the country's four cancer referral centres are commonly regarded as such.

## Quality monitoring

Quality monitoring is mainly done through the cancer registry data and the ongoing implementation programmes, which give some insight on the evolution of quality over time (e.g. time to diagnosis, survival data). Patient associations are involved in the implementation programmes, but not in quality monitoring as such.

Data gathering and reporting for the cancer registry is done through standardized paper forms that are filled out by the cancer hospitals and returned on a regular basis to the non-communicable diseases (NCD) office. Patient information is anonymized before transfer of the data to the national database.

## Future perspective

Botswana is in the process of writing its first national cancer plan, in collaboration with the WHO. The plan is due for costing and implementation in 2025. This plan will include the

recording and auditing of pre-set QIs. The main goal for the breast cancer plan will be to attain the three WHO Global Breast Cancer Initiative (GBCI) objectives.

## The Egyptian perspective

In Egypt, healthcare reform, under the umbrella of Egypt Vision 2030, aims to transform the nation's healthcare system by enhancing the quality and accessibility of services (<https://www.mohip.gov.eg/EgyptVision2030>). A critical aspect of this reform is the implementation of high-quality standards in hospital care, particularly for breast cancer patients which is a significant health issue in Egypt.

### Quality monitoring

Presidential Initiative for Women's Health (PIWH) is launched in July 2019 and part of Egypt's broader 100 Million Health campaign (<https://www.mohip.gov.eg/initiatives/presidential-initiatives/women-health>). It prioritizes early detection of breast cancer, non-communicable disease screening, and reproductive health promotion. By April 2024, the initiative had screened millions of women (49,072,198), trained thousands of healthcare providers (29,046), and established mobile health units to reach underserved areas, leading to the screening of 81,273 women (<https://www.mohip.gov.eg/initiatives/presidential-initiatives/women-health>).

General Authority for Healthcare Accreditation and Regulation (GAHAR) is responsible for accrediting healthcare facilities in Egypt, ensuring they meet international standards of quality and safety. The GAHAR Handbook outlines comprehensive criteria for accreditation, emphasizing patient-centred care, safety, and quality management (<https://www.gahar.gov.eg/>). Implementation involves gap analysis, action plans, staff training, and compliance monitoring. Strategies for high-quality breast cancer care include early detection through screening programmes, multidisciplinary treatment approaches, and patient education and support services.

The Breast Cancer Comprehensive Centre (BCCC) at Cairo University's National Cancer Institute is Egypt's first centre dedicated solely to breast cancer care. Since 2013, it's transformed treatment through patient-focused care, advanced facilities, and ongoing research (10, 11). In 2023 alone, the BCCC registered 4,661 new patients, with a majority coming from Greater Cairo (76%), followed by Upper Egypt (10%), and the Nile Delta (9%). The BCCC employs a multidisciplinary approach to breast cancer treatment, involving oncologists, surgeons, radiologists, pathologists, and psychologists. This collaborative model provides tailored, evidence-based care using the latest research and guidelines. Furthermore, a comprehensive educational programme for patients and caregivers is developed. It includes communication skills training, disease understanding and management, nutrition counselling, psychological support, and post-traumatic stress disorder (PTSD) management. By December 2023, 1177 patients and 821 caregivers attended the compulsory educational sessions with a patient satisfaction rate exceeding 90%. A quantitative study showed a 47.7% knowledge increase post-session, proving the programme's effectiveness in enhancing understanding of breast cancer management for patients and caregivers.



In April 2022, the ‘patient navigation system’ was introduced. This tool assists with appointment coordination, information dissemination, and emotional support, resulting in a notable reduction in the time from diagnosis to treatment and improving patient satisfaction and outcomes. As example, registration to the multidisciplinary team (MDT) meeting decreased to 31.51 days for patients without prior investigations and 23.2 days for those with some prior investigations.

## Future perspectives

To sustain high standards in breast cancer care, Egyptian hospitals should invest in continuous staff training, maintain robust quality assurance programmes, and foster a culture of patient-centred care. Expanding initiatives like the PIWH to more regions is crucial for broader impact and comprehensive care. Furthermore, policymakers must ensure adequate funding, support research and innovation, and develop policies that promote equitable access to care for all women. By focusing on these elements, the quality of breast cancer care can be further enhanced, ensuring better outcomes for patients nationwide.

## The Japanese perspective

The Japanese Breast Cancer Society (JBCS) was established in 1993. The members consist of surgeons (5924), radiologists and oncologists (1015), pathologists and basic scientists (1015), associate members (e.g. nurses and pharmacists, 1453) and others (e.g. patients, 25). This society aims to promote study, research, education, and training related to breast cancer among its members, while also contributing to public health initiatives. The organization hosts academic events and publishes articles and books (own official journal *Breast Cancer* releasing six issues annually), communicates with national audiences and collaborates with international associations on breast cancer and related academic associations. Additionally, they accredit the certification of excellent institutions concerned with breast specialists.

Since the publication of the Medication Therapy Guidelines in 2004, JBCS has published guidelines for five fields: surgery, radiation therapy, screening, diagnosis, and prevention/epidemiology. Since recent advances in medical technology and drug therapy are remarkable, and in order to respond quickly to the changes, the JBCS prepared an online guideline that integrates all fields and opened it publicly in September 2011. In accordance with the online version, books are issued concurrently and revised every two years.

## Quality monitoring

JBCS has been accumulating breast cancer patient data since 1975, which totalled 188,265 cases over 29 years. Since 2012, the JBCS Registry has been combined with the NCD 5-year and 10-year prognostic data dating from 2004. In 2016, this registry covered 84% of the official annual breast cancer incidence in Japan. Nowadays, more than 90% of cases have been registered.



A QI subcommittee within the clinical practice guidelines committee developed eight QI items, such as Tamoxifen administration rate as postoperative endocrine therapy for premenopausal hormone receptor-positive stage I–III invasive breast cancer patients, based on clinical practice guidelines. These QI are not integrated on a hospital level yet.

In 2016, studies were done to measure the adherence rate of breast cancer QIs of 308 hospitals. One study used administrative claims data (17), and another used a retrospective record review of hospital data representing nearly half of all Japanese breast cancer patients (18). In the retrospective study, the quality data of 15,227 patients with breast cancer were analysed. Drug adherence had a low score (52.8%). A great variation was observed across facilities for HER-2 testing and for radiation therapy after breast-conserving surgery.

## Future perspectives

The JBCS Registry is summarized in conjunction with future perspectives including quality indicator analysis, guideline evaluation using prognostic outcomes, and development of a real-time personalized survival analysis tool using the NCD Breast Cancer Database.

## The Australian and New Zealand perspective

The Breast Quality Audit (BQA) is a bi-national repository of breast cancer data that captures approximately 80% of all breast cancers treated in both Australia and New Zealand. The purpose of the BQA is to standardize and centralize a breast cancer database of surgical activity in Australia and New Zealand; assess management trends in breast cancer, development of key performance indicators (KPIs), promote the uptake of evidence-based medicine, research, and to ensure quality of surgical practice and benchmarking across both countries.

## Quality monitoring process

The BQA was founded in 1998, originally an initiative of the Royal Australian College of Surgeons and the Section of Breast Surgery, now under the auspices of Breast Surgeons of Australia and New Zealand (BreastSurgANZ) since the Society's formation in 2010 (19). The key aim is for bi-nationwide quality monitoring of breast cancer care to improve cancer treatment practices and patient outcomes. It is the largest repository of breast cancer data in the southern hemisphere with over 350 participating surgeons with 263 participating hospitals (20). There were over 30,203 episodes entered into BQA during the period of 2020–2021 (21). In 2023, an updated BQA was launched with newly added KPIs with a total of 13 KPIs being assessed currently. Participation is required by all members of BreastSurgANZ and participants are encouraged to self-assess their clinical performances against KPIs through a user-friendly online interface.

Data is collected for all patients with early and locally advanced breast cancer with data being recorded through an account for each BreastSurgANZ member. Currently membership can be maintained with at least 10 breast cancer cases annually and this is being reviewed to be increased to at least 25 cases per annum. Currently, there is no standardized

credentialling of individual units and data is maintained by members. Surgeons are strongly encouraged to enter data for all their patients. All patients are informed of this audit process prior to having their data entered and work under an opt-out system. A complete data set includes patient demographics, cancer diagnosis, tumour pathology, surgical procedures, adjuvant and neoadjuvant therapies and patient refusal of any recommended treatment. Data is anonymized and gathered via a secure online interface platform by individual surgeons and institutions or uploaded in partnership with other national breast cancer stakeholders such as Cancer Australia (<https://www.canceraustralia.gov.au/>), Breast Cancer Foundation New Zealand (<https://www.breastcancerfoundation.org.nz/>), Clinical Oncology Society of Australia (<https://www.cosa.org.au/>), ANZ Breast Cancer Trials group (<https://www.breastcancertrials.org.au/>), Australasian Society of Breast Disease (<https://www.asbd.org.au/>) and Breast Cancer Network Australia (<https://www.bcna.org.au/>).

Data manager access was introduced in 2017 where a data manager account can access logged data with a signed consent from a participating surgeon. This was to support surgeons who are time poor and to allow maintenance of integrity of complete data. Data manager access allows review of incomplete cases and is able to tabulate total annual episodes for each surgeon. Data manager access does not allow access to an individual surgeon's performance against the KPIs which is only available to individual surgeons directly. Participants can self-assess against 13 KPIs with quality thresholds set by the BQA subcommittee (Table 7.1). These KPIs have been produced according to evidence-based guidelines for care of early breast cancer patients, as well as expert advice.

The data collected for the BQA is protected under federal law in both Australia and New Zealand as a declared quality assurance activity. The confidentiality of the information received is protected accordingly and high-level data security procedures are maintained. The BQA data request process allows participants and external researchers to request data or analyses from the audit. This can either be extraction of customized data of individual participants or of a hospital unit (with permissions from all participating surgeons of the unit). The data is available for quality assurance, planning, and research purposes. All requests for data are reviewed by the BQA subcommittee.

BQA data is also used by BreastSurgANZ for research into trends in the diagnosis and management of early breast cancer in Australia and New Zealand. Multiple successful collaborations with Cancer Australia, BreastScreen Aotearoa, Breast Cancer Network Australia, and the Australian Commission on Safety and Quality in Health Care have resulted in a number of publications which are available from the audit website (<https://www.bqa.org.au/>). Funding for the BQA comes from BreastSurgANZ membership.

## Future perspective

The BQA is constantly working towards developing the audit into the future by prioritizing coverage and data quality, and enhancing the audit's relevance and benefits. Key perspectives include incorporating PROMs assessing how health services and interventions have affected their quality of life, daily functioning, symptom severity, and general health. In addition, overall breast cancer outcomes and associated registry trials will be closely observed. Technical aspects such as oncoplastic surgical strategies, and their benefits and cost are being explored.

**Table 7.1** Revised 13 KPIs by BreastSurgANZ

| Key performance indicators (KPIs) |                                                                                                                                                                                                      |
|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1                                 | Percentage of invasive cases undergoing breast-conserving surgery referred for radiotherapy (excluding patients $\geq 70$ years old with ER+/PR+, HER2- cancer, having $<20$ mm primary tumour size) |
| 2                                 | Percentage of oestrogen-positive invasive cases referred for (adjuvant or neoadjuvant) hormonal therapy treatment                                                                                    |
| 3                                 | Percentage of invasive cases undergoing axillary surgery                                                                                                                                             |
| 4                                 | Percentage of axillary clearance cases with zero positive nodes entered (excluding cases with any neoadjuvant therapies)                                                                             |
| 5                                 | Percentage of high-risk invasive cases undergoing mastectomy referred for radiotherapy (invasive tumours $\geq 50$ mm or $\geq 4$ positive lymph nodes)                                              |
| 6                                 | Percentage of high-risk cases referred for chemotherapy                                                                                                                                              |
| 7                                 | Percentage of cases with involvement of a breast care nurse in management of the patient                                                                                                             |
| 8                                 | Percentage cases with discussion at a multidisciplinary meeting                                                                                                                                      |
| 9                                 | Percentage of triple negative or HER2+ cases undergoing neoadjuvant chemotherapy, for patients $<70$ years old and tumour size $\geq 20$ mm                                                          |
| 10                                | Percentage of DCIS cases undergoing mastectomy receiving immediate reconstruction                                                                                                                    |
| 11                                | Percentage of invasive cases undergoing mastectomy receiving immediate reconstruction                                                                                                                |
| 12                                | Percentage of cases with breast conservation for invasive T1 ( $<20$ mm)                                                                                                                             |
| 13                                | Percentage of cases proceeding to surgery within 45 days of histological diagnosis, e.g. date of core biopsy (excluding cases receiving neoadjuvant therapy)                                         |

Source: data from Kollias J. The history of BreastSurgANZ. Breast Surgeons of Australia and New Zealand, 2022.

## The Turkish perspective

### Introduction

The Turkish Federation of Breast Diseases Societies (TFBDS) was founded in 2001. It is a nationwide multidisciplinary non-profit organization with healthcare professionals involved in the diagnosis and treatment of breast cancer. The TFBDS collaborate with the Cancer Control Department of Ministry of Health. The aims of the TFBDS are to improve quality in breast cancer care with different initiatives, including the registration of breast cancer, distribution, and adaptation of national guidelines, standardization of measurements, development of QIs, audits, and implementation of PROMs.

### Quality monitoring

The Department of Health Efficiency, Quality, and Accreditation, established by the Ministry of Health, tries to carry out quality controls in hospitals in the country (12). A number of standards have been prepared for diagnosis, screening, and treatment of breast cancer, but

a study on its implementation and results has not yet been. The breast cancer screening, diagnosis, treatment and follow-up protocol is available on the website of the Ministry of Health (<https://shgm.saglik.gov.tr/TR-67115/meme-kanseri-korunma-tarama-tani-tedavi-ve-izlem-klinik-rehberi-yayinlanmistir.html>). The Breast Cancer Registry Programme, and detailed analyses of patients have been published as books and articles (13). The European Journal of Breast Health is the official publication of TFBDS, the Senologic International Society (SIS) and the National Consortium of Breast Centers (NCBC) are the official supporters of the journal. Furthermore, TFBDS conducts inspections and receives information about the work of breast health centres where it has member societies.

The results of the Bahçeşehir Community-Based Organized Mammographic Screening Programme (2009–2019) conducted by the Breast Health Association, a non-profit non-governmental organization affiliated to this federation, reduced the age of starting mammographic screening in Turkey from 50 to 40, showing that mammographic screening is feasible and cost-effective in Turkey (14). In another study, it was found that there was a delay of approximately 14 weeks in the treatment of breast cancer in Turkey, one-third of which was related to patients and two-thirds to the health system (15).

As a result of our Breast Cancer and Mammography Knowledge and Awareness study, which was carried out with a grant provided by The Breast Health Global Initiative in 2009, the rate of mammography in women of screening age (40–69) was found to be 45%, and >50 years of age, regular gynaecological examination, good education level and the presence of breast cancer in the family were found to be important factors (16).

With grants from The United Nations Institute for Training and Research, UNITAR, PROMs are being conducted in 2023 regarding delays in breast cancer screening and treatment in two studies. The Department of Cancer Control of the Ministry of Health, TFBDS, and other scientists are involved in this study.

## Future perspective

In order to see and align with the Turkish Ministry of Health's 'Patient-Related Outcomes Reports on Quality and Patient for Breast Cancer', there will be a greater focus on outcome indicators, quality of life, and shared decision-making. The results of ongoing studies on PROMs and their sharing with the system will have very important consequences for patients.

## Conclusion

There is a wide range of national quality programmes and quality monitoring aimed at improving the quality of care for breast cancer patients. Different forms of quality management include audits, certification, accreditation, and the focus of these programmes differ between continents and even within countries.

In Latin America, most countries do not have a national cancer control programme. This significantly contributes to disparities in access to care. Prioritizing the development and implementation of comprehensive national cancer control programmes is crucial to address disparities and improve cancer outcomes globally. Argentina and Brazil are two countries in Latin America that do have such programmes. However, the disparities described earlier

are also evident within these countries. For example, Brazil will focus in the coming years on telemedicine and navigation programmes for patients in small cities and rural areas, while in more developed areas, the focus will be on shortening lead times to diagnosis and treatment and improving screening.

In Egypt, rural areas exist as well. Mobile health units have screened 81,273 women in underserved regions over the past five years. Quality initiatives will extend further into these areas in the coming years. Notably, Egypt emphasizes patient-centred care and education for both patients and caregivers. Additionally, a 'patient navigation system' streamlines care processes and offers emotional support, leading to enhanced patient satisfaction and outcomes.

In Oceania and Western Europe, there has been a great focus on quality improvement. Most countries are working multidisciplinary on continuous data gathering, QIs, and benchmarking hospitals to initiate conversations between healthcare professionals on how to improve (best practices). It differs between countries whether all breast cancer patients participate in a registry or only a selection (e.g. only non-metastatic breast cancer registry). Furthermore, it varies if the outcomes of QIs are publicly available. For example, in the Netherlands, an annual assessment selects valid and reliable indicators, enhancing transparency, as new indicators or those not proven as valid remain non-transparent or are even deleted from the set. Valid transparent outcomes of QIs provide valuable information to patients. In Eastern Europe, quality assurance is shared among various healthcare organizations, with no specific national quality assurance system for breast cancer. As multiple parties are involved and there is no harmonization or standardization, there is still variation across the region. This highlights the importance of standardization and harmonization of data gathering and reporting.

In Japan, the national quality programme also places significant focus on promoting study, research, education, and training for healthcare professionals. Their data includes more than 90% of all patients, and QIs are developed. The next step for Japan is to analyse the QIs at the hospital level to benchmark hospitals.

Most countries included in this chapter do gather data on a regular basis, but there are differences in the level at which this data is collected (country level, hospital level, or surgeon level). As far as we know, the assessment of outcomes at the surgeon level is unique to Australia and New Zealand, with direct access restricted solely to individual surgeons. Automatic data extraction is only implemented in some of the UK programmes, whereas in all other countries, data is still entered manually into a system by medical specialists or data managers. In Sweden, there is a great focus on data automation, and they are already putting efforts into achieving this. In contrast, in Botswana, data is gathered with standardized paper forms that are sent on a regular basis to the Ministry of Health. Automatic data extraction can improve data quality, reduce registration burden, and facilitate timely performance feedback based on recent data.

There is an increased focus on outcome-oriented and patient-centred care and a crucial aspect for the further development of quality registries is patient participation and the inclusion of PROMs. This focus is shared by advanced registries in countries such as Australia and New Zealand, Netherlands, Sweden, UK, and Turkey. These PROM outcomes can be connected to outcome indicators in the future. Nevertheless, it will be a big challenge to collect this data adequately, considering it comes from patients and not directly from the medical record. Furthermore, it can be an opportunity to extend benchmarking and best practice learning beyond national boundaries, facilitating a global approach. Adherence to more widespread or continental initiatives, such as the QIs of the European Commission Initiative

on Breast Cancer (ECIBC), can facilitate this process. An important note is that the significance of QIs can vary by country, and it is essential to critically assess which comparisons are valid (22).

## Key messages

- Prioritizing the development and implementation of comprehensive national cancer quality programmes is crucial to address disparities and improve cancer outcomes globally.
- Programmes should encourage regular multidisciplinary quality monitoring and improvement initiatives within and between hospitals.
- Harmonization and standardization of data items, quality indicator definitions, and algorithms are necessary to compare hospitals and countries.
- For further development of existing quality registries, patient perspectives are crucial, and the focus will be on outcome indicators and PROMS data, preferably through automated data gathering.
- It can be an opportunity to extend benchmarking and best practice learning beyond national boundaries, facilitating a global approach.

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# 8

## Quality of life measurements

### Improving patient experience

*Francois P. Duhoux, Razvan Andrei Popescu, and Gabriëlle Speijer*

#### Introduction

Symptoms and the composite measure termed ‘quality of life’ are inherently subjective. The most accurate description originates from the patients themselves. These are termed as patient-reported outcomes (PROs). The US Food and Drug Administration (FDA) has defined PROs as ‘a report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else’. Recently, PROs and satisfaction have been given more weight in the assessment of treatment quality (Figure 8.1) (1).

Not observable or measurable symptoms are frequently underestimated by healthcare providers (HCPs) but can adversely impact well-being. Many publications have shown a lack of concordance between symptoms rated by HCPs and PRO measures (PROMS). In a large trial in early breast cancer (BC), many patients rated tamoxifen-related symptoms like hot flushes, weight gain, night sweats, sleeping difficulties, and loss of libido as severe, but there was no more than chance agreement in HCPs rating (2). Lesley Fallowfield argued early that ‘PROs should be mandatory in and outside clinical trials to guide management of patients with metastatic BC’ since ‘it is an incurable disease and thus improving the quality of life (QoL), not merely the length of life, is an important parameter of benefit’ (3).

#### European perspective

A European Society of Medical Oncology (ESMO) Clinical Practice Guideline on PROMs contains extensive discussion of benefits of PROs use, including compilation of the clinical studies data and recommendation for routine use of electronic PROs. It is one of the most valuable freely available resources today (4).

EUSOMA has recently included ePRO use for early BC as a quality of care criterion for BC Centres (5). Assessment of ePROs has been shown to help with appropriate management, even more in metastatic patients (6). Meticulous eliciting of symptoms and assessment of needs is worthless unless these are acknowledged and addressed by adequate interventions. Ideally, PROMs should lead to adaptations of care, goals of treatment, and support for family and patients in accordance with their values and priorities (7).



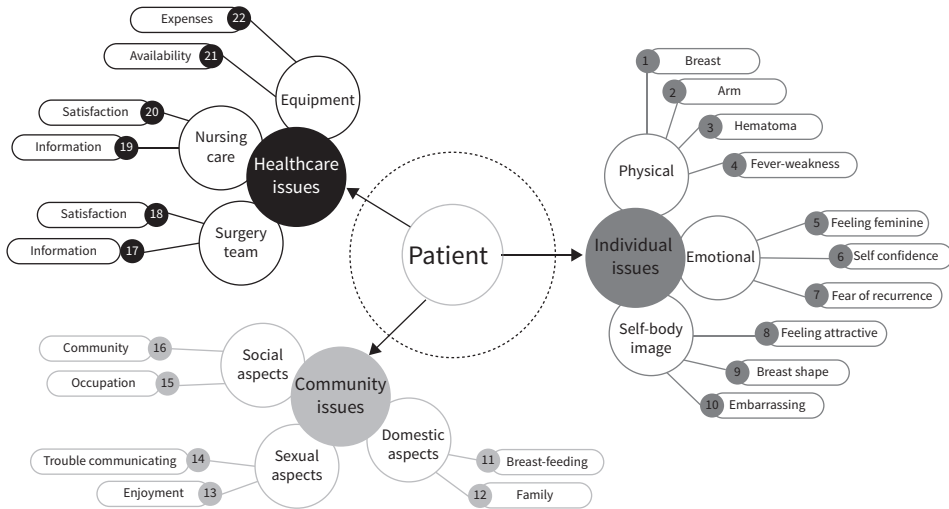


**Figure 8.1** Domains of PROMs after breast cancer treatment.

Adapted from Marzban S, Shokravi S, Abaei S et al. Patient-Reported Outcome Measures of Breast Cancer Surgery: Evidence Review and Tool Adaptation. *Cureus* 2022;14(8):e27800 under a Creative Commons CC-BY-4.0 licence (<https://creativecommons.org/licenses/by/4.0/deed.en>)

## International Consortium on Health Outcome Measures (ICHOM)

The International Consortium on Health Outcome Measures (ICHOM) was established to develop sets of patient-centred outcome measures for the most frequent diseases. These sets focus on patient-centred results and provide an internationally agreed-upon method for measuring each of these outcomes. The aim of these sets is to compare performance globally, allow clinicians to learn from each other, and rapidly improve patient care.

The sets include initial conditions and risk factors to enable meaningful case-mix adjustment globally, ensuring that comparisons of outcomes will take into account the differences in patient populations across not just providers, but also countries and regions. The sets are freely accessible to healthcare institutions worldwide. They place a particular focus on healthcare delivery (8).

The breast cancer standard set (9) was developed by 26 healthcare providers and patient advocates. It encompasses survival, cancer control, and disutility of care outcomes (e.g. acute treatment complications) to be collected through administrative data and/or clinical records. Selected case-mix factors are to be collected at baseline. It relies on a combination of multiple PROM tools to capture the long-term degree of health outcomes. The following outcomes are thus captured in all patients: overall well-being, physical, emotional, cognitive, social, and sexual functioning, ability to work, anxiety, depression, insomnia, financial impact, pain, fatigue, and body image. In addition, patients treated with surgery and/or radiotherapy are asked to complete questionnaires about satisfaction with breast(s), arm symptoms, and breast symptoms, whereas patients receiving systemic therapy are interrogated on vasomotor symptoms, peripheral neuropathy, vaginal symptoms, and arthralgia.

The ICHOM breast cancer standard set can be used for both the early and the metastatic setting. Some outcomes that are traditionally gathered in the context of breast cancer have been removed, such as progression-free survival, because these were judged non-essential for patients.

Implementing the standard set is both complex and time-consuming. It requires a dedicated team and good collaboration with the hospital IT team. It is, of course, essential to have a database in place, but the parameters used for exporting the data must be adapted to ICHOM's requirements. The patient's individual treatment plan must be considered, because patients receiving different treatment modalities will complete different questionnaires. It is also essential to have the ability to collect these PROMs in a timely manner. The pen-and-paper approach is probably easier to implement initially, but it also requires more staff to encode the answers from the questionnaires into a database. On the other hand, electronic completion of the questionnaires does not require any additional handling of the data by the site staff, but it has been shown that patients prefer the paper-based versions (10).

The breast cancer set has been implemented in several large, mostly academic institutions. Discussions are ongoing to launch a benchmarking platform, which would allow cross-institutional comparisons, as has already been done for birth care in the Netherlands (11).

In countries delivering care through digital systems like electronic health records (EHRs), ICHOM, and PROMs can save time and help physicians deliver personalized care, as it gives a view of the entire health situation of patients.

## Monitoring at home

Basch et al. (12) showed in 2017 that systematic monitoring of patients' symptoms using electronic PROs (ePROs) at home helped to detect problems earlier in patients receiving palliative chemotherapy. When followed by appropriate interventions, this led to improved QoL, fewer hospitalizations or emergency room visits, and more time on anticancer therapy, with increased survival. The main benefit of ePROs, other than capturing the 'patient experience', is thus conferred by targeted rapid intervention following a newly reported problem. As we argued recently, 'given the wide availability of smartphones, even in developing countries in which primary care structures are often weak and access to specialist care is constrained, such strategies, often managed by experienced nurses, may significantly improve outcomes' (13).

## Future perspective

Guided by our professional value—the Hippocratic oath—to provide the best healthcare under confidentiality, we are called upon to leverage information communication technology (ICT) so that it supports a transition from episodic to continuous interactions, while maintaining this trust relation (14). Consultations will stay the mainstay of our work, but getting an overview of patients' health situation, balancing mutual expectations and creating an unbiased space to be open with our patients requires us to ensure that when we follow the patient through their care pathway, every interaction is recorded and made securely available to learn from.

It doesn't matter where a patient lives to implement PROMs, as symptoms of disease are the same. In time, studies will be needed to evaluate understanding and optimal descriptors of symptoms in different cultures—wording of PRO-CTCAEs, e.g. may need to be adapted. Standardization of these symptoms through PROMs supports global knowledge development. It's about measuring what matters to achieve high-quality care (15).

This can help countries without legacy technology, like Africa, to implement PROMs much faster and with less complexity based on mobile technology and the new process that places the patient and health professional at the centre.

AI solutions will help us reduce the clinical burden and will accelerate the adoption of ICHOM into clinical practice because it will replace legacy systems (15). The legacy systems were designed decades ago to support the clinical administration process. The research legacy systems were developed for population islands with optimization for cost and efficiency. Two legacy worlds. What we need is a holistic clinical research innovation process centred around the patient and health professional, that continuously evolves as part of a population-based ecosystem. One world with a multitude of digital spaces connected through trusted health client-professional relations.

Next to PROMs, PREMs (patient-reported experience measures) measure healthcare providers' services and the satisfaction with the service received from the patients' viewpoint. The service provider (e.g. hospital) is usually the subject. PREMs are usually anonymous due to the potential sensitivity of feedback (16). The integration of patient-reported data into the EHR will help in more efficient administration of breast cancer care (17).

## Key messages

- PROMs are direct reports from patients on their health, offering an unfiltered view of their QoL, essential for personalized care.
- The International Consortium on Health Outcome Measures (ICHOM) has developed patient-centred outcome measures to standardize and improve patient care globally, with specific sets like the breast cancer standard set, which considers a wide range of patient outcomes.
- The use of ePROs for at-home symptom tracking has led to significant improvements in patient outcomes, including better survival rates.
- The future of healthcare lies in leveraging ICT to maintain continuous patient interaction, utilizing AI to reduce clinical burden, and adopting PROMs globally to provide high-quality, patient-centred care.

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## Educational and training harmonization in breast cancer

*Lynda Wyld, Sue Down, Giuseppe Catanuto, Alexandru Eniu, Danny Burke, and Christos Markopoulos*

### Introduction

Cross-disciplinary training and education in modern breast cancer treatment are critical to the delivery of optimal care. Breast cancer treatment has changed beyond all recognition in the past three decades with the advent of oncoplastic surgery, highly sensitive imaging (tomosynthesis, digital mammography, MRI, PET-CT), complex surgical de-escalation protocols (breast conservation, management of the axilla), neo-adjuvant, adjuvant, and post-neo-adjuvant systemic therapies, hereditary genetic mutation testing, and complex radiotherapy protocols. These treatment advances, coupled with earlier diagnosis through screening, have not only improved five-year survival rates from 50% fifty years ago to over 80% today, but have also improved the quality of life of long-term survivors.

The development of breast surgery has been rapid. It has gone from being one of the least popular subspecialties of general surgery in the 1990s, when surgery was largely mastectomy, lumpectomy, and axillary clearance, to a popular, vibrant, and rapidly progressive evidence-based discipline. In the UK 25 years ago, general surgical posts focused on breast surgery struggled to recruit, with the lowest ratio of candidates to jobs (1). During the 1990s, there were significant technical developments in reconstructive techniques available, such as implant and ADM reconstruction, LD flaps, TRAM flaps (now largely replaced by the DIEP flap), and various oncoplastic conservation techniques. However, the majority of women did not benefit from these advances, as the majority of 'breast surgeons' were general surgeons with limited knowledge or skills in these techniques. Hub and spoke arrangements, often informal and poorly developed, were the norm, with patients wanting these techniques referred to a regional Plastics Unit. The majority of women (53%) were not counselled about these extended options (2). At the turn of the millennium in the UK, a new initiative was launched whereby up to 10 hybrid, one-year plastic and general surgery training posts were funded nationally. The aim was to train up the next generation of breast surgeons with oncoplastic skills such that over the next few decades the necessary skill set would be present in every breast unit (3). The programme has been hugely successful, making oncoplastic techniques much more widely available across the UK and seeing rates of reconstruction rise (4). Similar initiatives were launched elsewhere, with advanced fellowships in the USA and Australia and New Zealand. However, many countries still lack such training resources even today.

There are therefore still inequalities due to lack of proper integration of breast surgery and plastic surgery with patients often not offered the full range of techniques (5). Some now advocate for breast surgery to become a specialty in its own right (6), no longer just a subspecialty of general or gynaecology surgery, to facilitate standardized high-quality training. There are potential problems with this proposal which may limit its adoption: lack of flexibility once training has started, workforce capacity issues during transition, and potential issues in moving between training jurisdictions where training may no longer be recognized. There is still a lot of development necessary before this can happen at both national and international levels.

## Optimal breast surgery training

What constitutes optimal training in breast surgery? The complex nature of modern breast cancer management mandates that the training be multidisciplinary (7, 8), incorporating elements of pathology, radiology, psychology, medical, and radiation oncology as well as both general and plastic surgery. An international curriculum has been proposed for breast surgery training which incorporates all of these elements, specifying both practical skills and theoretical knowledge (9). Delivery of such a complex curriculum within general surgery or gynaecology generalist training is challenging, and it is likely that a specialist fellowship during, or on completion of generalist training will be required to deliver the necessary knowledge and skills.

Key elements of this training are summarized in Figure 9.1 and Table 9.1.

While the above may represent the ideal, the reality in most of the world is very far from this and many women do not get the care they deserve for their breast cancer. Survival rates for breast cancer are widely variable between countries (10). Mortality rates are lowest in countries with a high human development index (HDI) such as Australia/New Zealand, Western Europe and the USA, and highest in sub-Saharan Africa, largely due to late diagnosis and poor health infrastructure (10). However, there is also significant variation within countries and between European member states. Some of this variation is economic, with variations in access to screening and the latest systemic therapies (such as HER2 targeting agents, CDK4/6 inhibitors, PARP inhibitors, and immunotherapies) and also limited access to locoregional advances such as modern radiotherapy (and risk-adapted strategies such as

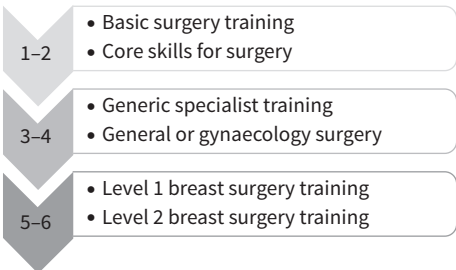


**Figure 9.1** Proposal for integration of breast surgery training into specialist general or gynaecology training from years 1–6.

**Table 9.1** Table showing elements of the knowledge and practical skills that are essential in the training of a breast surgeon within general, gynaecology, or plastic surgery training pathways

| Training domain            | Basic level 1                                                                                                                                                  | Advanced level 2                                                                                                                                                                                                                                                                                |
|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Evidence/<br>certification | Years 1–4                                                                                                                                                      | Years 5–6                                                                                                                                                                                                                                                                                       |
|                            | Outpatient skills and experience, including management of benign disease and basic cancer diagnosis and management. Certified by case-based discussions        | Outpatient skills and experience including advanced management of benign disease and atypias, advanced cancer management, familial risk management, reconstruction planning. Certified by case-based discussions                                                                                |
|                            | Logbook meeting minimum numbers of index procedures performed personally (basic and intermediate level). Procedure-based assessments for qualitative standards | Logbook meeting minimum numbers of index procedures performed personally (advanced level oncoplastics and oncology). Procedure-based assessments for qualitative standards                                                                                                                      |
|                            | Evidence of CPD such as attending basic and intermediate level courses and congresses                                                                          | Certificate of completion of training<br>Evidence of CPD such as attending advanced level courses and congresses                                                                                                                                                                                |
|                            | Communication skills training: Basic certification<br>Evidence of service improvement or audit activities                                                      | Communication skills training: advanced certification<br>Evidence of research engagement (presenting or publishing breast-specific research)<br>Optional but desired: Specialist examination/higher degree to certify advanced knowledge                                                        |
| Practical skills           | Practical office procedures such as core biopsy, punch biopsy, fine needle biopsy, and seroma drainage                                                         | Implant expander inflation. Surgical mark-up for oncoplastic surgery                                                                                                                                                                                                                            |
|                            | Communication skills                                                                                                                                           | Higher-level communication skills, including breaking bad news and explaining complex management strategies, including reconstruction planning and counselling. Genetic counselling                                                                                                             |
|                            | Simple mastectomy, SLNB, axillary clearance, wide excision, localized wide excision, total duct excision                                                       | Skin and nipple sparing mastectomy, therapeutic mammoplasty, targeted axillary dissection, completion axillary clearance, lipomodelling, implant insertion and revision, reconstruction (immediate, delayed, and revision) and nipple reconstruction<br>(Free flaps only if plastic background) |

*(continued)*

**Table 9.1** Continued

| Training domain | Basic level 1                                                                                         | Advanced level 2                                                                                                                                                      |
|-----------------|-------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Knowledge       | Basic physiology and pharmacology of the breast                                                       | Advanced physiology including endocrine effects, pregnancy, development                                                                                               |
|                 | Pathology of breast diseases including breast cancer stage, biology, and prognosis                    | Pathology interpretation, nodal staging, margins, cancer subtypes, and biomarkers                                                                                     |
|                 | Genes causing breast cancer                                                                           | Genetics of breast cancer and how to manage gene carriers with and without cancer                                                                                     |
|                 | Radiology for screening, diagnosis, and staging. Mammograms, US, and CT scans                         | Radiology for treatment planning including Mmg, US, MRI, CT, tomosynthesis, PET scans                                                                                 |
|                 | Microbiology                                                                                          | Microbiology                                                                                                                                                          |
|                 | Screening at population level                                                                         | Screening high risk women and different age groups. Overdiagnosis and screening harms                                                                                 |
|                 | Service evaluation                                                                                    | Research methods including trial design, trial critique, and basic statistics                                                                                         |
|                 | DCIS and atypia: diagnosis and basic management                                                       | DCIS and atypias: advanced knowledge of diagnosis and management                                                                                                      |
|                 | Epidemiology of breast cancer: basics of prognosis and risk factors                                   | Advanced epidemiology of breast cancer including prognosis, risk factors, use of online prognostic tools. Understands research evidence                               |
|                 | Breast cancer management: surgical options for intermediate level breast surgery to breast and axilla | Advanced level management of breast cancer including mastectomy types and indications, conservation types, and indications, axillary options including SLNB, ANC, TAD |
|                 | Basics of reconstruction                                                                              | Advanced level reconstruction, including implants, free, pedicled, and perforator flaps. Indications and adverse events                                               |
|                 | Basic complications of breast cancer treatments                                                       | Advanced knowledge about adverse events, including late effects/long-term side effects, and how to manage them                                                        |
|                 | Basics of benign breast disease                                                                       | Advanced-level knowledge about the diagnosis and management of benign breast disease, including implant issues                                                        |
|                 | Diagnosis of locoregional and systemic recurrence                                                     | Management of locoregional and systemic recurrence                                                                                                                    |
|                 | Basic knowledge of systemic adjuvant and neo-adjuvant therapies                                       | Advanced knowledge of systemic adjuvant and neo-adjuvant therapies, including endocrine, chemotherapy, bisphosphonates, and biologicals                               |



Table 9.1 Continued

| Training domain      | Basic level 1                                                                                 | Advanced level 2                                                                                                                                              |
|----------------------|-----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                      | Basic knowledge about radiotherapy use in breast cancer                                       | Advanced knowledge about radiotherapy use in breast cancer, including indications, regimes, whole and partial breast, post-mastectomy, and nodal radiotherapy |
| Training environment | Smaller breast units with a specialist MDT, offering basic and intermediate level breast care | Large breast unit with a specialist MDT, ideally quality assured and offering a full range of oncology and oncoplastic treatments                             |

partial breast radiotherapy) and more aesthetically acceptable oncoplastic and reconstructive surgery options.

However, training and education limitations are also restricting access to optimal care with variations in treatment seen within the same country. For example, rates of reconstruction, access to chemotherapy and biological therapies vary within the UK, for example (4, 11).

What strategies are currently in place or could be implemented to improve this situation?

## Generic training plus optional specialist fellowships

In the majority of countries training is generic and only the minimum necessary breast content is included, which is not adequate for modern oncoplastic breast training without some form of supplemental training. For many trainees, specialist fellowships may be optionally added at the end of training, often for one or two years. This is quite common, and many such schemes exist but are usually optional and therefore there is no guarantee for the patient that they will see an adequately trained specialist. This model has been adopted in the USA, Australia and New Zealand, and the UK for example, where formal specialist fellowships with national level quality assurance exist.

## USA and Canada

Surgical training in the USA is tightly regulated with formal residency programmes in general surgery or plastic surgery, professional exam certification at the end of residency programmes, and mandatory recertification at intervals. Specialist breast surgery training fellowships, approved by the American Society of Breast Surgeons, American Society of Breast Diseases, and the US Society of Surgical Oncology are offered by many large US centres and Universities. These follow centrally dictated curricula, have formal quality assurance, and have been in existence since 2004. These fellowships are usually of 12 months duration and include training in the management of breast diseases and cancer, participation in the multidisciplinary aspects of patient care (including radiotherapy, systemic therapy,

imaging, plastic surgery, and pathology), and engagement of fellows in clinical research activities (12). The length of training in the USA, from the start of medical school to completion of training, is also one of the longest, and specialist fellowships are common but not mandatory and many women are still managed by non-specialists. Feedback on the fellowships is excellent (13).

Canada also offers a small number of high-quality specialized fellowships (14).

## Australia and New Zealand

In 2010, a new system was launched based around completion of generic general surgery training with optional fellowship training offered by BreastSurgANZ (15). After a centrally administered application process, fellows enter a two-year part-time programme with placement in one of 30 centres of excellence, for hands on training, alongside a dedicated educational programme, which may culminate in an optional Graduate Diploma in Breast Surgery from the University of Sydney.

## United Kingdom

The UK also has a similar system to the USA and ANZ, with training based around generic general surgery training with an optional one-year fellowship after completion of training. These are centrally administered by the UK Joint Committee on Surgical Training (JCST) Training Interface Group (TIG) which offers a minimum of 10 annual, centrally quality assured, hybrid (general and plastic surgery) training posts across 18 tertiary breast units across the UK (16). There is also an education programme with lectures and workshop days as well as a formal online system to assure operative and management competencies (ISCP). This system was introduced in 2002 and has therefore now trained a pool of over 200 oncoplastic surgeons. These have cross pollinated across UK breast units, upskilling the workforce, and passing on their knowledge to their own trainees. The Royal College of Surgeons of England also accredits several Senior Clinical Fellowship posts in both Advanced and Oncoplastic Breast Surgery throughout the UK, which are quality assured programmes providing advanced training over a period of 12 months (17). There are also a range of less formal independent breast fellowships offered by large teaching centres.

All fellowships are still optional and not undertaken by every breast trainee, leaving a skills gap for some surgeons. To address this and to recognize the increasing divergence of the requisite skill set for breast surgery from that of general surgery, the UK introduced stratified training for all breast surgeons a few years ago. In this new model, trainees with a defined interest in breast surgery at the start of their 6 years of specialist surgical training pass through three phases. Phase 1, specialist general training with two years of generic general surgery with emergency on calls. Phase 2, two years of intermediate level breast training plus some on calls (reduced intensity to prioritize elective breast surgery skill acquisition). Phase 3, two years of full-time elective breast surgery in a high-level training centre. At the end of this period candidates must pass the Fellowship of the Royal College of Surgeons (FRCS) exam and may specify a special interest in breast surgery, wherein a tailored exam with 70% general surgery and 30% breast surgery is taken. This is still not ideal as the final exam still

includes a high proportion of generic general surgery, for which these candidates may now be at a disadvantage, and the level of assessment of specialist breast knowledge is limited.

The UK Association of Breast Surgery has made representation to the regulatory authorities in 2023 to consider breast surgery as a specialism in its own right, but so far have not been successful. The regulator wants to evaluate the impact of the new stratified training system for a few years before making further changes.

## Europe

Training in Europe has some degree of harmonization. Since 1996, European Law mandates that all European member states (plus European Economic Area (EEA) states) mutually recognize each other's primary and specialist medical qualifications. Therefore, a surgeon who has completed training in one member state should be able to apply for a consultant post in any other member state (subject to ability to speak the host language). In most states there is a regulatory body (competent authority) that oversees the process of confirming eligibility (based on certification and experience) and linguistic competency. In theory, at least, there should be parity of skills, knowledge, and practice across Europe. However, national guidelines vary widely across Europe, and national funding models have different priorities and thresholds. Again as breast surgery is not recognized as a specialty in its own right, the training in breast surgery is limited, largely unregulated, and highly variable. There is also a complicating factor that in many European countries breast surgery sits within gynaecology rather than general surgery. There are also variations in what constitutes breast surgery. Some European countries include breast reconstruction as integral to breast surgery training (the UK or Germany, for example), whereas in others, reconstructive surgery is part of plastic surgery training with the breast surgeon attending only to the oncological resection before handing over to a plastic surgeon to complete an oncoplastic procedure. Many trainees seek formal fellowships during training or after completion of training (18) to ensure that they have the necessary, non-mandatory, competencies. The duration and rigour of surgical training is regulated at national level to varying degrees. Some countries have very detailed systems with curricula, multiple objective assessments, logbooks, and annual progress reviews with examinations (the UK Joint Committee for Higher Specialist Training and Royal Colleges, for example). Other countries have very informal arrangements with simple, local peer review.

There have been efforts to develop a training curriculum for breast surgery (9) to support the Union of European Medical Specialists (UEMS) Breast Examination, but this has no national or pan-European mandate, and taking the exam is voluntary. A recent survey of the level of training of European breast surgeons found a high level of variation in training systems (Table 9.2, based on but updated from (19)). Of the 671 surgeons surveyed, 71% were predominantly practising breast surgery at least 50% of the time and the majority had done some form of additional training, either a formal fellowship (20%), dedicated time in a specialist breast unit (33%) or a higher degree or diploma (24%). However 8% had not done any addition training (19).

For medical and radiation oncologists, training is usually generic and non-disease site-specific, and covers a wide range of disease sites. The European Society for Therapeutic Radiotherapy and Oncology (ESTRO) has published a curriculum for radiotherapy training

**Table 9.2** Summary of specialist training and certification in breast surgery in Europe

| Country     | Specialty                                        | Postgraduate breast training                                                     | Postgraduate breast examination/certification                                    |
|-------------|--------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Spain       | General surgery or gynaecology                   | No—generic                                                                       | No                                                                               |
| UK          | General surgery—rarely plastic surgery           | Yes, stratified training with increasing focus on breast training with seniority | Yes. FRCS exam may be tailored to focus on breast surgery at the end of training |
| Italy       | General surgery or gynaecology                   | No—generic                                                                       | No                                                                               |
| Sweden      | General surgery, plastic surgery, or gynaecology | Yes                                                                              | Yes, UEMS breast exam advised                                                    |
| Denmark     | General surgery or plastic surgery               | Yes                                                                              | UEMS breast exam optional                                                        |
| France      | General surgery, plastic surgery, or gynaecology | Yes                                                                              | No                                                                               |
| Germany     | Gynaecology                                      | Yes                                                                              | Yes (AWO-Gyn) practical examination                                              |
| Switzerland | General surgery, plastic surgery, or gynaecology | Yes                                                                              | Optional senology diploma from Swiss Society of Senology                         |
| Netherlands | General surgery or plastic surgery               | No                                                                               | No                                                                               |
| Hungary     | General surgery, plastic surgery, or gynaecology | No                                                                               | No                                                                               |
| Greece      | General surgery or gynaecology                   | Yes                                                                              | No                                                                               |
| Turkey      | General surgery                                  | Yes                                                                              | No                                                                               |

which has led to improved standardization of training in Europe for radiation oncologists. This curriculum now includes quite detailed objective assessments and logbook review to enhance reliability and reproducibility (20). Similarly, the European Society of Medical Oncology (ESMO) developed a European training curriculum in collaboration with the American Society for Clinical Oncology (ASCO) (21). None of these curricula, however, are specific for breast cancer.

As can be seen from this, heterogeneity of training is an ongoing issue across the European Union (EU), and harmonization of training would help to improve and standardize outcomes. To address this issue the UEMS was established in 1958 and now comprises 50 specialist sections, each representing an independently recognized discipline. Breast surgery is a specialist division within the section of surgery, and breast care is formally represented as a pan-European multidisciplinary joint committee (MJC) at the UEMS in recognition of the highly multidisciplinary nature of its management. In addition, there are sections for medical and radiation oncology and for plastic and reconstructive surgery, which include aspects of breast care.

Many of the sections have examination boards and run pan-European exams, of which the European Breast Exam is one. The exam is discussed in more detail next.

## India

Breast surgery in India has been developing rapidly in the past decade with very active Breast Societies and huge growth in high-quality care, including oncoplastic surgery. High-volume centres often offer specialist two-year fellowships but these are not mandatory for training in breast surgery. The majority of breast surgeons are surgical oncologists and also offer a wide range of other types of disease sites, although a growing number now focus on breast surgery. Completion of training is usually after completion of a Master of Surgery degree but there is no centralized standard or administration for this. BreastGlobal has been established by a group of like-minded individuals in India who believe that access to specialist breast training should be universal, regardless of geographical location. Their online portal has been created to bridge the gaps in knowledge by providing a single platform where experts, trainees, and industry can have access to a plethora of global learning and training opportunities. A lot of educative webinars are available.

## Pakistan

Again interest in breast surgery is growing and there are now two-year College of Physician and Surgeons of Pakistan recognized fellowships offered by a number of larger institutions, although specialist training in breast surgery is not mandatory (22). There is also interest in the UEMS breast exam with a steady flow of candidates each year.

## Egypt and the Middle East

Again, training is generic, in either general surgery or surgical oncology, but there is a high level of interest in specialist training with a lot of candidates seeking breast fellowships abroad or in high-volume centres. Again, the UEMS exam is popular.

## International fellowship opportunities

Many organizations have developed fellowships to help train breast surgeons globally. Some are organized by National Breast Societies. In the UK, these are offered by the UK Association of Breast Surgery (ABS), either for UK-based or International graduates and also by the Royal College of Surgeons Fellowship programme and the Training Interface Group (TIG) programme. In Australia, BreastSurgANZ also offers training fellowships. The USA Society for Surgical Oncology (SSO) has a well-established fellowship scheme, which is quality assured. In Europe, BRESO (Breast Surgical Oncology Certification Scheme) was launched in 2019, which aimed to provide European Fellowships and certify breast surgery expertise at a standardized level (23). There are also many stand-alone Institutional Fellowships. There

are limitations to these schemes in that international graduates may need to obtain national certification before they can practice clinically, which may be a barrier if their previous medical degree or training is not recognized. However, observerships are also possible. There are also potential issues for graduates from lower-income countries visiting wealthier countries where the health systems are very different. The relevance of the training may be of limited applicability when trainees return to their own health system, which may be unable to afford application of their new skills, and where disease and patient factors may preclude their use. For example, in high-income countries, some 90% of all breast cancers are stages 1 and 2 at diagnosis, whereas in low-income countries this falls to 40% or less. Therefore, techniques such as sentinel node biopsy and breast reconstruction surgery may be inappropriate for the majority of women, even if they were able to afford them and have also not been scientifically validated in these populations.

## **Examinations, diplomas, and degrees in breast care**

There are a number of high-quality examinations, certifications, or academic degrees or diplomas available. A number of key offerings are described next.

### **European Board of Surgery Breast Exam**

The European Board of Surgery Breast Examination (EBSQ) is an annual exam run by the UEMS, which is a body set up to harmonize medical training across Europe. The exam was established in 2010 as a joint endeavour between the UEMS, European Society of Breast Cancer Specialists (EUSOMA), and European Society of Surgical Oncology (ESSO), and the number of applicants is growing steadily (89 candidates in 2024). A curriculum for training has been established (9), and eligibility criteria for the exam map to this. The exam assesses candidates against the standard of a newly qualified European consultant surgeon who has just completed training. It comprises a written exam and a rigorous oral exam with complex case management discussions and academic critique of a recent scientific publication. Knowledge of oncoplastic and reconstructive techniques is embedded in the syllabus, as is awareness of the latest evidence-based guidelines and research interpretation. The exam is now recognized by the UK GMC for non-UK trained surgeons alongside detailed evidence of training using the CESR route to certification of completion of training. It is gaining in popularity and is widely recognized as a marker of high-quality practice.

In a similar way, the UEMS section of plastic and reconstructive surgery has a training syllabus and exam which cover aspects of breast care from a plastic surgery perspective.

### **University of Ulm (Germany)/European School of Oncology Certificate of Competence in Breast Care**

This is a European-based University course and assessment run by ESO and the University of Ulm. The Certificate of Competence in Breast Cancer is a comprehensive programme designed to provide healthcare professionals with specialized knowledge and skills in the

diagnosis, treatment, and management of breast cancer. This certification encompasses a multidisciplinary approach, covering aspects such as pathology, radiology, surgery, medical oncology, radiation oncology, and supportive care. Through a structured curriculum, participants gain in-depth understanding of the latest advances in breast cancer research, evidence-based practices, and multidisciplinary teamwork, preparing them to deliver high-quality care to breast cancer patients. ESO's certification signifies proficiency in the field and a commitment to continuous professional development.

## ESCO

In July 2020, the European School of Oncology (ESO) launched the College of the European School of Oncology (ESCO, <https://www.esco.org>) to guide and support oncologists (medical, radiation, or surgical oncologists) to actively improve their oncology careers by giving order and direction to ESO's activities. It provides a dedicated educational pathway, encouraging, and awarding self-education and career achievements, giving members the opportunity to network and collaborate with each other and giving members access to benefits to help them further develop their careers (24). All ESO activities that have a competitive selection process are organized into the ESCO Educational Pathway, which encourages members of ESCO to follow structured training.

## University of East Anglia (UK) master's degree in oncoplastic breast surgery

This course is online and runs part-time over three years to achieve a full master's level. It has six modules mapped across the full ISCP curriculum in breast disease. It provides interactive online learning covering all aspects of benign and malignant breast disease and oncoplastic breast surgery, and is supported by an excellent faculty of experts. It is global in its reach, teaching in over 60 countries, and very popular, although access is somewhat limited by the cost, which is discounted for participants working in LMICs (25).

[https://www.uea.ac.uk/course/postgraduate/ms-master-of-surgery-in-principles-of-breast-oncoplasty-part-time#course\\_overview](https://www.uea.ac.uk/course/postgraduate/ms-master-of-surgery-in-principles-of-breast-oncoplasty-part-time#course_overview)

## Continuous medical education in breast care

Breast surgery benefits from a wide range of excellent international and national conferences each year, which provide high-quality evidence-based updates for both trainees and established practitioners. The largest is the San Antonio Breast Conference in Texas. Other excellent meetings include the St. Gallen Conference, the European Breast Cancer Conference, the London Breast Meeting, the Milan Breast Meeting, Senaturk, and many others. Many National Breast Societies also host high-quality meetings, such as the UK ABS. There are also numerous excellent webinars run by various organizations such as ESSO, iBreastBook, EUSOMA, Breastics, and many more. The majority of these are free, which makes them accessible in lower-income countries. Several exemplars are shown below.

## eCancer

As well as the above initiative, eCancer offers a wide range of high-quality, free educational resources through their educational platform, [ecancer.org](https://ecancer.org). These include 1,780 educational videos covering a wide range of breast cancer topics, e-learning courses covering topics such as breast cancer surgery, pain management, TNM staging, CDK 4/6 inhibition and palliative care. They also host over 300 articles covering breast cancer in an open-access journal which operates a 'pay what you can afford' model for authors' fees to support the oncology community in low- or middle-income countries. All of these are available for free at [ecancer.org](https://ecancer.org).

## Grand rounds global quality care

In early 2023, eCancer decided with faculty members of this book, chaired by Didier Verhoeven to create the 'Grand Rounds Breast Cancer Global Quality Care' series of live educational webinars. The webinars take place four times per year and promote peer-to-peer discussion of high-value breast cancer care within resource-limited settings for healthcare professionals globally.

The live webinars, as well as the on-demand recorded versions, can be viewed through [ecancer.org](https://ecancer.org) and are available for free for the global oncology community.

 <https://ecancer.org/en/conference/1454-grand-rounds-in-breast-cancer>.

## iBreastBook

This is a web-based platform which offers a regular series of high-level webinars across a range of breast surgery topics, delivered by some of the world's most prominent experts. Its focus is on oncoplastic and reconstructive surgery (26).

## Key messages

- Breast surgery training is currently not widely recognized by national certification bodies and is part of generic general surgery or gynaecology training. This limits the quality and depth of training and permits non-specialists to practice. Steps urgently need to be taken to enhance specialist training within generic curricula or mandate specialist fellowships and/or examinations.
- Integrated standardized high-quality international curricula for training in breast care that cover surgery, radiology, pathology, medical oncology, radiation oncology, and genetics need to be adopted by training regulators to ensure that breast surgery training is fit for the modern practice of breast cancer care.
- Standardized certification in breast care disciplines, either via professional examinations (e.g. UEMS), degrees, or diplomas should be mandatory before a specialist may be appointed.



- A standard curriculum to which the content of EACCME-accredited courses may be mapped.
- Formal recognition of certified training centres regulated nationally in accordance with high international standards.

Only then will all patients be able to benefit from the huge advances that have transformed survival and quality-of-life outcomes for breast cancer patients globally.

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**PART 3**

**THE GUIDELINES**



## Context-appropriate guidelines

### The importance of situational analysis

*Catherine Duggan, Alexandru Eniu, Laure-Anne Teuwen,  
Lopamudra Das Roy, Neha Goel, Cheng-Har Yip, and Didier Verhoeven*

### Introduction

Clinical practice guidelines (CPG) synthesize the latest research and expert consensus to outline optimal approaches to screening, diagnosis, treatment, and follow-up care for breast cancer patients. By adhering to these guidelines, healthcare providers can standardize practices, improve treatment outcomes, minimize variations in care, and ultimately enhance the quality of life for individuals affected by breast cancer. However, effective implementation of evidence-based guidelines and practices relies not only on their quality and acceptance by both clinicians and the public, but also on their ease of implementation. This is an often-underappreciated barrier given guideline complexity and the need for an integrated approach where policymakers, advocates, financial officers, and clinicians can prioritize and implement the most cost-effective and appropriate interventions for their context (1, 2).

In this chapter we review the impact of integrating CPGs into routine practice, adherence and compliance to CPGs, or differences in approaches taken by institutions in interpreting and implementing CPGs. We also discuss the importance of understanding the local context and setting during the implementation process through situational analyses, outline the first steps in this process present three case studies, and provide quotes from key opinion leaders on these topics.

### Clinical practice guidelines: impact on outcome

We previously examined international CPGs for the management of breast cancer, and their uptake and effectiveness; adherence to evidence-based guidelines is associated with improved patient outcomes (3).

A retrospective study of 3976 patients with primary breast cancer reported a significant association between adherence to the German national treatment guidelines and improved recurrence-free and overall survival rates. At the same time, they observed a linear association between an increasing number of violations in guideline adherence and decreased overall survival (4). A second study examined the association between guideline-adherent adjuvant treatment and survival outcome in 371 patients with triple-negative breast cancer

(TNBC) nested within Breast Cancer Care under Evidence-Based Guidelines (BRENDA), an observational, retrospective, multicentre, cohort study. 66.8% of patients with TNBC were found to have one or more guideline violations, which was also associated with worsened survival outcomes. A further evaluation of this cohort demonstrated that rates of guideline adherence were lower in TNBC versus non-TNBC subtypes, especially among TNBC patients aged over 65 years. However, there were no differences in survival between any TNBC age subgroup among patients who experienced 100% guideline-adherent treatment (5). Another retrospective study in 3100 women with stage I–III breast cancer conducted in Malaysia, a middle-income country, examined the adherence to the Malaysian GCP in terms of adjuvant chemotherapy, radiotherapy, hormonal therapy, and anti-HER2 therapy. Adherence was 61.7%, 79.2%, 85.1%, and 26.2%, respectively, and patients treated according to the GCPs had better overall survival and event-free survival (6). By contrast, a large retrospective study of early-stage breast cancer identified from the Netherlands Cancer Registry reported that while adherence to treatment guidelines was affected by age, and noting that breast cancer patients aged  $\geq 75$  years are less likely to receive guideline-concordant treatment, adherence to guidelines was not associated with overall survival in any patient subgroup (7). A meta-analysis of 21 observational studies from European Union countries assessed the impact of adherence to breast cancer GCPs as a prognostic factor on healthcare outcomes and processes. The authors concluded with moderate certainty that adherence to GCPs was associated with an increased disease-free survival and overall survival, with 336 more patients free from recurrence and 138 more alive for every 1000 patients treated according to GCPs versus those receiving non-adherent treatment at five years follow-up (8).

## Resource appropriate guidelines and the importance of context

It is now widely accepted that guidelines designed for high-resource settings may have unintended harms in lower-resource settings. In such contexts, clinical guidelines may advocate for costly interventions that are either unaffordable or reduce the availability of financial and other resources that could develop effective, lower-cost services more appropriate to the local context (1, 9).

Over five Global Summits, the Breast Health Global Initiative (BHGI) developed resource-stratified evidence-based guidelines for breast healthcare delivery across different resource settings (10). The BHGI 2018 Sixth Global Summit subsequently developed a series of implementation pathways to implement evidence-based approaches to increase breast healthcare capacity in the context of available resources (11). These tools and guidelines formed the basis for the Global Breast Cancer Initiative (GBCI) Implementation Framework (12, 13) (see Chapter 40). The framework provides a roadmap for implementing key strategies for countries with diverse health systems, using three pillars corresponding to the breast cancer patient pathway, with accompanying key performance indicators (KPI) Pillar 1, health promotion for early detection (prevention and pre-diagnostic interval) with a goal of  $>60\%$  stage I or II invasive cancers, excluding unstaged and stage 0 at diagnosis; Pillar 2, timely breast diagnostics (diagnostic interval), goal  $> 80\%$  of patients to receive a diagnosis within two months of initiation of diagnostic evaluation at a facility with capacity for diagnosing breast cancer; and Pillar 3, comprehensive breast-cancer management (treatment interval), goal

>80% of patients with a diagnosis of invasive breast cancer initiate and complete their recommended course of treatment without abandonment (Figure 10.1).

A recent publication highlighted the need for methods supporting implementation of integrated strategies in under-resourced health systems, in response to the World Health Assembly endorsement of the Global Action Plan for the Prevention and Control of NCDs 2013–2030 (NCD-GAP) (14). The field of implementation science emerged after evidence showed that less than 50% of evidence-based practices are successfully integrated into clinical practice. It examines how to effectively apply proven methods in real-world settings, using frameworks and theories to understand how an intervention interacts with the setting and intervention recipients; (15) and ensures the consideration of relevant variables such as

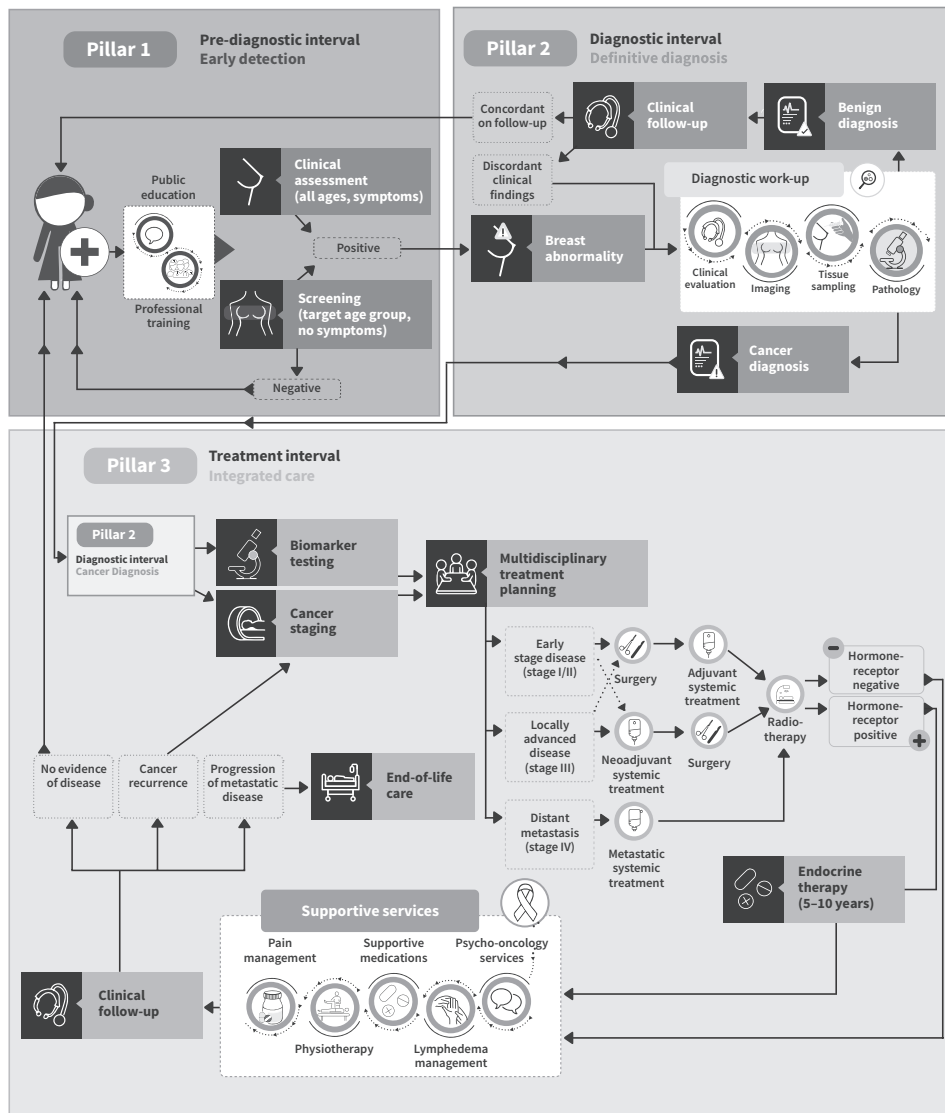


**Figure 10.1** The three pillars of the GBCI breast cancer patient-care pathway.

Reproduced with permission from Global Breast Cancer Initiative Implementation Framework: Assessing, strengthening and scaling up services for the early detection and management of breast cancer, p.36. WHO 7 March 2023. Available at <https://www.who.int/initiatives/global-breast-cancer-initiative>

equity and context, allows for cross-comparison and evaluation, and represents a common language guiding the implementation process.

A key component of implementation is understanding the setting or context within which they will be implemented. Figure 10.2 shows a seven-step process from stakeholder engagement to a situational analysis, which analyses the setting—or context—where the intervention will take place, priority setting, and strategy selection, which is dependent on local context. Context includes facilities, trained health workers, and patient needs. Finally, outcome measurements (monitoring and evaluation) are key to evaluating the success of any strategy.

## Situational analysis

Simply applying guidelines developed in high-resource settings can lead to excessive burdens on underfunded healthcare systems (3). Countries aiming to enhance national cancer outcomes must thus tailor and customize their implementation strategies according to the local disease burden, existing resource limitations, and competing healthcare priorities.

Situational analysis for the implementation of CPG is a systematic process used to assess the current context, resources, needs, and barriers within a specific setting to effectively implement evidence-based recommendations. This type of analysis helps healthcare providers, policymakers, and stakeholders understand the environment in which the guidelines will be applied and ensures that the implementation is tailored to the unique characteristics of the population and healthcare system (1).

Several organizations including BHGI have developed situational analysis tools that have been used to assess health system gaps in breast healthcare delivery, and GBCI underlines the importance of assessing the local setting as part of the implementation pathway (16, 17). These pathways are designed to conduct situational analyses of existing resources and provide guidance for applying evidence-based strategies to enhance breast healthcare capacity within the constraints of available resources (18).

## Steps in conducting a situational analysis

Before conducting a situational analysis, careful planning is required to define the objectives and scope of the analysis, by developing a detailed plan outlining the methodology, data sources, and timeline. Data collection is the next step, by gathering quantitative and qualitative data from various sources, including medical records, surveys, interviews, focus groups, and policy documents (Box 10.1). This information needs to be analysed to identify trends, patterns, strengths, weaknesses, opportunities, and threats. Field visits are key to interpreting the various information gathered. Findings should then be compiled into a comprehensive report and provide actionable recommendations for the implementation of breast cancer guidelines based on the analysis. The report findings should be shared with key stakeholders and incorporate their feedback to foster collaboration and build consensus on the implementation strategy (25).

Situational analyses provide several advantages.



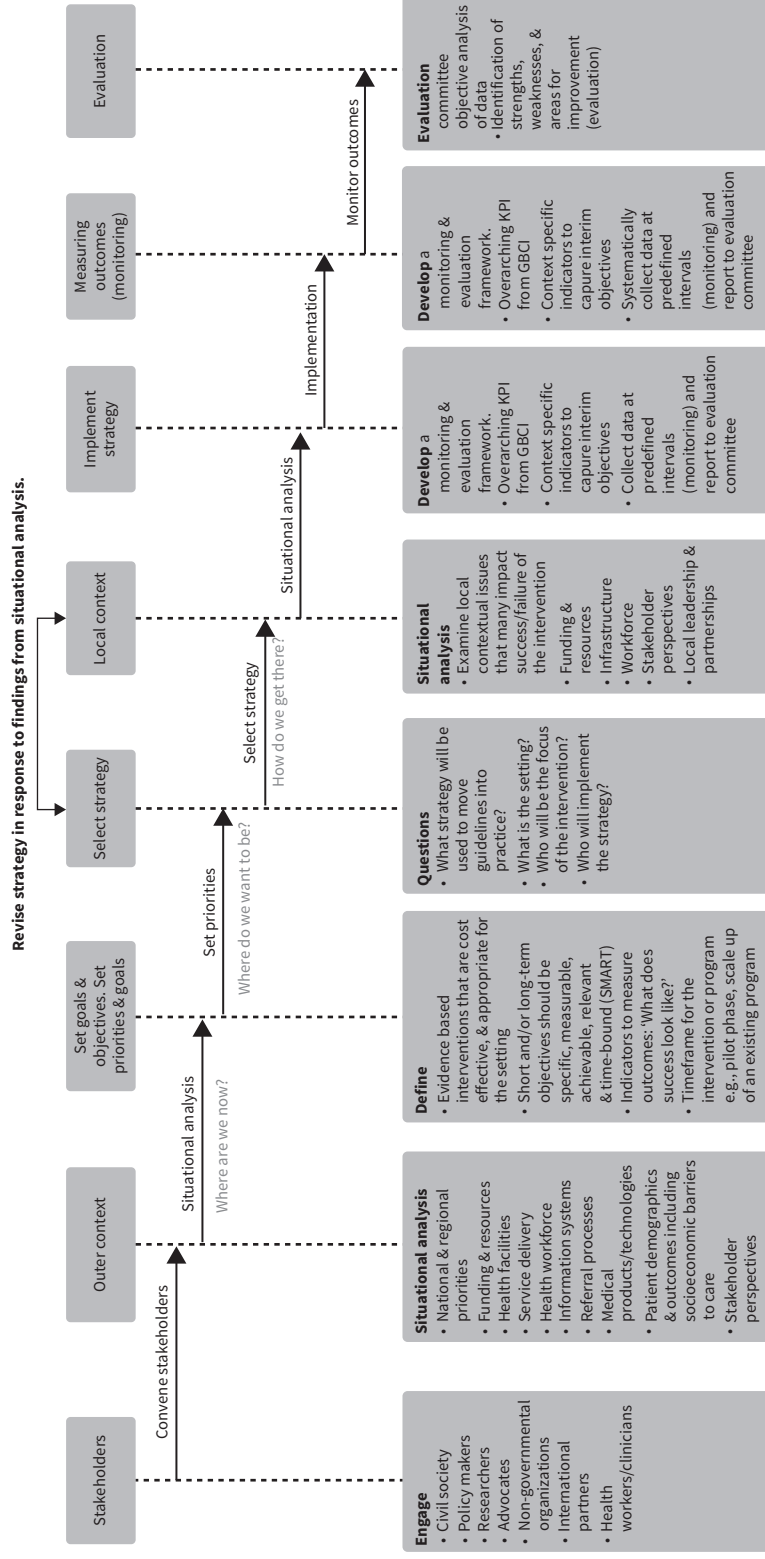


**Figure 10.2** Structured approach to implementation.

### Box 10.1 Key components of a situational analysis

#### 1. Assess current breast cancer care practices

Review existing practices, protocols, and outcomes related to breast cancer diagnosis, treatment, and follow-up. Identify gaps and areas needing improvement in current care delivery. If local guidelines exist, special attention should be devoted to understanding whether they were developed by national stakeholders who are knowledgeable about the local context, in contrast to a ‘cut-and-paste’ approach using international, resource-agnostic guidelines. Evaluate current metrics (stage at diagnosis, time to diagnosis, percentage of patients starting/completing treatment) to allow for the assessment of the effectiveness of existing breast cancer care protocols and to identify areas for improvement in patient outcomes and healthcare delivery systems (19).

#### 2. Assess healthcare infrastructure and resources

Evaluate availability and quality of healthcare facilities, equipment, and technologies needed for breast cancer care. Assess workforce capacity, including the number and expertise of healthcare professionals involved in breast cancer care. These data should provide the context for understanding if the local guidelines/care practices are anchored into the reality of local resources, or they are simply “wish-lists” to be used in negotiations with the local payers with the goal to increase reimbursement and access. Often local authorities such as the Ministry of Health are unable to provide detailed information, therefore ground work in collaboration with other stakeholders will be needed to gather the required intelligence (20).

#### 3. Population health data

Analyse epidemiological data on breast cancer incidence, prevalence, mortality, and survival rates in the population. As this information might be missing in limited resource environments, extrapolation of institutional-level registries might be used, in conjunction with an understanding of the demographic and socio-economic factors that influence breast cancer outcomes (21).

#### 4. Policy and regulatory environment

Review existing policies, guidelines, and regulations related to breast cancer care to identify any legal or regulatory barriers to the implementation of new guidelines. Interviews with local stakeholders might be needed to better understand the environment (22).

#### 5. Stakeholder analysis

Identify and engage key stakeholders, including healthcare providers, patients, advocacy groups, and policymakers, to understand their perspectives, interests, and potential influence on the implementation process. Include patient and community needs, by assessing the awareness, knowledge, attitudes, and beliefs about breast cancer among patients and the broader community, as well as identify specific needs and preferences regarding breast cancer screening, diagnosis, and treatment (23).

**6. Financial and economic considerations**

Evaluate financial resources available for breast cancer care, including funding sources and cost-effectiveness of interventions, as well as assessing the economic impact of breast cancer on patients and the healthcare system.

**7. Barriers and facilitators**

Identify (1) potential barriers to the implementation of breast cancer guidelines, such as cultural, logistical, financial, or systemic challenges; (2) facilitators that can support the successful adoption and integration of the guidelines. Analysing the actual patient pathway flow enables the identification underlying dysfunction in referral processes that hinder women from receiving timely diagnosis and treatment (24).

1. The contextual relevance ensures that the contextual issues, including implementation barriers and facilitators, are mapped.
2. Evidence-based CPGs can be tailored to the specific needs and conditions of a health-care setting.
3. Resource optimization helps allocate resources efficiently and prioritize interventions that will have the greatest impact.
4. Engaging stakeholders early in the process fosters support and collaboration, which in its turn Increases the likelihood of successful implementation and better health outcomes for breast cancer patients.

In summary, situational analysis for the implementation of breast cancer guidelines is a crucial step to ultimately improving the quality of breast cancer care and patient outcomes.

## Case studies: implementing CPG in low-resource settings

### India

In deprived regions in India, assessing specialized cancer treatment, from pathology testing to surgery and adjuvant therapy is challenging and guidelines must be adapted to the local situation. To meet these needs, the Breast Cancer Hub (BCH) (see Chapter 33) provides comprehensive support, including transport, costs, counselling, and follow-up care, and ensures completion of treatment. Collaborations between NGOs and Cancer Institutes improve service access for cancer patients. Such partnerships are indispensable, especially in these areas where sociocultural diversity, infrastructural, or psycho-social barriers could influence the timely treatment of cancer patients.

## Malaysia

In Malaysia, a middle-income country, national CPGs for the management of breast cancer were published in 2002 under the Health Technology Assessment Unit at the Ministry of Health. However, manpower and budget constraints remain an important barrier to developing and implementing these guidelines. These include: (1) Delays in planned updates for guidelines on a four-year cycle. Due to staffing shortages, the second edition was published in 2010, and the third in 2019, representing gaps of eight and nine years, respectively. (2) Recommendation for trastuzumab as a treatment for HER-2 positive breast cancer. Due to budgetary constraints, only 26% of eligible patients had access to this therapy (6). (3) Cancer NGOs in Malaysia have repeatedly appealed to the government for increased funding for cancer treatment, with little impact.

## Sergipe, Brazil

BHGI, in collaboration with the Ministry of Health of Sergipe and the Municipal Secretary of Health of Aracaju, performed a comprehensive assessment of breast cancer healthcare delivery in the state of Sergipe, Brazil (16). Prior studies identified deficits in breast healthcare delivery, including inefficient referral pathways, low breast screening coverage, a high proportion of advanced-stage diagnoses, and deficits in treatment delivery. The research was based on methods developed by BHGI and assessed 18 primary, secondary, and tertiary care institutions, interviewed breast cancer survivors, and 35 primary healthcare providers.

Key findings highlighted strong political support and commitment from clinicians, established public-private partnerships supporting imaging and pathology service delivery. Barriers included unclear and inefficient clinical pathways for women with breast health concerns, resulting in significant delays in detection, diagnosis, and treatment, with ~60% of women diagnosed at advanced stages. Although treatment is free for all women, financial barriers and interruptions to drug supply hinder access to systematic treatment, and limited access to radiation therapy persists. Recommendations included establishing effective breast cancer triage at lower levels of the healthcare system using clinical evaluation and clinical breast examination (CBE) of patients with breast symptoms, educating patients on signs and symptoms of breast cancer, train providers in clinical breast examinations, and establishing and implementing referral protocols to higher levels of care, enhancing access to equipment and technology, and reviewing underlying causes of chemotherapy and other medication shortages.

## Opinions from faculty experts

Faculty members in various countries were contacted by email and asked for their opinions on guidelines for breast cancer management (Box 10.2).

### Box 10.2 Quotes from faculty experts on CPGs

*ESMO clearly confirmed that routine staging is not required in stage I–II, not even in many stage III patients, yet it is commonly done in the case of even T1aN0 cases! Waiting lists for MRI, PET-CT are not because of a shortage of infrastructure, but rather because of excessive non-indicated use, causing stress, false-positive findings and only from now and then an unexpected finding that either will have no therapeutic consequence or, more likely, cause a Will Rogers phenomenon due to stage migration.*

**Philip Poortmans, Belgium**

*International guidelines may be preferable if they are drawn up critically (read: effectively) and thus improving the quality of care and potentially increasing the accessibility of anti-cancer drugs in a broad sense.*

**Agnes Jager, The Netherlands**

*They are very helpful in maintaining consistent and high-quality standards in dealing with breast cancer throughout the country. The guidelines have very much improved the quality of the treatment of breast disease in Germany.*

**Hans Junkermann, Germany**

*Guidelines can be very useful in certain circumstances. For example, the Australian Optimal Care Pathways provide timelines in which treatment should occur and provide a framework for what services are needed which is most useful for smaller or non-specialist cancer units. Other guidelines, such as the Australian eviQ ([www.eviq.org.au](http://www.eviq.org.au)), provide protocols for chemotherapy and management advice for carriers of genetic mutations.*

**Christobel Saunders, Australia**

*Health insurance needs to support guidelines that are based on evidence, it doesn't matter if private or public. Guidelines are based on level 1 evidence, but for example the EUSOMA and ABC have quality indicators for more controversial topics, to recommend quality care driven by academic considerations, on topics without level 1 evidence, to influence stakeholders, governments, and insurance.*

**Orit Person, Israel/Dana Casey, US**

*There is always a tendency to second-guess the guidance documents (e.g. 'My patient is different... They have only 1 positive node... I have not seen that issue in my practice'). [However] guidance documents lag behind the data, so they are, maybe, out of date.*

**Lawrence Marks, US**

*Guideline implementation is challenging as I work in diverse communities and with different socioeconomic sectors. Therefore, implementation cannot be standardized with the accessibility to healthcare facilities, resources available, and the economic conditions in the respective urban and rural sectors. Therefore, for each province, the guidelines need to be improvised.*

**Lopamudra Das Roy, India**

## Key messages

- Resource-stratified evidence-based CPG allows for breast healthcare delivery across different resource settings. The GBCI Implementation Framework provides a roadmap for implementing key strategies for countries with diverse health systems, using three pillars corresponding to the breast cancer patient pathway, with accompanying KPI (1). 60% invasive breast cancer diagnosed at stage I or II (2). 80% of patients diagnosed within two months of presentation (3). 80% of patients with a diagnosis of invasive breast cancer initiate and complete their recommended course of treatment without abandonment.
- Situational analysis for the implementation of breast cancer guidelines will help health-care providers, policymakers, and stakeholders understand the environment in which the guidelines will be applied and ensures that the implementation is tailored to the unique characteristics of the population and healthcare system.
- Adherence to CPG for the management of breast cancer is associated with improved patient outcomes in high-resource settings, and recent evidence also show an improved survival in low-resource settings.
- Manpower and financial constraints are major barriers to evidence-based treatment of breast cancer. The financing and governance of cancer care need to be revised and optimized to better outcomes.

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**PART 4**

**THE MULTIDISCIPLINARY MEETING**



## The multidisciplinary breast conference

*Terry Sarantou, Dominique van Uden, Beth Overmoyer, Christobel Saunders, Sabine Siesling, Pankaj G. Roy, Cary S. Kaufman, and Didier Verhoeven*

### Introduction

Over the past 100 years, the care of patients with breast cancer has changed from radical surgical intervention with mastectomy to less aggressive surgical intervention and includes systemic therapy and radiation therapy. New developments in imaging, pathology, genetics evaluation, medical oncology, radiation oncology, reconstruction, rehabilitation, and survivorship have become integral to breast cancer treatment. Management of many patients may be straightforward; however, some patients present with diagnostic and treatment dilemmas associated with their age, family history, genetics, psychosocial factors, or tumour biology. In the progression towards more personalized medicine as well as patients presenting with unique problems, international guidelines, such as the National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) guidelines may be difficult to interpret in some instances (1, 2) (see Chapter 10). Many breast programmes are developing their own breast care guidelines based on consensus and evidence-based data. This promotes teamwork, a sense of ownership, and leads to better multidisciplinary participation. Consequently, a more robust multidisciplinary approach with the cooperative efforts of those providers treating patients with breast disease has become increasingly important. Prospective presentation of breast cancer cases at a multidisciplinary breast conference (MBC) or tumour board promotes effective evidence-based care. Universal and disease-specific quality indicators of care can be assessed at breast care conferences. The COVID-19 pandemic has rapidly accelerated the use of virtual video-based tumour boards that are increasingly becoming the norm.

### Multidisciplinary breast conferences and multidisciplinary teams

The MBC allows experts to review either all cases or selected complex cases of patients with breast cancer and work together to develop and refine therapeutic strategy. In the United States of America (USA), the cancer tumour board is a required component for achieving accreditation through the Commission on Cancer, a quality programme using evidence-based standards and organized through the American College of Surgeons with input from multiple provider organizations. A formal accreditation programme for breast centres also exists, the National Accreditation Programme for Breast Centres (NAPBC), who accredit

breast centres in the USA and internationally (3). The Commission on Cancer and NAPBC accredit cancer programmes through compliance with evidence-based standards for cancer care. The NAPBC requires a formal breast cancer conference with specific guidelines for presenting patients and provider attendance thresholds as part of its accreditation process (see Chapter 6).

Multidisciplinary breast cancer clinics (MDC) also exist, where patients are seen by multiple providers in one setting, including review of pathology and imaging. MDCs are more common in Europe, and they can represent best practice. MDCs are often seen in academic settings and require resources that may not be available to all providers and/or breast centres.

Multidisciplinary tumour decision teams (MDT) are required by accreditation services for breast units in several countries and are mandatory in the UK. The MDT is defined as 'A group of people of different healthcare disciplines which meets together at a given time (whether physically in one place or by video or teleconferencing) to discuss a given patient and who are each able to contribute independently to the diagnostic and treatment decisions about the patient'. The UK National Cancer Peer Review Programme Manual for Cancer Services ([https://assets.publishing.service.gov.uk/media/5a7c777de5274a559005a0fd/dh\\_125890.pdf](https://assets.publishing.service.gov.uk/media/5a7c777de5274a559005a0fd/dh_125890.pdf)) establishes that for breast cancer care, core membership of the MDT includes two designated breast surgeons, a radiation oncologist, a medical oncologist, two imaging specialists, two pathologists, two breast cancer nurse specialists, and an MDT coordinator/secretary. Extended team members include a reconstructive/plastic surgeon, physiotherapist/lymphoedema specialist, psychiatrist or clinical psychologist, and a social worker.

## European perspective

The European Society of Breast Cancer Specialists (EUSOMA) has developed requirements for specialist breast units and quality indicators in breast cancer care (4) (see Chapter 5). EUSOMA's recommendations aim at improving the quality of breast cancer care and specify that 'the breast centre must hold at least weekly a multidisciplinary case management meeting (MDM) to discuss diagnostic, preoperative, and postoperative cases, as well as any other issues related to breast cancer patients, which require multidisciplinary discussion'. At least 90% of all breast cancer cases should be discussed prospectively. Advanced breast cancer cases must also be discussed. At least 95% of all early and locally advanced breast cancer cases and at least 50% of metastatic cases must be discussed at the meeting (but in future, the goal is that all cases, early and metastatic, are discussed at the MDM). At preoperative stage, the MDM must consider patient-related factors, tumour-related factors, and treatment options.

Team members who must be present:

- *Discussion of preoperative breast cancer cases:* radiologist, pathologist, medical oncologist, surgeon, radiation oncologist, breast nurse, and breast data manager
- *Discussion of postoperative cases:* pathologist, surgeon, medical oncologist, radiation oncologist, breast nurse, and breast data manager
- *Discussion of metastatic breast cancer cases:* medical oncologist, radiation oncologist, breast nurse, radiologist, pathologist, nuclear medicine physician (mandatory if the breast centre performs and uses positron emission tomography-computed tomography

(PET-CT) and recommended if the nuclear medicine service is not inside the hospital), palliative care specialist, and breast data manager.

Additional members are encouraged to participate and should be available for consultation. These include a nuclear medicine specialist, clinical geneticist, psychologist/psychiatrist, physiotherapist/lymphatic drainage specialist and breast care social workers. General practitioners are encouraged to participate (Figure 11.1).

Radiological images must be available at the MDM. A photograph of the breast should be available to decide the best surgical strategy. Macroscopic pictures or the histology of special cases preferably from slides (video microscope or scanned slide) should be shown to support understanding of difficult histopathological reports.

Evidence on decisions taken for each patient at the meeting must be formally recorded. The name of all team members participating in each meeting must be formally recorded.

As the patient is usually not present at the MDM and patient preferences must always be taken into account, and because the available clinical documents could miss key information, an MDM decision might, in some cases, be modified at the time of communication with the patient. For this reason, it is important that the breast care nurse present knows the patient's wishes and expectations to ensure they can be shared at the MDM. The clinician who informs and discusses the MDM conclusions with the patient must have the competence to understand why the patient wants a change of the recommendation. The reason for change must be documented in the patient chart and the MDM must be informed.

The breast centre must have a nominated breast centre coordinator, who can be a health-care professional from any specialty within the core team, responsible for the multidisciplinary approach and the full involvement of breast experts from the core disciplines and their regular participation in the MDM. The coordinator must ensure there is training and continuing medical education of MDT members; ensure the centre has certain breast related



**Figure 11.1a** Members of the breast team with the EUSOMA auditors.



**Figure 11.1b** Breast team during MDT in the presence of the CORE disciplines.

research; and ensure the centre's performance is based on high-quality data collection and indicators.

## Why do we need MDTs?

Multidisciplinary breast care should be the goal of all breast programmes. The MBC serves as an organizational structure of a breast programme which facilitates collaborative care between physicians and allied health staff. Breast conference presentation encourages patient review and provides opportunities for physician and staff education so that patients receive the most up-to-date and relevant treatment. Breast conference presentation also serves as an opportunity to review clinical trial participation, participation in other research, complementary therapies, the need for psychosocial support, and other supports such as fertility or genetics input.

With increasing knowledge and technological advances, breast healthcare has become more complex. Patients see multiple specialists for their care, and at times, communication between providers and the patient is not ideal. Cancer care 'office shuttling' may lead to delays and gaps in patient care treatment. Multidisciplinary breast care 'tumour board clinics' were described in the USA in the 1980s and provided second opinions for care (5). Although multidisciplinary breast clinics were popular in the 1990s and remain so today, they face challenges due to costs, required resources, the time commitment of physicians and other staff, and the overload of information for patients from seeing multiple providers in one setting. The restrictions placed upon in-person patient visits by the COVID-19 pandemic have led to an interruption in formal multidisciplinary breast clinics. Programmes are now evaluating their patient care models moving forward, and some are returning to a multidisciplinary

**Table 11.1** Key components of multidisciplinary clinic (MDC) clinical care

| Benefits                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Pitfalls                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Single site of care</li> <li>• Improvement of information presentation and quality of teamwork</li> <li>• Decreased cost (volume)</li> <li>• Enhanced communication</li> <li>• Coordinated treatment plan</li> <li>• Adherence to guidelines</li> <li>• Best diagnostic and treatment plan</li> <li>• Broad based patient education</li> <li>• Review quality of professional care</li> <li>• Coordinated follow-up</li> </ul> | <ul style="list-style-type: none"> <li>• Impact on outcome not proven</li> <li>• Increased complexity of staff function/ training/ personnel needs</li> <li>• Increased cost (volume) and high time expenditure</li> <li>• Turf wars, politics</li> <li>• Low quality of reports and information</li> <li>• Excessive not strictly clinical information leading to contrasting opinions</li> <li>• Legal issues related to responsibilities and anonymity of patients presented at MTB</li> <li>• Accessibility owing to socioeconomic conditions</li> <li>• Risk of treatment delays</li> </ul> |

Source: data from Berardi, R., Morgese, F., Rinaldi, S., Torniai, M., Mentrasti, G., Scortichini, L., & Giampieri, R. (2020). Benefits and limitations of a multidisciplinary approach in cancer patient management. *Cancer Manage Res*, 12, 9363–74.

clinic format with either an in-person or virtual format in a more limited time setting of once per week.

MBCs as outlined in the USA, and MDTs as outlined in Europe and other settings, as opposed to breast multidisciplinary clinics, provide a practical method for case presentation with review. The observation is that there is an ongoing blending of MBC and decision team presentation leading to enhanced patient care plans.

MBC and MDT review also provides an opportunity to identify patients for clinical trial and research participation.

Tables 11.1 and 11.2 below illustrate some key components of the multidisciplinary breast clinic (MDC) with benefits and challenges (6, 7).

Observational studies have shown the benefits of receiving cancer treatment at a specialist centre, and evidence continues to accrue from comparative studies of the clinical benefits of an MDT approach. A Scottish study reviewed 13,722 patients between 1990 and 2000 in western Scotland undergoing cancer care (8). Prior to the introduction of multidisciplinary care (September 1995), mortality was 11% higher in the intervention area than in the non-intervention area (hazard ratio = 1.11). The authors concluded that with the introduction of MDTs, mortality was 18% lower in the area where MDTs were introduced (hazard ratio = 0.82) than in other areas in the region.

**Table 11.2** Key components of multidisciplinary clinic (MDC) research efforts

| Benefits                                                                                                                                                                                                                                                                           | Pitfalls                                                                                                                                                                                                                                                         |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Pooled resources</li> <li>• Correlations and input across specialties</li> <li>• Enhanced development of evidence</li> <li>• Cross training/education across disciplines</li> <li>• Ability to train beyond primary discipline</li> </ul> | <ul style="list-style-type: none"> <li>• Increased complexities and incompatibilities</li> <li>• Scientific disagreements</li> <li>• Different 'cultures' and educational backgrounds</li> <li>• Politics of different departments and research units</li> </ul> |

Reproduced from Murthy, V., Nobre, S., Sparber, L., Schaefer, S., Santoro, E., McDermott, J., Chamberlain, R., and Blackwood, M. (2014) Multidisciplinary Breast Conference Improves Patient Management and Treatment. *Surg Sci* 5, 314–19 under a Creative Commons (CC-BY-4.0) licence.

Murthy et al. (7) described that patients presented at MBC had improvement in patient management and treatment: 42% of patients had modified changes in management after presentation at MBC; 38% of treatment changes were for surgery, 33% for medical oncology (chemotherapy and endocrine therapy), 17% for radiation oncology, 6% for both medical and radiation oncology, and 6% for imaging (see Figures 10.1 and 10.2). Most of the changes were made to AJCC Stage IA (27%) followed by AJCC Stage 0 (21%).

Newman et al. showed changes in recommendations for surgical management resulting from review of patients presented at MDC, with 45% of cases having a change in interpretation from imaging review (9). This resulted in a change in surgical management in 11% of patients. Review of pathology resulted in changes in interpretation in 29% of patients, with a 9% change in surgical management. 34% of patients had a change in surgical management after discussion with surgeons, medical oncologists, and radiation oncologists, not based on reinterpretation of radiology or pathology. Overall, the second evaluation of patients reviewed at MDC led to changes in the recommendation of treatment in 52% of patients.

The recent advancements in systemic therapy including immunotherapy, novel antibody treatments and antibody drug conjugates (ADC) both in the adjuvant and neoadjuvant setting potentially allow a more minimally invasive surgical approach to both the breast and axilla, dose reductions or elimination of radiation therapy for selected patients, and refinements in reconstruction, and these have emphasized the importance of a multidisciplinary discussion to provide patients with personalized treatment. MBT discussion is slowly shifting away from that of just surgical approaches to discussion and changes regarding the use of systemic therapy and targeted radiation therapy.

As breast cancer care becomes more complex with important, relevant, evidence-based information provided by multiple specialties and allied health staff, patient care presentations at MBC can increasingly organize the chronology of care. Many centres have adopted a format of presenting all new cases and selected ongoing or post treatment patients for multiple presentations to ensure ongoing care with input from all specialties caring for the patient while keeping it sustainable seeing the often increasing number of patients per hospital/breast centre.

Remote technologies can also assist providers with quality breast care in rural or low-income environments that may not have readily available resources for organization of MBC/MDT.

## How to organize a successful MBC/MDT

A breast programme leadership committee should be formed to organize the MBC/MDT, ensure multidisciplinary representation, monitor, and evaluate meeting frequency unique to individual disciplines and practices, establish attendance thresholds, review prospective and annual case presentation, and include staging and discussion of pertinent treatment guidelines. This committee is composed of a core group of physicians, nurses, and appropriate ancillary staff who are charged with the organization and administration of the breast centre. Support and input from hospital administration is extremely important (Figure 11.2).

All physicians who manage breast cancer patients at a particular institution should be formal members of the breast programme/centre and agree to present their patients at MBC/MDTs and participate in multidisciplinary care. The agreement to present cases at breast



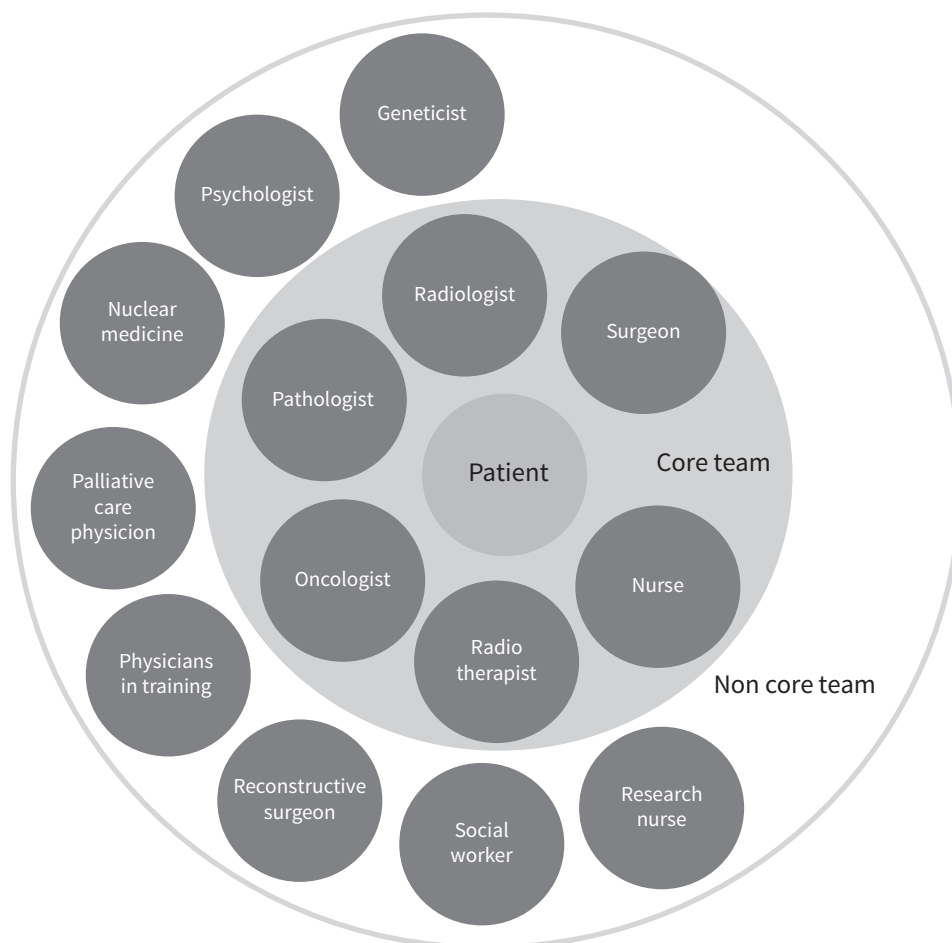


**Figure 11.2** MBC/MDT conference attendees.

MBC/MDTs provides recognition to members of a multidisciplinary breast programme. Good leadership is essential to ensure positive team dynamics, adequate administrative support, data recording, and sufficient staff time and funding for the MBC/MDT. Ideally, the majority of new patients with breast cancer would be presented in varying formats as practical with attendance of the caring physicians at MBC to ensure evidence-based recommendations and care plans are communicated to all members of a patient's care team.

## To discuss

- A personalized unique treatment plan for each patient
- Clinical trials and data metrics review

The MBC/MDT should present in a prospective fashion. An MBC/MDT coordinator should be responsible for reaching out to the physicians or staff who wish to present a case,

organizing the case presentations with the relevant necessary materials, and collaborating with pathology, radiology, and pertinent ancillary staff. Sufficient time should be available for members to prepare for case presentations. Adequate time for educational topics related to the cases discussed is important.

As defined by the NAPBC, MBC/MDT presentations should include:

- A presentation of relevant history and physical elements, including family history;
- A discussion of stage, risk profile, surgical options/pre-surgical options;
- Visual display of pathology slides and radiology imaging, and a discussion regarding radiology-pathology correlation for clinically relevant cases;
- Discussion regarding clinical trials, genetic risk, and reconstructive options;
- Consideration of nationally recognized guidelines at the conference;
- Discussion of psychosocial determinants of health;
- An open discussion among all conference participants.

The NAPBC defines prospective case review as:

- Newly diagnosed breast cancer where treatment has not yet been initiated;
- Newly diagnosed breast cancer where treatment has been initiated, but discussion and additional treatment are needed;
- Previously diagnosed, initial (often surgical) treatment completed, but discussion of adjuvant treatment or treatment recurrence or progression is needed;
- Consideration for clinical trials;
- Previously diagnosed and discussion of supportive or palliative care is needed.

Programme circumstances will determine the timing and frequency of case presentation. If there is likely a delay in care while waiting for the breast MBC/MDT presentation, physicians can also initiate multidisciplinary communication via electronic methods, email, electronic health record, telephone, text, or conference call.

Physicians and ancillary staff may face challenges regarding the scheduling and timing of the MBC/MDT conference. They may feel there may be competing priorities with the time required to attend multiple meetings and conferences. The breast programme must specifically create a dialogue with physicians and other health professionals and emphasize and reinforce the importance of MBC participation. The breast MBC/MDT is often identified at the 'central piece' of a breast programme, and robust participation is vital to the success of the breast centre. Physician and other staff participation in MBC should be thought of as an institutional function, not an individual or department function. Although many cases are not applicable to 'my' specialty or pose no treatment challenge for providers, and indeed may seem like a lot of preparatory work, especially for diagnostic colleagues in routine cases, discussion of all cases is advisable as some patients need re-discussion because of incomplete workup, or have co-morbidities which limit treatments, and it is important to record the suggested treatment plans for all.

Clinicians stated that attending and preparing MDTMs is time-consuming and indicated the need for optimal execution in order to ensure that MDTMs remain feasible in the near future. In the study by Walraven et al., four themes emerged that are relevant to achieving an optimal MDTM: 1. organizational aspects; 2. participants' responsibilities

and requirements; 3. competences, behaviour, and team dynamics; and 4. meeting content (10).

To remove some of these barriers, a MBC must have a good organization, a sound structure, and functioning information and a communication technology facilitating high-quality MDTMs. Multidisciplinary collaboration and adequate communication are essential competences for participants; a lack and the existence of a hierarchy are hindering factors. Moreover, the MDT could be allowed to provide credits for continuing medical education. Another option is to have the most challenging cases discussed first or streamlining could be considered and improvements to the efficiency of patient flows (11). Moreover, the meetings should be supported by up-to-date technology, such as the availability of data (e.g. images) within the electronic health record and video conferences for consultants from a reference hospital. A simultaneous breakfast or lunch can be helpful in teambuilding. Interestingly, video-based formats have been available since the introduction of SKYPE in 2003 with limited interest in using these technologies. The COVID-19 pandemic has brought both positive and negative changes to live meetings. Many MBCs are now virtual video meetings. This has caused the loss of personal interaction between clinicians, and MBC has become a more formal 'business' conference. Using team meeting software programs has introduced many uncomfortable pauses, and choppy flow of discussion may occur due to 'share screen' switching. Nevertheless, some benefits are recognized. The meetings are easier to attend by saving travel time and improving access to patients' clinical data. The discussion could be held in 'safe environments' with a more focused discussion and without distractions or side discussions. Whether in-person or virtual, MBC remains the springboard for research and integrated treatment plans and the forum for second opinions and optimizing the management of patients with breast cancer (12).

Ideally, providers should commit to a prescribed time to attend MBC as part of their patient care routine. Advances in video technology allow providers to access conference presentations and review patient information, radiology, and pathology. Providers can also access MDTs from their smartphones or tablets. These technologies are efficient and give providers a sense of active conference participation. Many programmes have adopted a 100% video-based format or hybrid approach for MBC. This format allows providers to access MBC from multiple locations allowing enhanced participation due to alleviation travel and multiple priorities. Although the general consensus is that MBC participation has increased as a result of video technology some question whether provider engagement has decreased. It is the responsibility of the breast programme directorate to ensure that all members of the breast centre are encouraged to participate (Figure 11.3).

A breast programme should determine the number of cases to be presented at each tumour board. This number can be obtained from reviewing the analytic case load of a breast programme. Depending on resources available, centres may choose to present all cases (ideal), or select cases that may ideally benefit from multidisciplinary presentation. Other methods of case review also exist, including a 'working conference' held on a regular basis, where most breast patients who will be seen at a centre will have their relevant history (including pathology report) and images reviewed and an initial treatment plan formulated. These working conferences allow for more rapid review of many cases and allow time for a more thorough didactic presentation for those cases presented at formal breast MBC/MDTs. The core group of physicians caring for the patients presented at MBC/MDT should be available and participate in the discussion of the patients presented.

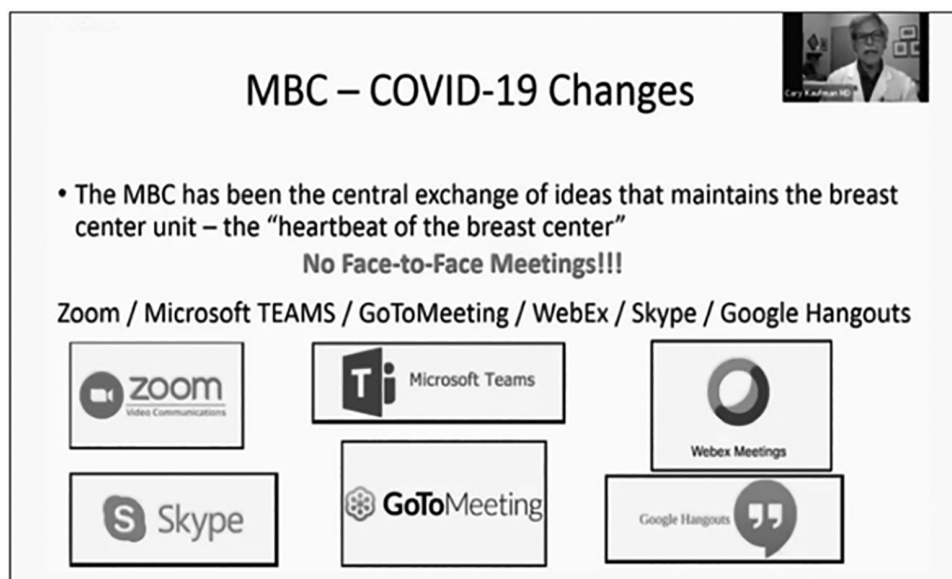


**Figure 11.3** Multidisciplinary Conference via electronic avenues.

Reproduced with permission from Verhoeven D, Allemani C, Kaufman C et al. *New Frontiers for Fairer Breast Cancer care in a Globalized World*. *Eur J Breast Health* 2021; 17(2): 86-94

A conference organizer can record the recommendations and treatment plan discussed at the MBC. Ideally, an evidence-based and unique treatment plan should be completed for each patient presented. Options include creating a conference ‘tracking sheet’ where the conference recommendations can be recorded. In addition to a patient identifier, the tracking sheet should record the stage of breast cancer, brief description of treatment recommendations including relevant surgical, medical, and radiation oncology therapies. Additional topics to be listed in the tracking sheet include discussion of national and breast centre treatment guidelines, genetics, psychosocial support, rehabilitation, and relevant clinical trials. Other information can be recorded at the discretion of the breast programme. The breast centre should discuss how this information will be used. The information can be forwarded to the relevant medical providers, including the primary care provider or general practitioner, to be placed into the medical record. The breast programme can audit the information to assess compliance with MBC/MDT recommendations as a quality measure. The confidentiality of all patient information disclosed at MBCs must be maintained by all participants.

### **Example of a multidisciplinary approach: ‘inflammatory breast cancer’**

*Special thanks to Beth Overmoyer and Dominique Van Uden*

Even though survival of patients diagnosed with inflammatory breast cancer (IBC) has increased over the past decades, the common denominator of the current literature and studies remains the generally poor prognosis of IBC (13). As discussed earlier, prospective presentation of breast cancer cases at a multidisciplinary breast cancer conference improves evidence-based care. IBC is eminently worth discussing in a multidisciplinary setting, since it is a rare diagnosis accompanied by diagnostic and treatment challenges.

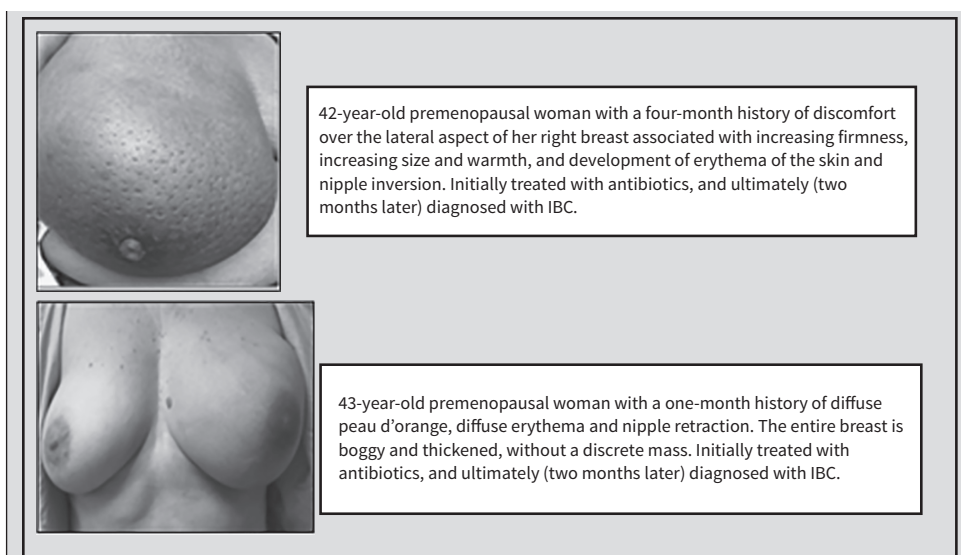


**Figure 11.4** Examples of two female patients presenting with IBC.

Reproduced from Jaggi R, Mason G, Overmoyer BA, et al. Inflammatory breast cancer defined: proposed common diagnostic criteria to guide treatment and research. *Breast Cancer Res Treat.* Apr 2022;192(2):235–43 © The Author(s) 2022.

### Increasing awareness of IBC

Although IBC is a rare form of breast cancer, there is a global variation in incidence, with European and Western countries having 1–5% of women with newly diagnosed breast cancer presenting with IBC, whereas North African and Middle Eastern countries have a higher incidence of IBC, estimated to be 10–18% (14). The signs and symptoms of IBC can also present as a local recurrence of a tumour, but only within an intact breast. IBC progresses rapidly, often in a matter of weeks or months. Because IBC is often misdiagnosed as non-puerperal mastitis, a delay in diagnosis can be life-threatening; therefore, it is imperative to have a correct diagnosis as soon as possible (15). Early detection of IBC is an important part of the general practitioner's (GP) work. Therefore, the multidisciplinary team may include all caregivers involved in diseases of the breast (e.g. GPs, surgeons, OB/GYNs, etc.). The involvement of a larger group of practitioners in a multidisciplinary breast cancer conference will increase awareness of this uncommon disease and improve early recognition and referral for appropriate treatment (Figure 11.4).

### Standardization of diagnostic criteria for IBC

The skin changes in IBC are caused by tumour emboli within the dermal lymphatics, and not by infiltration of inflammatory cells. Although microscopic detection of tumour emboli in dermal lymphatic vessels is supportive of the diagnosis, it is not required. Furthermore, dermal lymphatic invasion without typical clinical findings is not sufficient for a diagnosis of IBC (Figure 11.5) (16).

The diagnosis of IBC remains a clinical diagnosis with pathological confirmation of invasive breast cancer, lacking additional pathological criteria, and has therefore been open to subjectivity. This subjectivity contributes to the undertreatment of patients with IBC if the diagnosis is not properly made. Inaccurate diagnosis also leads to the loss of identified

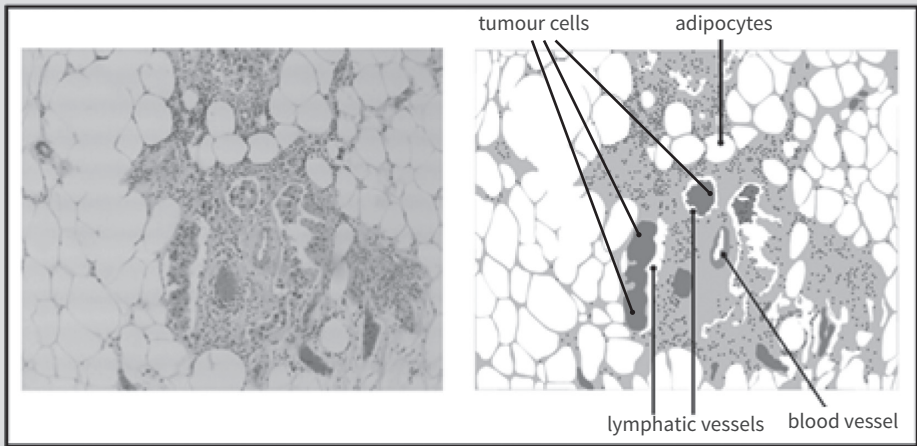


**Figure 11.5** Tumour emboli within the dermal lymphatics  
Reproduced with permission from Dominique J.P. van Uden, A.H. (Helen) Westenberg, Hanneke W.M. van Laarhoven, Jos W.R. Meijer, J.H.W. (Hans) de Wilt en Charlotte F.J.M. Blanken-Peeters, ‘Mastitis als uiting van een maligniteit’ . Ned Tijdschr Geneeskd. 2014;158:A7591

patients with IBC from trials or registration databases. The standardization of diagnostic criteria is essential and will help minimize such subjectivity.

In the absence of distinct molecular factors, a composite clinical definition of IBC has been proposed based upon a graded scoring system (Table 11.3). The classification scheme consists of four diagnostic possibilities: not IBC, weak possibility of IBC, strong possibility of IBC, and definitely IBC (16).

The proportion of breast involvement or size criteria for erythema (or oedema), might be open to interobserver variability. It is difficult to assess the proportion of discoloured skin in relation to the entire breast and earlier detection of the disease might result in a smaller proportion of visually involved breast compared with the extent of disease seen at a later time. Therefore the external appearance of the affected breast should be photographed, capturing more clinical details than a narrative description alone. The availability of a database

**Table 11.3** Clinical, pathological, and imaging characteristics of the IBC scoring system

| Characteristics                                                                                                                                                                                                                                                                              |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li>• Timing of signs/symptoms</li><li>• Skin changes</li><li>• Swelling/engorgement of the breast</li><li>• Erythema or other skin discoloration</li><li>• Nipple abnormalities</li><li>• Lymphatic tumour cell emboli</li><li>• Breast imaging</li></ul> |

Adapted from Jaggi R, Mason G, Overmoyer BA, et al. Inflammatory breast cancer defined: proposed common diagnostic criteria to guide treatment and research. *Breast Cancer Res Treat* 2022;192(2):235–43. © The Author(s) 2022.

of photographs of the clinical presentation of IBC is useful given its rarity and will lead to increased knowledge not only in the medical centre in which the patient is treated, but also for research purposes.

### **Centralization of knowledge and care using a multidisciplinary panel for IBC**

Data show that patients with IBC receive various treatment regimens that can result in sub-optimal care and outcomes (17). Known factors that are associated with IBC treatment that are not guideline-concordant include: age of the patient, race, and hospital size. Younger physicians were more likely to adhere to guideline recommendations compared with older physicians (18). For breast cancer in general, survival benefits are reported if the patient is managed in a high-volume hospital, suggesting more frequent application of guideline-concordant care. Since IBC is rare, a centralization process, such as the development of a multidisciplinary IBC treatment panel, will provide the volume of patients needed to optimize care. The consistent use of a panel of IBC experts involved in a regional or national multidisciplinary panel will not only result in an increased understanding of IBC but will also accelerate the diagnoses and subsequent treatment of this aggressive disease. The multidisciplinary panel will also facilitate the accurate registration of cases, enhance collaboration between research institutes, and aid in the most efficient use of research resources (19).

### **Treatment of IBC**

Optimal treatment strategies for patients with IBC rely on accurate initial staging. [<sup>18</sup>F] FDG PET/CT has been demonstrated to be a sensitive technique, providing information on locoregional and distant disease complementary to conventional imaging modalities.

Systemic therapy is one of the cornerstones in the treatment of IBC and monitoring of treatment response is essential. Lack of clinical response to systemic therapy may lead to a change in patient management and the avoidance of futile treatments. All subtypes of breast cancer are represented in IBC; however, the triple-negative subtype is more prominent and makes up 24% of stage III and 17 % of stage IV IBC. HER2-positive disease is also more frequent among patients with IBC, accounting for 40% of all IBC cases. Although personalized (or precision) medicine represents an effort to target therapeutic vulnerabilities at the individual patient level, the primary treatment for newly diagnosed IBC includes a chemotherapy backbone (19). The addition of targeted therapy to the chemotherapy backbone, such as using anti-HER2 therapy for HER2-positive IBC or immunotherapy in the case of triple-negative IBC, supports a personalized medicine approach to the treatment of this disease. Continued adherence to appropriate systemic treatments and the discovery of novel therapeutics will be crucial to improving the overall survival of IBC patients.

Neoadjuvant systemic therapy is the preferred treatment administered before surgery. Following the completion of systemic therapy resulting in a clinical change in the affected breast representing a return to a clinically normal breast, the current recommendation is that all patients with IBC should undergo a complete mastectomy and axillary lymph node dissection. The role of targeted axillary dissection in IBC has been explored in limited clinical trials, and concerns for the accuracy of sentinel node localization (increased false negative



rate due to aberrant lymphatic drainage) are certainly an issue and should not be considered as standard of care.

Trimodal therapy for IBC is the standard approach, which includes radiation therapy to the chest wall and axilla following mastectomy.

Endocrine therapy should follow the completion of surgery if the IBC is hormone receptor positive, consistent with the care of patients with non-IBC.

### **Moving forward in improving care for IBC**

Increasing knowledge of molecular aberrations, clinical behaviour, and patterns of response to systemic treatments (i.e. understanding resistance mechanisms to systemic therapies) in IBC is necessary to improve the poor outcome associated with this disease. While we await the implementation of innovative approaches to clinical practice (e.g. the use of gene signatures, molecular profiling, and liquid biopsies), the current standard of care for IBC should include the presentation of all patients with suspected or confirmed IBC to a multidisciplinary panel to facilitate a rapid diagnosis followed by a prompt referral for neoadjuvant chemotherapy, surgery, and postoperative radiation therapy. This is crucial in patients willing and able to undergo multimodality therapy. Furthermore, collaborations between research institutes and the most efficient use of research resources and existing data should be pursued on a global level to impact outcomes in IBC.

## **Does presentation of patients and participation in MBC/MDT lead to increased quality?**

Efforts have been made to investigate the role and efficiency of tumour boards in medical systems. The endpoints evaluated in these studies have included patient satisfaction, clinical outcomes, team dynamics, and communication (20). A major goal of MBC/MDT participation is to reduce delays in patient treatment and improve patient satisfaction. Unfortunately, measuring the efficacy of a tumour board is complex and multifactorial, and this creates challenges to objectively quantify endpoints (21). Participation in tumour boards can lead to increased clinical trial participation (22).

MBC/MDT should serve as a mechanism to review specific quality metrics of a breast f. Attending and presenting at MBC/MDT facilitates discussion regarding the direction of a breast programme's care for patients. Decisions regarding review of treatment decision pathways and quality metrics can be outlined at MBC/MDT. Treatment pathways can be updated with a review of recent literature. Reviews of metrics and pathways should be performed on at least an annual basis.

Review of breast programme metrics, either group or individually based, encourages provider engagement in the breast programme and identifies the MBC as the centrepiece of a breast programme. Some physicians will participate in a specialty society or an individual data collection/registry. The MBC is an ideal forum for presentation and self-review of both the breast centre and individual physician metrics. As the electronic medical record and the use of artificial intelligence mature, it is expected that more of the quality metrics will be incorporated. Tumour board metrics can be divided into universal measures and



disease-specific measures. Universal measures assess quality through organization, process, outcomes, and balancing.

Universal metrics include:

- Frequency of the conference (weekly or bi-monthly?);
- Specialty and individual attendance;
- Documentation of conference discussion and recommendations for patient care;
- Number of patients discussed;

Presentation: prospective, prior to medical and/or surgical treatment, ongoing care, and survivorship;

Specialty and individual physician quality metrics (determined by breast programme leadership).

Disease-specific measures capture data relevant to the disease. Examples of breast disease-specific measures include:

- Diagnostic and staging indicators
- Treatment and follow-up indicators
- Organizational indicators

## Future perspectives

### Genomics

The contemporary treatment of breast cancer has increased in complexity, and combined modality therapy is the standard of care. An MBC recognizes the need for multimodality treatment in a collaborative setting. Incorporating genomics into patient care is becoming increasingly important.

Multidisciplinary molecular tumour boards are emerging as a post-analytical tool for patient care. Due to the increasing use of high-throughput genomic technologies, clinicians are increasingly faced, in daily practice, with the question of how best to deal with this enormous amount of genomic information. A classical test cycle is defined as having three main components:

- The pre-analytical phase, defined as the phase before testing where it is important that all conditions of sample handling, like fixation for example, are adequately controlled.
- The analytical phase, defined as that part of the cycle that concerns performing the assay, where it is important to rigorously validate the assay in terms of sensitivity, specificity, etc.
- The post-analytical phase, defined as that part of the cycle concerned with for example data analysis.

It has become apparent that at the pre-analytical and analytical level, there may not be sufficient constraints to impede an adequate implementation of genomic-driven clinical practice.

However, the interpretation of genomic data is still a major hurdle for an important proportion of clinicians (23). In a recent study by Johnson and colleagues, only a minority of clinicians felt comfortable in interpreting, using, and discussing somatic as well as germline test results (24). The authors reasonably conclude that ‘To optimize the integration of genomic sequencing into cancer care, methods must be developed to improve basic competencies around cancer-based genomic testing. Given the complexities surrounding variant interpretation and genotype-phenotype relationships, interdisciplinary collaborations are warranted’.

The concept of a Molecular Tumour Board (MTB) is defined as a multidisciplinary board comprised mostly of oncologists, pathologists, research scientists, bioinformaticians, and genetic counsellors. Conceptually, this board reviews a patient’s chart including pathological, radiological, and molecular information. The goal of an MTB is to advise on the most optimal use of the genomic variants encountered. This advice can range from concluding that the obtained genomic information does not lead to a clinical intervention, which is unfortunately still mostly the case, to identifying clinical trial options and/or investigational/off-label targeted drug use.

It is becoming apparent that the added value of the use of high-throughput genomic technologies in a daily healthcare setting will depend on the most optimal interpretation and subsequent use of identified variants. This necessitates the development of MTB-infrastructure, not only at a local level, namely in the hospital where these high-throughput technologies are being used, but also at a regional and even national level, since patients are highly mobile and may visit different centres. The further development and integration of genomic-driven daily practice will not only be impeded by the under-use of the encountered genomic variants due to inexperienced and suboptimal training of clinicians in genomic medicine, but also the discrepant use of the variants of an individual patient in different hospital settings by different clinicians specifically due to the lack of training and/or harmonization of the use of these variants across different hospital settings. The latter is also of legal importance, since patients are increasingly better informed on the use of this information, and they may not accept that important treatment options are withheld.

Therefore, with the increased uptake of genomic profiling in clinical practice and the need to be properly interpreted and integrated into an individualized care plan ESMO made recommendations to regulate the composition and workflows of MTB. Recommendations should be appropriately adapted according to local resources, legislation, and centre volume. In addition, they developed a list of quality indicators to facilitate benchmarking and support the structured implementation of MTBs (25).

All the above illustrate that the post-analytical phase is becoming an increasingly important element to consider and develop within this ever-evolving context of genomic-driven medicine.

Incorporate the results of the MDT in the Electronic patient files with different prediction models and supporting data.

## Restructuring

Presentation and participation in MBC/MDT will also become more important within the current evolving landscape of reimbursement models. It is conceivable that organ-based tumour boards will review patient treatment plans with evidence-based consensus of care, with

costs including diagnostics such as imaging, surgery, systemic therapy, radiation therapy, palliative care, and other key components of care, while also educating patients on the costs of testing.

The interdisciplinary setting promoted by MBC/MDT leads to an environment to produce an organized evidence-based approach to cancer care. The knowledge and experience of MBC/MDT participants enhances education among participants and leads to enhanced individual participation in MBC/MDT. Nevertheless, remarkable differences are noted in the mandatory aspects of MDT in different geographic regions in the world (26).

Streamlining and the use of computerized clinical decision support systems (CCDSSs) are two major ways to restructure MDTMs. Streamlining is the process of selecting the patients who need to be discussed and in which type of MDTM. Using CCDSSs, patient data is automatically loaded into the minutes, and a guideline-based treatment proposal is generated. Still, the methods of streamlining should be further developed and introduced. Physicians still have doubts about the value of CCDSSs (10).

## Key messages

- Multidisciplinary team input in managing those diagnosed with breast cancer ensures the best options and treatment.
- Although the optimal management of breast cancer requires expertise of different disciplines and multidisciplinary meetings, it is not mandatory in many countries.
- Many patients presented at the MDT discussion have a change in management as a result of the discussion.
- To have the MDT discussion sustainable for future teleconferences in need of efficient technologies and optimal presenter preparation, streamlining, or clinical decision support systems might be of help.
- Multidisciplinary molecular tumour boards will become more important with increasing use of genomic technologies.

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**PART 5**  
**QUALITY CONTROL**

*Diagnosis and treatment*



# 12

## Imaging

*Hans Junkermann, Wolfgang Buchberger, Sylvia H. Heywang-Kobrunner, Alexander Munding, Carol Benn, and Sophia Zackrisson*

### Methods for assessment of breast symptoms and screening

#### Mammography

##### Imaging principle

Mammography is an X-ray examination of the breast. The image results from the differential absorption of low-energy X-rays by the components of breast tissue. Calcifications are the strongest absorbing structures. The absorption of the other structures (fibrous tissue, cysts, benign and malignant tumours) is determined by their water content. The lowest absorption is displayed by fatty tissue.

Digital mammography systems are now commonly used. Digital breast tomosynthesis has emerged during the last decades as a complement to, or as a replacement for, conventional digital mammography. Tomosynthesis is often described as 'pseudo three-dimensional mammography'. Basically, the X-ray tube moves in a limited arch (typically 11–50°) over the breast, acquiring multiple low-dose projection images, which are mathematically reconstructed into an image volume with around 50–70 slices, usually 1 mm thick, that can be viewed individually or in collapsed thicker 'slabs', scrolled through, or shown as a cine loop on a computer screen. The major advantage of tomosynthesis is that it reduces the effect of overlapping tissue (especially in dense breasts) making suspicious lesions more visible compared with two-dimensional mammography while simultaneously reducing the simulation of malignant lesions by superimposition of normal structures. All vendors have combined units capable of both mammography and tomosynthesis. To avoid the need for double acquisition of mammography and tomosynthesis, the generation of so-called synthetic mammograms from the tomosynthesis volume is of help for detecting asymmetries and comparing with prior mammograms.

Tomosynthesis is widely used in the USA both for screening and diagnostic purposes, while in Europe it has an established role in diagnostic work-up. A recent update of the ECIBC (European Commission Initiative on Breast Cancer) guidelines (1) now prefers tomosynthesis over digital mammography for women of average breast cancer risk, especially in women with dense breasts, but tomosynthesis has been introduced in only a few European screening programmes so far.

The most recent addition in X-ray imaging of the breast is contrast-enhanced mammography (2). Like contrast-enhanced MRI, the differentiation of lesions is based on the effects

of tumour angiogenesis, i.e. the development of blood vessel growth that is more limited in benign tumours, whereas malignant tumours exhibit intense blood vessel growth resulting in leaky vessels. These vessels allow contrast leakage into the interstitial space, which can be visualized. In contrast-enhanced mammography, an iodinated contrast agent is administered intravenously and low- and high-energy images are taken with the breast compressed (in any standard mammography view). These images are used to create a re-combined image that highlights contrast-enhancing regions. The dose is within the limits of regulatory agencies, and the procedure takes about 5–8 minutes. Kidney function as well as risk factors for iodine contrast side effects must be taken into account. According to initial, smaller studies, contrast-enhanced mammography seems to perform at a similar accuracy as contrast-enhanced breast MRI. Biopsies guided by contrast-enhanced images are available, and the development of contrast-enhanced tomosynthesis is emerging. The technique promises to be a cost- and time-saving alternative to contrast-enhanced MRI within the same range of indications, although larger prospective studies are needed to fully confirm this.

Artificial intelligence (AI) has matured to become a useful tool to support screen reading as a second reader with evidence from two recent prospective Swedish trials showing equal or even improved cancer detection, no significant increase in recalls or consensus discussions and hence a reduction of workload by 44–50% compared to standard double reading (3, 4). AI has already been implemented in some Scandinavian screening centres. AI is also expected to be introduced as a decision support in diagnostic imaging and is now being developed further for tomosynthesis and CEM.

### **Quality assurance**

Quality assurance (QA) programmes for mammography are highly developed and exist in many national adaptations. A driving force for their development and for their incorporation into national regulations was the importance of radiation protection in the use of a method applied to large numbers of healthy women. Typical examples for QA programmes are the European Guidelines of Quality Assurance in Mammography Screening and Diagnosis (5) and the ACR Manual for QA (6). QA systems for AI will be fundamental in the future in order to be prepared for version updates of the software, changes in the imaging platforms, etc.

### **Demands on the surroundings**

The mammography machine must be installed in a temperature-controlled environment (digital detectors are temperature sensitive). The room must prevent radiation from escaping into the surrounding environment where non-involved persons sojourn. Most mammography machines are operated in stationary units; for screening especially, they are also operated in mobile units (e.g. trucks or buses). This helps in reaching out to less densely populated regions. Mobile units, however, are costlier.

### **Investment and running cost**

Mammography machines cost upwards from €60,000. If mammography is used for the assessment of screen-detected lesions and in cases of symptomatic women, then magnification, tomosynthesis, and stereotactic-guided vacuum-assisted biopsy must be available. For reading mammograms, monitors with higher resolution than usually used in radiology



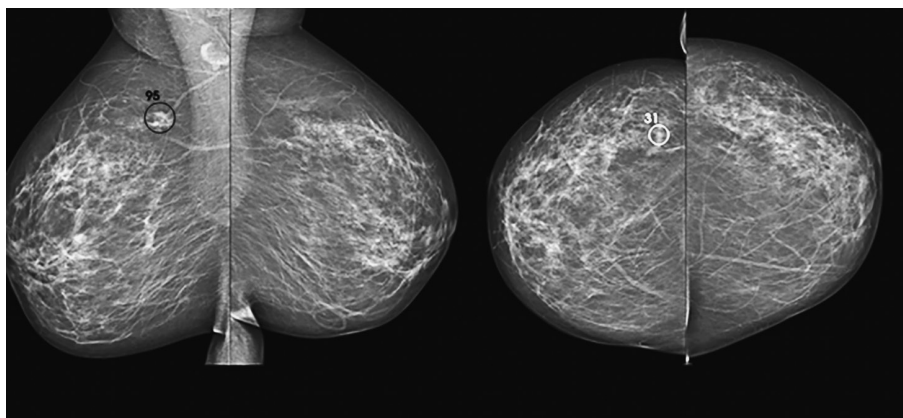


**Figure 12.1** Example of a small invasive cancer in the right breast that was not detected by two readers in a screening programme but clearly marked with a high risk score by a commercial software (Transpara 1.7, ScreenPoint Medical). The AI lesion score was highest in the mediolateral-oblique view (95, left circle) and this leads to a total cancer probability score of 10 for the whole examination, which is the highest score.

Image courtesy of Sophia Zackrisson, Lund University, Malmö, Sweden, on behalf of Region Skåne (<https://www.skane.se/>)

are necessary (two 4K or one 8K monitor). A workstation for reading mammograms costs around €30,000. Running costs for digital mammography encompass maintenance of the equipment and the cost for running and maintaining a PACS (picture archiving and communication system) to store and distribute the images.

### Demands on personnel

For the acquisition of mammograms, well-trained radiographers are needed who have sufficient regular practice. The positioning and compression of the breast has been described as an art. Existing guidelines should be considered in the performance of mammography. All efforts must be made to visualize as much of the breast tissue as possible (Figures 12.2, and 12.3) while avoiding unnecessary pain during the procedure. The performance of the radiographers should be systematically monitored as part of the QA programme. The examination time for the woman is about the same for a mammography as a tomosynthesis. One technician can perform up to 10 mammographic examinations per hour.

Reading of the mammograms should only be done by specially trained persons (usually radiologists, in UK also trained radiographers as one of two readers in screening) with sufficient regular practice. The European Guidelines as well as the ACR guidelines define minimum requirements for the reader (480–1000 cases per year) (5, 7). The European Guidelines also suggest a minimum of 5000 cases per year together with double reading of all cases in screening. Reading time is an issue, especially in screening. Using batch reading in screening, one reader needs about 30 s per case. A reading session usually should not last longer than 40 min, since it is not possible to maintain concentration continuously for a longer time. The time for reading tomosynthesis (including synthetic two-dimensional images) is about 50–100% longer, but is most probably shortened with experience and smart reading protocols,

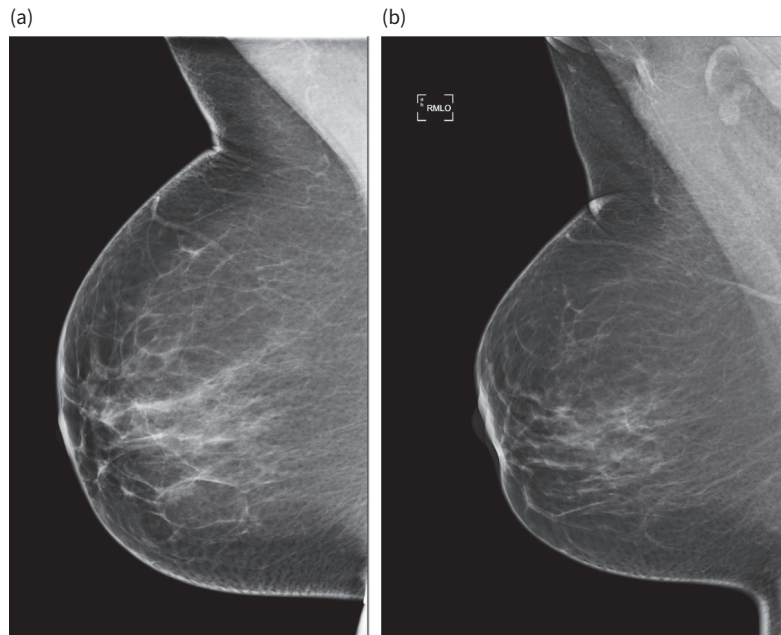


**Figure 12.2** (a) Inadequate positioning of mediolateral-oblique (MLO) view. The pectoral muscle is only marginally visible on the image, indicating that peripheral parts of the breast tissue are not imaged. (b) Adequate positioning of MLO view. The pectoral muscle is seen down to the nipple line. Peripheral parts of the breast are covered as demonstrated by the imaging of (benign) axillary lymph nodes.

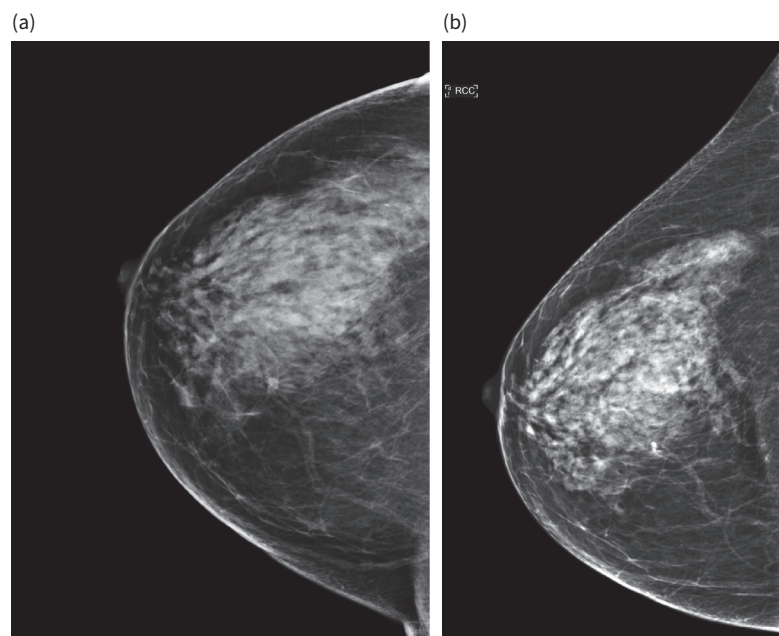


**Figure 12.3** (a) Inadequate positioning of the craniocaudal (CC) view. The mammilla is deviating laterally and the lateral part of the breast is not imaged. (b) Adequate positioning of the CC view. The mammilla is pointing centrally and the lateral part of the breast is included, containing some benign microcalcifications.

potentially involving AI. Reading time for tomosynthesis as short as 36 seconds in batch screen reading has been reported (8).

### Medical physicists

The technical quality control needs specially trained physicists or regular maintenance by qualified service personnel from the vendor of the equipment.

## Ultrasonography

### Imaging principle

Since its introduction in the 1950s, breast ultrasound has evolved significantly and is now an indispensable tool for the detection and staging of breast cancer and for guiding breast interventions.

The technical principle is the transmission of high-frequency sound waves into the tissue, which are absorbed, scattered, partially reflected, and received by the ultrasound probe. From the position of the reflecting interface and the propagation time and amplitude of the reflected sound wave, a two-dimensional greyscale image is calculated (B-mode, brightness mode). High contrast and spatial resolution are achieved by using high-frequency linear-array broad-bandwidth transducers, usually with a frequency range of 5– $\geq$ 12 MHz. Lower transducer frequencies are used for deeper lesions, and higher transducer frequencies are used for more superficial lesions.

Three-dimensional imaging can be achieved either by manually pivoting a two-dimensional linear transducer over a certain volume of the breast or by using matrix array transducers that electronically scan a three-dimensional volume. With a single pass of the ultrasound beam, a three-dimensional volumetric image and three perpendicular reconstructed planar sections—sagittal, transverse, and coronal—are displayed.

Automated breast ultrasound (ABUS) uses 6–15 MHz large transducer paddles, which are automatically moved over the whole breast under light compression. The images are reconstructed to produce a 3D examination of the breast. Comparative studies showed that ABUS has a similar diagnostic performance to handheld ultrasound (HHUS) in the detection and characterization of breast lesions (9). Its major advantages are less operator dependence and better reproducibility; disadvantages include the inability to assess the axilla and the absence of information regarding the vascularization and the elasticity of a lesion.

### Indications for ultrasound

Sonography was initially used only for the distinction between cysts and solid lesions. Simple cysts are correctly identified with an accuracy of nearly 100%. Complex cysts and clustered microcysts have a low probability of malignancy (0.8%) and require short-term imaging follow-up or occasionally ultrasound-guided fine-needle aspiration.

With more advanced ultrasound technique and increased experience, distinction between benign and malignant lesions became possible, allowing to avoid immediate histological clarification of solid lesions with a very low probability of malignancy. Ultrasound is frequently used for the assessment of palpable breast abnormalities. Approximately 10–15% of palpable carcinomas are occult on mammography but are detectable sonographically. On the

other hand, negative mammography and ultrasound in a palpable lesion exclude malignancy with 97–100% confidence. In symptomatic women of average cancer risk aged <30 years in whom the risk of malignancy is less than 1%, assessment can be done with ultrasound alone, provided it demonstrates a benign cause of the symptoms. Otherwise, further imaging with mammography, magnetic resonance imaging (MRI) (especially in high-risk women), and/or needle biopsy is recommended.

Another common indication for breast ultrasound is evaluation of abnormal findings on mammography, including masses, architectural distortions, or asymmetries. Ultrasound is also used for the assessment of MRI-detected abnormalities. These lesions are frequently occult on mammography and can be identified, in part, with second-look targeted ultrasound. A systematic overview demonstrated a wide variation between 22.6% and 82.1% (pooled average 57.5%) in the effectiveness of this procedure. Besides further lesion characterization, ultrasound can be used to guide core needle biopsy. Although mammographically occult multifocal or multicentric disease can be detected sonographically, ultrasound is inferior to MRI in preoperative local staging of breast cancer. It is the method of choice, however, for the assessment of axillary, supraclavicular, and internal mammary lymph nodes.

Because of its easy availability and real-time capacity, ultrasound is the primary technique for guiding interventional procedures. Most palpable lesions, as well as many lesions detected with mammography or MRI, can be biopsied under sonographic guidance. With a false-negative rate of 1.5–3% and a complication rate of less than 1%, automated 14-gauge core needle biopsy is a safe and accurate diagnostic procedure and is adequate for most ultrasound-guided biopsies. Although vacuum-assisted biopsy has lower underestimation rates in high-risk lesions such as atypical hyperplasia, it is a much more expensive and invasive procedure and should only be considered for microcalcifications or intraductal or intracystic lesions and very small masses (below 5 mm).

### **Qualitative demands and quality management**

Specifications on the technical equipment and QA, the required qualification of the examiner, and adequate documentation of the examination are summarized in various guidelines, e.g. in the ACR practice parameters or the EFSUMB guidelines (10, 11). Minimal technical requirements are linear-array and broad-bandwidth transducers operating a centre frequency of at least 12 MHz. Gain settings, focal zone selections, and field of view should be optimized to obtain high-quality images. Equipment performance should be monitored regularly in accordance with existing guidelines. Conspicuous findings should be documented and measured in two perpendicular planes, and the clock position and distance to the nipple should be indicated. The report should be written according to the BI-RADS classification scheme.

### **Budgetary impacts: investment in machinery, running costs, and expert time needed**

The price for a real-time handheld ultrasound unit suitable for breast ultrasound begins at around €40,000. The annual maintenance costs are 5–10% of the acquisition costs. The time required for hand-guided sonography of both breasts performed by specially trained physicians or technologists is 15–20 min, which significantly adds to the cost of the method. The acquisition time of an ABUS is 10–15 minutes, and the radiologist's reading time is three to nine minutes per examination.

## Magnetic resonance

### Imaging principle

MRI uses the magnetic properties of hydrogen nuclei to image tissues based on their differing hydrogen content and chemical bonds within the tissue.

With standard dynamic contrast-enhanced MRI, the complete breast is imaged at 2 mm slices using pixel sizes of approximately  $1 \times 1$  mm and a slice thickness of 1–2.5 mm. The complete volume (usually both breasts including the chest wall) is imaged once before contrast agent (i.e. gadolinium chelate) and three to five times after contrast medium every 1–2 min covering about 7–10 min after intravenous injection. Fat signal, which may interfere with the signal of enhancing tissue on postcontrast sequences is eliminated by use of subtraction series or by use of fat-suppressed pulse sequences or by both.

For diagnostic studies, the complete dynamic series is often supplemented by T2-weighted images (with information on water contents of the imaged tissues) and mostly by diffusion-weighted images, which promise additional information for lesion characterization.

To improve the cost-effectiveness of screening MRI studies, abbreviated protocols have been proposed with an imaging time of only 3 minutes. They consist of only one pre- and one early postcontrast sequence, the corresponding subtraction images, and the 3D reconstruction of the latter. Equivalence to full protocols has been reported in a limited number of studies. They are not yet generally recommended.

Patient information and consent are required before any MRI study. Contraindications of MRI (most cardiac pacemakers, intracranial vascular clips, neurostimulators, most cochlear implants, some intrauterine devices, some ferromagnetic foreign bodies or electronic devices etc.) and of contrast agent (pregnancy; known or suspected allergy to MR contrast agent, renal failure) must be observed.

### Indications for MRI

Contrast-enhanced MRI is the imaging modality with the highest sensitivity for the detection of invasive malignancy. For clinical applications, sensitivities of up to 99% and specificities of 89% have been reported for MR differentiation of non-calcified mammographic masses, and lower sensitivities of 87% and specificities of 81% have been reported for MR differentiation of mammographic microcalcifications.

Regarding the excellent reliability of the conventional triple diagnostic process MRI is not needed for the assessment of the majority of symptomatic breast disease. Considering the high sensitivity and negative predictive value in case of non-calcified lesions, the use of MRI for exclusion of malignancy may be justifiable to avoid biopsy for certain non-calcified lesions or special indications (multiple lesions, extensive scarring, and lesions difficult to target by percutaneous breast biopsy).

Systematic reviews have shown a significant gain of sensitivity by the added use of MRI in women at high risk with and without gene mutation. One RCT on 675 and 680 women at high risk confirms the significant gain in sensitivity and stage distribution (12). This has been confirmed by the 10-year results of a large German single-armed multicentre study on 4573 women (13).

### Qualitative demands and quality management

Both national and international quality recommendations exist for breast MRI. As previously mentioned, breast MRI can be adequately performed on breast MRI units operating at 1.5–3 T. In addition, a special-purpose breast coil is mandatory, and dedicated software is needed for image evaluation. The use of a contrast agent is considered mandatory for cancer detection or exclusion.

Most guidelines require sufficient experience with, and availability of, mammography, breast ultrasound, and breast interventional techniques (14). Furthermore, the availability of MRI-guided interventions is considered requisite for anyone performing breast MRI. For MR-guided breast biopsy, a dedicated breast biopsy coil with a corresponding targeting unit and MRI-compatible vacuum pump are needed. For most institutions MRI-guided intervention is provided by cooperation with specialized institutions possessing the equipment and expertise needed for this procedure.

Whereas technical prerequisites are fulfilled in most countries, remaining quality deficits most often concern correct identification and interpretation of motion artefacts and the diagnostic capabilities of the interpreting radiologist. Benchmarks for assessing the quality of MRI performance and results are highly desirable, but may need to vary depending on the indication. Initial attempts are under way, and these demonstrate the existing limits of 'screening MRI' concerning false-positive rate, short-term follow-up rate, biopsy rate, positive predictive value of biopsy and accuracy in cases with motion or other artefacts. Even though QA is most important for any screening procedure, an effective QA programme for MRI screening is, to our knowledge, not yet installed in any healthcare system.

### Budgetary impact: investment in machinery, running costs, expert time needed

Costs per breast MRI study include costs for approximately 20 min MRI scanner time, costs of MRI contrast agent and blood tests (to assess kidney function before application of contrast agent), as well as additional costs for the dedicated breast coil, special pulse sequences (if applied), and dedicated evaluation software (for quantitative measurements and possibly motion compensation). Overall, these costs exceed the costs of most other MRI studies and amount to three to five times the costs of a mammogram. Abbreviated protocols may allow for reducing MRI scanner time. If proven successful, moderate cost reduction may be possible.

Based on a first modelling of data from the FamRiskTrial MR screening of women at high familial risk, the authors concluded that MR screening of women at familial risk every 18 months can be cost-effective (15).

### Pre-therapeutic tissue marking

The purpose is to ensure the localization of a needle biopsied lesion in follow-up imaging and at surgery. The markers used are usually small devices (clips or coils), which are visible in different imaging modalities.



### **Presurgical marking**

This process is aimed at guiding the surgeon to the target area to facilitate a margin-free resection of the specimen. It is important that the distance between the marker and the margin of the lesion is minimal. As a quality measure it should be less than 1 cm in at least 90% of localization procedures.

### **Marking during neoadjuvant therapy**

The marking should be performed before therapy begins or as long as the shrinking lesion is still visible. Migration of the markers away from the insertion site immediately after deployment is possible.

### **Practical performance**

The devices used for marking are inserted into the tissue under image guidance through pre-loaded introducer needles. A post-biopsy mammogram is recommended to confirm the correct localization of the marker. When multiple lesions within the same breast are biopsied, markers of different shapes should be used.

### **Marking tools**

Conventional non-radioactive markers include clip markers, hookwires, and charcoal powder. Radioactive markers (colloidal human serum albumin labelled with radioactive technetium (radio-guided occult lesion localization ROLL) or radioactive iodine seed localization (RSL)) can be detected by the surgeon using a gamma probe. With the radioactive markers the detection is not limited by the depth of the radioactive source from the skin.

Modern non-radioactive wireless marking devices include magnetic steel seed markers, radar reflectors, radiofrequency identification (RFID) tags, and superparamagnetic iron oxide nanoparticles. These systems have three components: a target seed or tag, a handheld intraoperative probe, and a platform for display of measured parameters. These nonradioactive devices have limited detectability in the depth of the breast. Magnetic markers cause strong artefacts severely impeding MRI assessment and magnetic tools require nonferromagnetic surgical instruments. The magnetic field can interfere with electronic devices.

All new techniques of preoperative marking are similarly reliable compared to the older techniques with respect to placement control, intraoperative detection, and negative free margin rate (70 to 97%) (16).

Price, local availability, and practicability as well as previous experiences of the surgeon determine the preferred marking technique. Though symptoms from metal (mostly nickel) allergies are rare the implantation of nickel containing markers should be avoided in patients with a significant history of metal allergy.

## **Emerging and future imaging modalities**

### **Physical principles to differentiate benign from malignant tumours**

Breast cancer lesions present with a variety of different characteristics such as density, stiffness, electrical activity, ultrasound impedance, and necrosis pattern compared to normal

tissue. The various tissue resorption and scattering patterns of benign and malignant breast tissue have stimulated research on almost all parts of the electromagnetic and mechanical wave spectrum.

### **Signal detection used by new breast imaging candidates**

Absorption, transmission, reflection, emission, and time of flight of energy are the cardinal principles that allow signal detection. The spectrum of energy is further assessed by spectroscopy. For photons and mechanical ultrasound waves, the time to pass through tissue is higher in the presence of scattering than without. The phase shift of waves travelling through scattering tissues can be expressed as phase contrast when compared with normal tissue and be used to enhance the basic signals. Optical imaging separates photons by their time of flight through non-scattering or scattering tissues. Further, phase contrast may enhance edges of tissue with ultrasound and X-ray imaging.

### **Multiparametric, multispectral, hybrid, and fusion technology**

These terms overlap to some degree and are not used consistently in the literature. Multiparametric imaging combines the various outcomes of one basic technology. One example is modern ultrasound computed tomography that co-registrates and combines the sound information generated by reflection, attenuation, and speed of sound within one ultrasound system to an integrated image.

Multispectral mammographic techniques fuse the results of images that have been generated at different energy levels. The final synthesized image of dual-energy spectral mammography brings together high-resolution and high-spectral information to an image that yields more information than any of the source images.

Hybrid technologies are the result of two parental technologies that are combined together, but comprise still the recognizable elements of each parent technology. Examples are combining mammography and ultrasound or digital breast tomosynthesis and microwave nearfield radar imaging.

Fusion technology synthesizes two or more different technologies to something uniquely new. For example, fusion algorithms merge simultaneously recorded absorption (conventional digital mammography), differential phase contrast (phase contrast mammography), and small-angle scattering signals (grating-based X-ray dark-field) that are combined by a single image. Higher edge contrast and indirect information about very small calcifications are the promises of this approach that override the information from the basic mammography.

### **Evolving cutting edge technologies**

Evolving cutting edge technologies have generated studies that are based on selected case series and have been prone to selection bias. A thorough evaluation has to be performed before new techniques are rolled out as standard into the whole population (see Box 12.1).

Abbreviated MRI as a screening tool is an encouraging candidate and offers higher detection rates than any other approach. In case of suspicious findings, an additional T2-weighted sequence could be added immediately.

Photoacoustic imaging or optoacoustic imaging applies pulsed laser light, and subsequent thermoelastic conversion of absorbed light to ultrasound. The near-infrared laser impulses are mainly absorbed by haemoglobin in vessels. A short heat-induced expansion and



### Box 12.1 Basic answers needed before new imaging modalities can be transferred into practical health policies

- Will the new method transfer a substantial benefit to the whole population or diseased single individuals compared to older standards regarding better detection or characterization of breast cancer?
- Do negative collateral effects exist that may compromise the intended benefit?
- Can the new method be implemented and controlled at reasonable costs and adequate quality standards?

contraction within nanoseconds reaches frequencies of ultrasound. The generated travelling ultrasound waves can be visualized by diagnostic ultrasound.

Dedicated breast computed tomography using total quantum counting promises an optimized detection and characterization of calcified ductal carcinoma *in situ*, and, if combined with contrast media, enhanced detection of masses compared to mammography.

Currently, integration of artificial intelligence (AI) is used to optimize data acquisition and performance of established and evolving technologies. Total photon counting will be the future ultimate weapon of X-ray (e.g. based on the Hall effect, dark-field X-ray), nuclear, and light-based techniques. Further, ultrasound and bubble imaging, magnetism, attenuation, microwave, electrical impedance, spectroscopy, and fusion of these modalities will benefit from dedicated AI tools to enhance detector readout and applications for AI diagnosis (17).

## Best practice: minimum and ideal requirements

### For assessment of symptoms

#### Introduction

The aim of the diagnostic assessment clinic for a patient presenting with breast symptoms is to provide a definite diagnosis of malignant or benign breast disease or physiological breast change. This is achieved by use of the multidisciplinary triple diagnostic method: (a) clinical examination; (b) imaging: ultrasound  $\pm$  mammography/tomosynthesis; (c) needle biopsy where indicated. The tests used in an individual patient will be determined by the presenting symptoms, the clinical findings (see Box 12.2), and the age of the patient. The use of the triple diagnostic method enables a diagnosis to be established in nearly all patients, and diagnostic excision is rarely required. The published rate of delayed diagnosis of breast cancer in symptomatic women following triple assessment is 0.2%. The diagnostic clinic should be arranged so that radiological facilities are integrated with or very close to the clinic and organized so that all necessary tests are carried out during the same clinical visit.

When referring the doctor should ensure that all relevant clinical information is provided to the clinic including the site and duration of symptoms and signs. This is best achieved using a standard referral document.

### Box 12.2 Symptoms to refer patient to the diagnostic clinic

- Lump, lumpiness, change in texture;
- Progressive change in breast size with signs of oedema;
- Skin distortion, dimpling;
- Nipple symptoms:
  - Unilateral blood-stained or serous nipple discharge;
  - Nipple eczema, nipple change, retraction/distortion;
- Breast pain: one-sided, persistent following initial treatment;
- Axillary lump.

#### (a) Clinical assessment

The clinical assessment should be carried out before imaging and should document the nature, site, and duration of symptoms and record the level of suspicion for malignancy. The clinical assessment should be carried out by a suitably trained member of the multidisciplinary team (radiologist, surgeon, breast clinician, or breast care nurse). The clinical information should be available to the staff conducting the imaging assessment.

#### (b) Imaging assessment (ultrasound and mammography)

Requirements:

- High-frequency ultrasound ( $\geq 12$  MHz);
- Full-field digital mammography with facilities for additional views (fine focus magnification, tomosynthesis), and X-ray-guided biopsy;
- Equipment for image-guided biopsy including core biopsy, vacuum-assisted needle biopsy. Fine-needle aspiration cytology has been largely replaced by core biopsy. If still used in certain situations (lymph nodes, cysts) sufficient expertise for the interpretation must be available;
- Breast MRI or contrast-enhanced mammography are not required for the initial diagnostic assessment of patients with symptoms except in special cases (see next).

#### (c) Needle biopsy

The clinical and imaging work-up should be completed prior to needle biopsy, and biopsy procedures should be carried out under imaging guidance in order to achieve optimum accuracy. The most commonly performed procedure in the symptomatic clinic is ultrasound-guided 14G core biopsy. Fine-needle cytology may also be helpful in assessing axillary lymph nodes. A clear local protocol for needle biopsy of breast lesions should be available based on clinical and imaging features and age. For example, a localized lump in a woman aged  $<25$  years with benign clinical features and ultrasound appearances of a fibroadenoma may not require biopsy.

### Use of imaging

Ultrasound should be performed for all patients with a lump or localized change of texture found on examination and should be the sole imaging required for most women aged

<40 years as well as women who are pregnant or lactating. The ultrasound examination should be targeted to the area of the patient's symptoms or signs and should cover the whole breast and axillary lymph nodes in patients with suspected malignancy.

Mammography/tomosynthesis should consist of mediolateral oblique and craniocaudal views of each breast and is used in the primary investigation of women aged  $\geq 40$  years (unless pregnant or lactating), although the lower age limit for X-rays may differ between settings. Mammography should also be used in younger women with suspicious clinical findings and should be considered in women with indeterminate lesions in whom ultrasound is normal as well as after malignancy has been confirmed. The level of suspicion for malignancy on imaging should be recorded on a standard scale (e.g. European imaging classification, BI-RADS lexicon (5, 18)). Further specialized mammography views, including tomosynthesis and magnification views are carried out following standard views for further mammographic assessment of equivocal and suspicious mammographic features and for all cases of malignancy.

MRI is the method of choice for work-up of pathologic nipple discharge (19). It is indicated in women with cancer of unknown primary (CUP) syndrome if conventional imaging is negative, and for improved differentiation of recurrence versus scarring in women after breast conservation or in women with silicone implant after breast cancer if conventional imaging is inconclusive. Considering the high sensitivity and negative predictive value in non-calcified lesions the use of MRI may be justifiable in rare cases to avoid biopsy in lesions not easily amenable to percutaneous biopsy, if the lesions do not show contrast enhancement at all and if the result of biopsy is inconclusive.

Preoperative MRI is indicated in cases with a newly detected breast cancer, if assessment of the breasts by mammography and/or ultrasound is impaired and in cases with increased risk of breast cancer or multicentric disease (20). This includes women with dense breast tissue, younger women with breast cancer; women with proven lobular breast cancer or proven or suspected multifocality or multicentricity.

MRI has advantages in the evaluation of the treatment response under neoadjuvant systemic therapy.

### Outcome and quality reporting of diagnostic assessment

Following assessment, patients should be clearly informed of the findings. Patients with normal, benign, or physiological changes are reassured. Patients who have undergone needle biopsy are provided with support and an appointment to discuss results. The assessment findings and results of all women who undergo needle biopsy should be discussed in a multidisciplinary meeting attended by radiologist, pathologist, surgeon, and breast care nurse to decide on further management (see Box 12.3).

#### Box 12.3 Key requirements for achieving high-quality assessment

1. Effective multidisciplinary working
2. High-quality diagnostic equipment
3. Specialist training for all disciplines
4. Audit for practice against key standards

The report on the results of imaging studies must be clear, exact, and understandable. To facilitate communication, standardized scales have been developed. Of these, the BI-RADS categories of the ACR have gained worldwide acceptance. Each imaging result is assigned to a category directly relating to further action that should be taken. The signs leading to each category are based on evidence and described in the BI-RADS lexicon (18).

## **Diagnosing symptomatic breast disease in low- and middle-income countries**

Also in low- and medium-income countries (LMICs), the aim is to offer all women with breast symptoms fast and competent diagnosis. The barriers to this are manifold and differ from country to country or even region to region. Acceptance of a service might be hindered by cultural beliefs, geographically difficult access including cost of travel and fees for the service. The establishment of a quality service can be hampered by a lack of trained specialists in rural areas, lacking funds for the high-quality equipment necessary and general instability of the infrastructure.

To tackle the task efficiently first an analysis of the problems preventing fast and competent diagnosis in the individual region is necessary (21). Administrative and governmental structures should be involved early. The institution of education and awareness programmes should include traditional structures if these are consulted by the women first, rather than scientifically based medicine. Where mammography and ultrasound are accessible for symptomatic women, issues such as the monetary cost of diagnosis and treatment may hinder the acceptance of the service. If travel distances are a major issue, it seems reasonable to deviate from the principle of complete imaging at the first visit and provide an accessible, perhaps mobile service using ultrasound together with needle biopsy in an outreach clinic. More expensive and less mobile mammography is then only secondarily applied in the treatment centre after malignancy has been established. Exchanging images over the internet in real-time is an option that is being tested in sparsely inhabited areas in sub-Saharan Africa where experts are only available in maybe difficult-to-reach larger settlements. Providing decision support by AI for different imaging modalities in LMICs is an attractive prospect, but needs to be planned and implemented in a structural way, not to just gain industry or high-income countries.

## **For screening**

Despite some pronounced critical discussion of the harm: benefit ratio, the majority of international experts judge that mammography screening for breast cancer fulfils the criteria for an effective screening programme. Mammography is the method of choice for women of average breast cancer risk. The European Commission Initiative on Breast Cancer (ECIBC) guidelines now prefer tomosynthesis over digital mammography for the screening of women of average breast cancer risk, especially in women with dense breasts (22).

The age group that benefits most is women aged 50–70 years with a mortality reduction of about 40% for participants (23). In view of the rising age at death, especially in high-income countries, the extension of mammography screening to 75 years is considered appropriate by

many experts and governmental bodies. The extension to the lower age range between 40 and 50 years of age has been more equivocal, but is supported now for the age range 45–49 by the ECIBC. The US Preventive Services Task Force recommends now biannual screening from 40 to 75 years (24).

To maintain a positive balance between the harm and benefit of a screening programme, the screening examination should be performed in a strictly quality-assured surrounding. Descriptions of all aspects of QA of an organized screening programme are available from the ECIBC (22), whereas the American College of Radiology Best Practice Guidelines address QA in a more open system (25). The aspects detailed in the following sections need to be considered for an effective screening programme.

### **Reach the target group as completely as possible**

An invitation model allows the best coverage of the whole target group. This requires suitable registers.

### **Maximize the early detection potential of the method used for screening**

Screening for early cancers demands that the methods used are brought to their highest level of performance in order to detect as many cancers in a stage, where effective treatment can be applied without maximum treatment intensity. In mammography screening, independent double reading of the images improves the sensitivity of the method by about 10% and is recommended in the European Guidelines.

### **Minimize inherent negative consequences of the screening programme**

Any screening programme has adverse effects, since no method of detection has complete sensitivity and, especially important in the screening situation, specificity. This leads to additional work-up for ambiguous (false-positive) lesions, which puts emotional and physical strain on healthy participants. To reduce the false positives, the decision to assess a lesion should be made by readers with a high level of experience (the European Guidelines demand 5000 readings per year). Regular feedback on the achieved sensitivity and specificity is necessary to allow readers to adjust their individual working point. To reduce the emotional strain until clarification of suspicious lesions, their assessment should be offered in a fast, but not overly rushed, structured process by experienced personnel.

The most serious adverse effect of any screening programme is that disease is detected and treated that may never have surfaced and may never have become a health problem if it had not been detected in the screening programme (overdiagnosis). In mammography screening, this may not only refer to some of the *in-situ* cancers that would be treated with local measures (surgery and irradiation) alone, but also to some invasive carcinomas that would be treated with aggressive or longstanding systemic treatment, because we are not able to determine which individual tumour will progress to endanger health during the remaining lifetime of the patient. Reliable estimates of the amount of overdiagnosis are extremely difficult to obtain outside of randomized studies with long-term follow-up and no screening of the control groups, which is the case in only two trials (Malmö and Canada, where the Canadian trials are flawed by mistakes in randomization (26). Long-term follow-up in the Malmö trial resulted in an estimate of 10% overdiagnosis in women invited to screening, 20% among actual attenders (27). Other estimates are based on modelling, and are, therefore, less reliable. Overdiagnosis, however, must be expected for all methods allowing earlier detection effectively.

### **Foster participation of the target group, while respecting an individual's right to informed decision-making**

A screening programme will only be implemented if there is broad consensus in society that it is justified considering the harm: benefit ratio. An individual woman, however, may judge harms and benefits differently. It is challenging to inform women, in a balanced way, about harms and benefits, so that they can make their individual informed decision about participation.

### **Provide adequate resources not only for the screening process but also for the consequential assessment of screen-detected lesions and the treatment of the detected tumours**

When a screening programme starts, a considerable proportion of women will have a suspicious mammogram. The majority of these will be benign after additional assessment.

Many prevalent cases will be detected in the first round. The European Guidelines expect a threefold detection of cancers over background. Since about half of all breast cancers are detected in the 50–69-year age group, and half of this target population will be invited every other year, between 12.5% (at 50% participation) and 19% (at 75% participation) of additional cancer treatments must be provided for in the introductory phase. This will level out in the following years, but additional treatments will be required for a long time, since the compensatory decrease will only appear after the women reach the upper age limit of the programme. In addition, some overdiagnosis must be reasonably expected.

The effect of a breast cancer screening programme cannot be evaluated at an individual level since the heterogeneity of breast cancer biology does not allow assessing the effect of early detection in an individual case. The effectiveness of a screening programme can only be evaluated epidemiologically with a view of the whole target group. This is the only way to ensure maximal effect for the individual participant. To maintain a positive balance between positive and adverse effects the highest reasonably possible level of evidence should be sought before introducing changes into an established effective screening programme.

### **Cost-effectiveness**

For developed high-income countries, mammography screening can be considered cost-effective. Experience shows that such a programme also promotes the quality of the diagnostic process for women who present with or without symptoms outside of the programme.

### **Personalized breast cancer screening**

#### *Ultrasound and MRI as additional methods in dense breasts*

The sensitivity of mammography is highly dependent on the density of the breast tissue. Data from various studies suggest that the addition of handheld ultrasound screening to mammography in women with dense breast increases cancer detection rates by 2.3–4.6 per 1000 (depending on the basic breast cancer risk) at the expense of higher recall rates, much higher biopsy and short-term follow-up rates and lower positive predictive values (28). The positive predictive value of a biopsy recommendation after full diagnostic work-up has been shown to be 22.6% for mammography, 8.9% for ultrasound, and 11.2% for combined mammography and ultrasound. Screening ultrasound with automated whole breast units yielded

similar results to screening with handheld ultrasound. Because of the increased recall rates, and especially the biopsy rates as well as the multifold expert time, additional ultrasound is currently not recommended in routine screening of women at normal risk for breast cancer. Based on the study designs, none of the existing studies can provide sufficient evidence for assessing the effect of additional ultrasound on breast cancer mortality.

In dense breast tissue MRI is known to achieve the strongest increase of sensitivity compared to mammography alone. Insufficient data, however, exist supporting MRI screening of women (at intermediate or low risk) with dense breasts. So far, only the DENSE-Trial (29) has an appropriate design that would enable assessing the effect of MRI screening on breast cancer mortality in the future.

To date, biopsy rates of 6–7% and rates of early recall of 6–7% in the first round are too high to recommend for systematic MR screening of lower risk groups. Even improved rates of 2.5–3% recalls and 2.5–3% early follow-up recommendations, as reported for follow-up rounds, remain critically high for screening of larger parts of the population. Since a significant proportion of MR-only detected tumours (>50%) in low-risk population prove to be low grade (G1), MR detection may also imply a significant risk of overdiagnosis. Finally, potential side effects from systematic application of contrast agents have to be considered. These risks are at least comparable to (or higher than) risks expected from radiation by mammography.

Compared to the high-risk group, a lower benefit of MRI concerning survival is probable, since fast-growing G3-tumours, which make up >50% of the tumours of *BRCA*-positive women, are by far less frequent among women at low risk (approximately 5%) (13).

To date, it still remains unclear whether a balance of benefits versus harms can be achieved that will justify recommending MRI for screening women with (very) dense tissue outside of the high-risk group.

### *Risk-adapted screening*

In women at very high risk and in *BRCA1* (and *BRCA2*) carriers in particular several factors occur, which require a different type of screening than for women at low risk: Due to the young age of onset, the very high proportion of fast-growing tumours and of tumours without microcalcifications, the higher proportion of dense breast tissue and the lower sensitivity of mammography, usual mammography screening has proven insufficient.

Instead, most industrialized countries have installed special programmes for women at genetic risk and high risk. For these women intensified surveillance using MRI and mammography is recommended.

The strongest increase of sensitivity regarding MRI vs. mammography has been observed for women at high risk, from 53–55% (mammography) to 89–90% (13, 30). MRI and mammography proved complementary, since mammography, too, increased the sensitivity from 84.4% (MRI only) to 94.1% (MRI + mammography). This contribution by mammography was statistically significant for women aged >50 years. In women <40 years, mammography contributed significantly to the detection of malignancy in *BRCA2* mutation carriers (with 30% only-mammography-detected cancers), whereas no additional cancers were detected by mammography in *BRCA1* mutation carriers.

Data concerning mortality reduction are sparse for the high-risk group (30). The high detection rates and low number of late-stage cancers in follow-up screening rounds of women at high risk examined by MRI make an effect on mortality probable.



Disadvantages of MRI concern potential overdiagnoses (which may occur with the high rates of reported G1 invasive cancers and low-grade DCIS) and high false-positive rates, high rates of biopsies, and early follow-up recommendations.

For women at high risk advantages are considered internationally to clearly outweigh potential disadvantages. Thresholds for classifying high risk differ between countries and range from 20% lifetime risk in the US to 30% lifetime risk in most European countries.

Data on the use of MRI for screening women at intermediate risk (>15% lifetime risk) are still limited. So far one RCT exists, which will after adequate follow-up in the future help analyse effects on mortality reduction. Advantages and disadvantages are the same as for the high-risk group. The balance, however, gets less positive with decreasing risk of breast cancer and the much lower proportion of G3-cancers in these women (31).

To date, MRI screening at intermediate risk remains under investigation for both women with very dense breast tissue (29), for status after diagnosis of ADH or LCIS and for status after breast cancer (32, 33).

The benefit of detection at earlier stages (as proven for women at high risk) has to be weighed against the costs for the increased number of histopathological assessments, the high costs of MR-guided biopsies, and costs for MR-guided wire-marking and diagnostic surgery in those cases where MR-guided vacuum-assisted breast biopsy is not available, not reimbursed, or not possible. Furthermore costs for a yet unknown rate of overdiagnoses may need to be considered, especially for MR screening beyond high risk.

Outside of the high-risk population, data are insufficient for recommending MRI screening. Thus, no recommendation for MRI screening exists yet for women at intermediate risk.

### **Screening in low- and middle-income countries**

For lower- and middle-income countries, other health problems may be of greater importance. Concerns as to rising incidences of breast carcinoma in lower-middle-income countries, however, have resulted in a new look at cancer screening programmes. Clinical breast examination has been reevaluated with inconclusive results. Before the introduction of a screening programme makes sense, the healthcare system must be able to offer effective and affordable treatment of symptomatic breast cancer. An attempt to improve breast health by early detection must be embedded in a holistic approach, considering societal aspects as well as the attitude of the medical profession. Mammography screening still is the only scientifically based screening method for women of average risk. The Canadian randomized studies that had claimed that clinical breast examination could be equivalent have recently been proven to have had mistakes in the randomization process (26). Modern information technology and AI may help to overcome the obstacles of distance and the shortage of expertise.

## **Overview of utility and expenditure for imaging and needle biopsies**

See Tables 12.1–12.4.



**Table 12.1** Comparative utility of imaging methods according to tasks

| Method     | Symptomatic disease | Screening average risk | Screening high risk | Assessment of detected lesions |
|------------|---------------------|------------------------|---------------------|--------------------------------|
| Mammogram  | +++                 | +++                    | ++                  | +++                            |
| Tomogram   | +++                 | ++                     | –                   | ++                             |
| Ultrasound | +++                 | –                      | –                   | +++                            |
| MRI        | +                   | –                      | +++                 | +                              |

MRI, magnetic resonance imaging

+++, essential; ++, useful; +, not mandatory; –, no role.

**Table 12.2** Comparative utility of image-guided needle biopsy methods according to tasks

| Method                        | Symptomatic disease | Assessment of detected lesions (average risk screening) | Assessment of detected lesions (high-risk screening) |
|-------------------------------|---------------------|---------------------------------------------------------|------------------------------------------------------|
| Ultrasound-guided core biopsy | +++                 | +++                                                     | +++                                                  |
| Fine-needle aspiration        | +                   | +                                                       | +                                                    |
| Mammogram-guided VAB          | +                   | +++                                                     | +++                                                  |
| MRI-guided VAB                | +                   | –                                                       | +++                                                  |

MRI, magnetic resonance imaging; VAB, vacuum-assisted biopsy.

+++, essential; ++, useful; +, not mandatory; –, no role.

**Table 12.3** Comparative expenditure for imaging methods

| Method     | Equipment, installation, and running costs | Time needed of well-trained personnel |
|------------|--------------------------------------------|---------------------------------------|
| Mammogram  | ++                                         | +                                     |
| Tomogram   | ++                                         | +(+)                                  |
| Ultrasound | +                                          | +++                                   |
| MRI        | +++                                        | ++                                    |

MRI, magnetic resonance imaging.

+++, high; ++, moderate; +, low.

**Table 12.4** Comparative expenditure for image-guided needle biopsies

| Method                        | Equipment, installation, and running costs | Time needed of well-trained personnel |
|-------------------------------|--------------------------------------------|---------------------------------------|
| Ultrasound-guided core biopsy | +                                          | +                                     |
| Fine-needle aspiration        | (+)                                        | (+) <sup>a</sup>                      |
| Mammogram-guided VAB          | ++                                         | ++                                    |
| MRI-guided VAB                | +++                                        | +++                                   |

MRI, magnetic resonance imaging; VAB, vacuum-assisted biopsy.

+++, high; ++, moderate; +, low; (+), negligible.

<sup>a</sup> Exceptional expertise required.

## Key messages

- Triple assessment (clinical examination, imaging, ultrasound ± mammography, and needle biopsy, where indicated) is the method of choice for women with significant breast symptoms.
- Working in multidisciplinary teams is highly recommended for diagnosis and treatment of women with breast diseases.
- Screening should be offered in a fully quality-assured environment in order to optimize the benefit/harm ratio.
- In developing countries, providing adequate care for women with symptomatic disease should have priority over screening, which may not cost-efficient under these conditions.
- The quality criteria for mammography should be systematically monitored in a quality-assured system.
- AI as a second reader in mammography screening is emerging as a feasible and robust tool.
- The role of ultrasound is mainly in the assessment of symptomatic disease and mammography-detected abnormalities and the guidance of needle biopsies.
- The role of MRI in the discrimination between benign and malignant disease is limited. It has an established role in high-risk screening and is useful in preoperative evaluation, follow-up under primary systemic therapy and special situations.
- The use of contrast-enhanced mammography as a time- and cost-effective alternative to MRI is under investigation.
- New methods must be vigorously tested to determine whether they will be able to improve the already high accuracy of existing diagnostics from a patient and an economic viewpoint.

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# 13

## Pathology

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### Introduction

Breast cancer has received remarkable attention at the global level, and as a result, substantial progress has been made over the past several years in the diagnosis and management of this disease. Minimally invasive sampling procedures such as fine-needle aspiration biopsy and core needle biopsy have almost replaced open surgical biopsy. Advances in molecular diagnostics and targeted therapies have opened more effective options for individualized breast cancer therapy. Pathologists have been central in the development, validation, implementation, and into assessing the appropriateness of providing diagnostic and predictive/prognostic information. Throughout the years, pathologists have evolved from being a morphologist into becoming clinicians/scientists with an in-depth understanding of integrated breast cancer care

### Definition of breast pathology

Breast pathology, defined as the study of breast disease, is the foundation of breast healthcare. There is no doubt that the quality of breast healthcare and the ultimate patient outcomes are directly related to the quality of breast pathology diagnosis. Without accurate diagnostic and predictive information, clinicians are misled and patients suffer from the wrong therapy and consequent adverse clinical outcomes. Therefore, measures should be taken to reduce barriers to providing optimal pathology service around the world.

### The contributions of pathologists in multidisciplinary breast health/cancer care

Advances in science and technology, molecular characterization of tumours, and participation of pathologists in the process of the delivery of integrated breast healthcare have provided significant change in the role of pathologists. As members of a multidisciplinary team, pathologists have become responsible for providing the most up-to-date morphological and biological information that is required for immediate therapy and long-term follow-up management of their patients. Currently, in a multidisciplinary breast health centre with patient-focused strategies, pathologists are an integral part of the system (Figure 13.1).

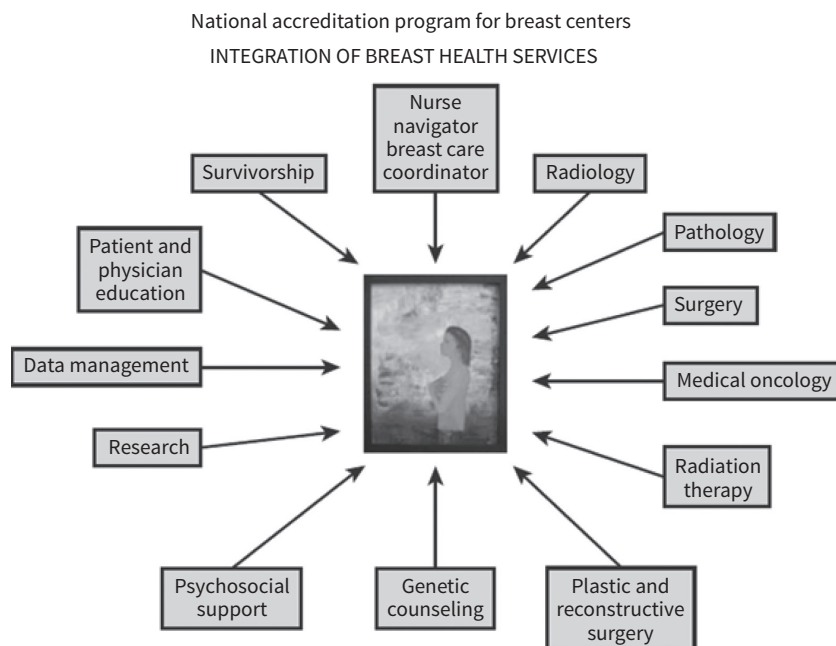


**Figure 13.1** Integration of breast health services.

Source: data from Masood S., 'Patient Safety in Breast Pathology'. In: Dabbs D, ed. Breast Pathology. pp. 57- Philadelphia, PA: Copyright © Elsevier 2012.

Pathologists are expected to establish a diagnosis, classify a neoplasm, differentiate between a primary versus a metastatic tumour, predict response to therapy, provide prognosis, and compose a comprehensive pathology report (Box 13.1).

For many years, the abovementioned roles were based on morphologic examination of the surgically excised samples. However, the introduction of minimally invasive diagnostic sampling procedures such as fine-needle aspiration biopsy and core needle biopsy and the availability of molecular targeted therapy have created a different challenge for practising breast pathologists. It has also been realized that breast cancer is not a single disease, and there

### Box 13.1 The changing role of pathologists in multidisciplinary breast care

- Establish a diagnosis
- Classify a neoplasm
- Differentiate between a primary versus a metastatic tumour
- Predict response to therapy
- Provide prognostic information
- Provide a diagnosis
- Compose a comprehensive breast pathology report
- Identifying potential treatments through validated and accessible biomarkers using current standard technologies
- Be involved in the evaluation and integration of novel technologies like AI.

are different subtypes of breast cancer with various morphological appearances, biology, responses to therapy, and outcome (Figures 13.2 and 13.3).

Pathologists are expected to identify novel biological markers for diagnosis and/or determination of prognosis of breast cancer patients, and pathologists continue to assist

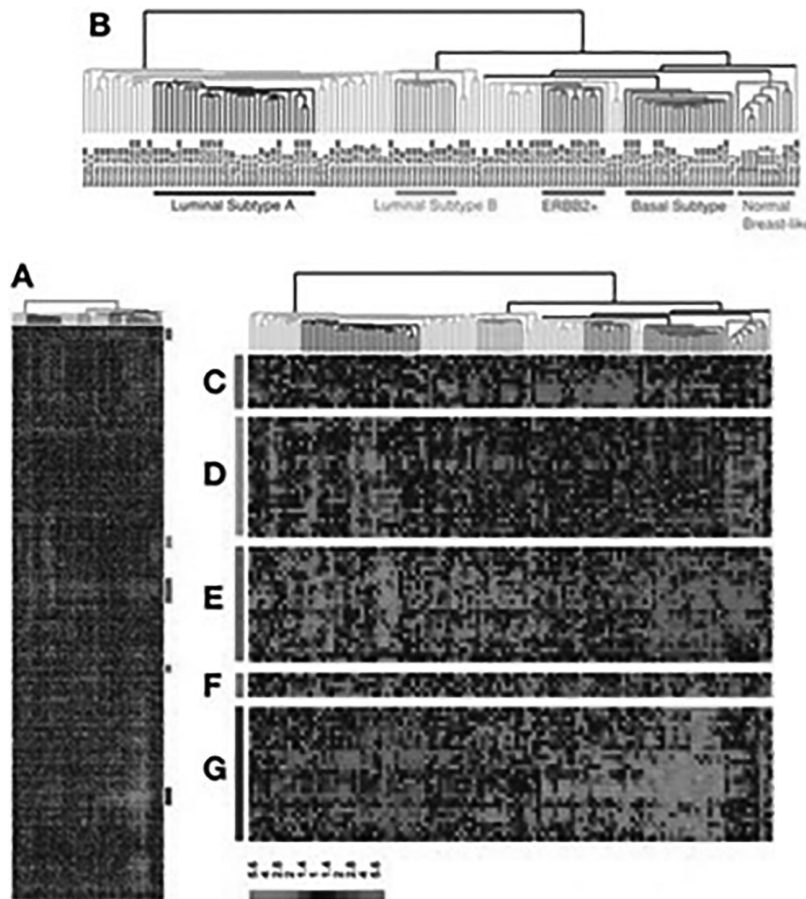


**Figure 13.2** Hierarchical clustering of 115 tumour tissues and seven non-malignant tissues by using the intrinsic gene set.

(A) A scaled-down representation of the entire cluster of 540 genes and 122 tissue samples based on similarities in gene expression.

(B) Experimental dendrogram showing the clustering of the tumours into five subgroups. Branches corresponding to tumours with low correlation to any subtype are shown in grey.

(C) Gene cluster showing the ERBB2 oncogene and other co-expressed genes.

(D) Gene cluster associated with luminal subtype B.

(E) Gene cluster associated with the basal subtype.

(F) A gene cluster relevant for the normal breast-like group.

(G) Cluster of genes including the ER (ESR1) highly expressed in luminal subtype A tumours.

Scale bar represents fold change for any given gene relative to the median level of expression across all samples.

*Reproduced with permission from Sorlie T. 'Molecular classification of breast tumours: toward improved diagnostics and treatments'. Methods in Molecular Biology. Volume 360. pp. 91–114. Copyright © 2007. Springer Nature. This figure is not covered by the Creative Commons licence terms of this publication. For permission to reuse please contact the rights holder.*



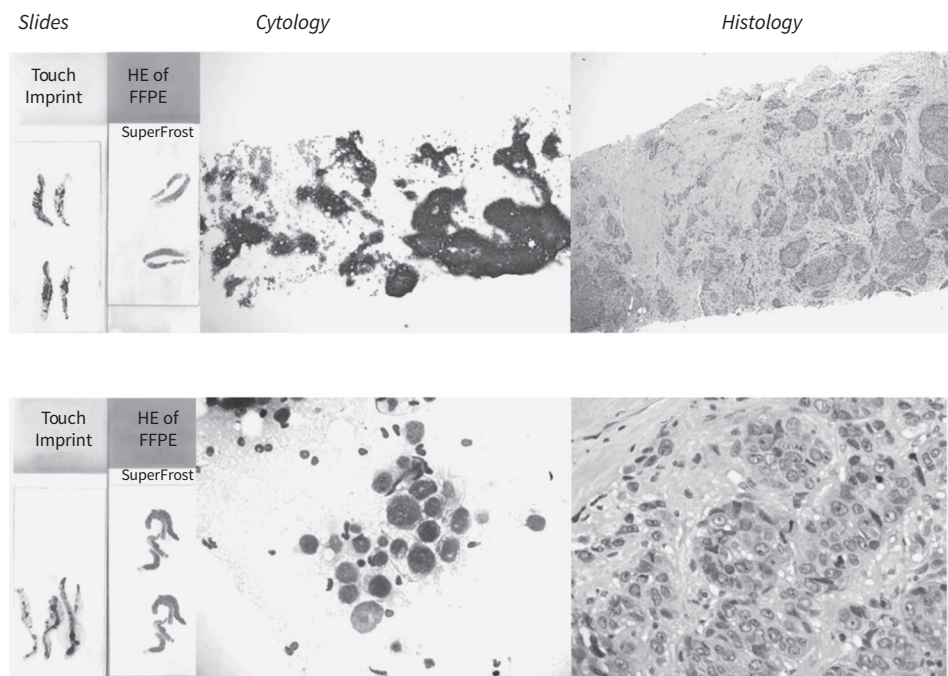


**Figure 13.3** Left side: Touch imprint slides aside final histology of formalin-fixed, paraffin-embedded breast carcinomas (HE). Middle: high cellularity and obvious atypia (Diff Quik); both are C5. Right side: HE of core needle biopsies showing breast carcinomas.

Reproduced courtesy of Dr Peter Regitnig.

in recognizing changes at the DNA level and consequent changes in gene expression involved in the multistep process of oncogenes in breast cancer. This is currently exemplified by technologies such as immunohistochemistry, *in-situ* hybridization, quantitative polymerase chain reaction, oligonucleotide cDNA microarray, Next-Generation Sequencing and others which permit localization of hormone receptors, oncogenes, tumour suppressor genes, and many other gene products at the cellular and molecular levels, as well as genetic profiling. The traditional prognostic factors such as tumour size, type, grade, and the status of lymph node metastasis have played an important role in selections of patients for systemic chemotherapy. However, within the good-prognostic groups such as axillary node-negative cases, there are differences in behaviours. Therefore, it is necessary to separate defined prognostic markers into low- and high-risk groups in terms of the probability of recurrence, and to offer adjuvant chemotherapy only to those patients at high risk. Novel prognostic biomarkers such as tumour-infiltrating lymphocytes are emerging as critical in certain subtypes of breast cancer, such as triple-negative breast cancer (TNBC). Prognostic biomarkers are used to identify high-risk patients who have such an excellent outcome that the benefit of systemic therapy does not outweigh the adverse effects of the systemic treatment. Attempts have also been made to identify parameters that can predict response to therapy, with ER, PR, HER2, and PDL1/TILs as important biomarkers. In order to achieve the goal of providing individualized therapy based on specific characteristics of each tumour, further markers have been identified. These factors relate to important cancer parameters such as cell cycle, proliferation, and



apoptosis, cell adhesion, and invasion, the status of hormone receptors and the immune system. Among various biomarkers, oestrogen and progesterone receptors and HER-2/neu oncogene are recognized predictors of response to endocrine and trastuzumab therapies, respectively. Trastuzumab is considered the first antibody originally developed for HER-2/neu overexpression in metastatic breast cancer. Other tests, such as Oncotype Dx, a 21-gene assay, and MammaPrint, a 70-gene assay, were developed to predict risk for distant recurrence among lymph node-negative and oestrogen receptor-positive breast cancer patients. When to perform prognostic/predictive testing, how to interpret the result, and how to use it to guide therapy requires communication and agreement between pathologists and oncologists. This can be achieved by open forum communication, such as tumour conferences and tumour boards, or more individualized case-based discussions.

## Molecular subtypes of breast cancer

The seminal article published by Perou et al. in 2000 brought a new understanding of the genetic profiles of breast cancer (1). The authors of that article introduced five subgroups based on 496 genes that differentiate breast cancer into separate groups according to gene expression patterns (Figure 13.2). It could be classified into five intrinsic subtypes (luminal A and B, HER2-enriched, basal-like, and normal-like), corresponding to hormone-receptor and HER2 status and further stratifies the luminal tumours based on proliferation (2). It was also reported that these subtypes differed markedly in prognosis and in the repertoire of therapeutic targets they express.

- Luminal A breast cancer, hormone-receptor positive, HER2 negative, and with low levels of proliferation (Ki-67), growing slowly, and having the best prognosis.
- Luminal B breast cancer, hormone-receptor positive, either HER2 positive or negative with high proliferation (Ki-67).
- Triple-negative/basal-like breast cancer, that are hormone and HER-2 negative, more common in women with *BRCA1* gene mutation, more common among younger and African-American people.
- HER2-enriched breast cancer, hormone-receptor negative, growing faster, having a worse prognosis, but with successful therapeutic options with targeted therapies, such as trastuzumab, pertuzumab, tyverb, T-DM1, and trastuzumab deruxtecan.
- Normal-like breast cancer, similar to luminal A disease but with a slightly worse prognosis.

Molecular subtyping of breast cancer is not yet universally incorporated in breast pathology reporting. However, the eighth edition of The American Joint Commission of Cancer, which remains the worldwide basis for breast cancer staging, has adapted the inclusion of prognostic factors such as tumour grade, hormone receptors, and HER-2/neu amplification in addition to TNM classification in breast pathology reporting. Recently, also high abundance of tumour-infiltrating lymphocytes was associated with significantly better survival in TNBC, suggesting it to be an important prognostic factor to be taken into account in cancer staging.

## **The essentials/requirements of optimal breast pathology reporting**

### **Diagnosis**

Rendering an accurate breast pathology diagnosis and providing optimal information about prognostic/predictive factors requires access to a well-established pathology laboratory with skilled and knowledgeable staff pathologists. There is no substitution for an accurate diagnosis with respect to securing patient safety and appropriate therapy. It is also essential to take proper measures for establishing effective communication between pathologists and other members of the breast health team. It should be understood that the accuracy of pathology diagnosis is a shared responsibility among pathologists, radiologists, surgeons, and oncologists/gynaecologists.

Accurate diagnosis of breast cancer requires knowledge about the type of procedure, pertinent clinical history, and breast imaging findings. These include personal and/or family history of breast cancer and other risk factors, history of any systemic disease, implants, nipple discharge, the site and the size of the lesion, any previous history of radiation and/or chemotherapy, and whether the patient is pregnant or lactating. Associated with a history of other malignancies, the possibility of a metastatic tumour to the breast should be seriously considered. In addition, knowledge about the breast imaging findings make it possible to correlate those with the pathologic features and to recommend resampling of the lesion, if there are any discrepancies between the results. More importantly, proper orientation of the intact tissue sample by the surgeon is critically important for assessing the surgical margins.

### **Risk prediction**

Identification of borderline breast lesions associated with an increased number of image-detected biopsies is the result of the widespread use of screening mammography. There has been an increase in the diagnosis of high-risk proliferative breast diseases that are considered a morphological risk factor for recurrence. Recognition of the spectrum of morphological features of these entities is important in identifying high-risk individuals, who may benefit from appropriate risk reduction modalities associated with early breast cancer detection and prevention.

### **Detection of tumour metastasis in sentinel lymph node biopsy**

Assessment of the presence or absence of metastatic tumour cells in sentinel lymph nodes has become an important task of pathologists. This information defines the course of surgical information with respect to the decision about the follow-up total axillary dissection.

### **Detection of tumour cells at surgical margins in lumpectomy specimens**

The status of surgical margins at the time of initial lumpectomy is considered an important predictive factor of tumour recurrence. The accurate assessment of lumpectomy surgical

margins by pathologists is directly related to appropriate orientation of the specimen by surgeons followed by proper handling of the sample in the surgical pathology laboratory.

Intraoperative assessment of lumpectomy surgical margins by gross examination of the specimen, imprint cytology, and/or frozen section is rapid and cost-effective. This assessment helps to minimize the possibility of local recurrence and reduces the number of unnecessary surgeries for re-excision.

## Prognosis: treatment planning

Providing individualized therapy for breast cancer patients requires detailed characterization of tumour cells. An optimal breast pathology report includes tumour size, tumour type, histological grading, presence or absence of lymphovascular invasion, tumour-infiltrating lymphocytes, the status of surgical margins and the lymph node metastasis, the presence of ductal carcinoma *in situ*, the status of multicentricity and multifocality, the presence or absence of skin/nipple involvement, and ulceration. The diagnosis of ductal carcinoma *in situ* requires the inclusion of size, nuclear grade, presence or absence of necrosis, and the type of growth pattern.

## Prediction of response to therapy

Assessment of oestrogen and progesterone receptors by immunocytochemistry is an important predictor of response to endocrine therapy and is currently measured in every newly diagnosed breast cancer. In addition, assessment of HER-2/neu oncogene amplification and overexpression by fluorescent *in-situ* hybridization and immunochemistry is used to predict the therapeutic response to adjuvant chemotherapy and endocrine therapy and to select patients for trastuzumab immunotherapy. Recently even Her-2 low breast cancers were responding to the new antibody-drug conjugate: Trastuzumab deruxtecan, making a correct detection even more relevant.

## The status of breast pathology in different regions of the world

A majority of the world's population resides in resource-poor countries. These people have limited access to optimal standard of life, quality medical care, long life expectancy, and predictable disease outcome. The gap between the available resources of those who live in countries of limited resources versus those who enjoy a different lifestyle in resource-rich countries is significant. An emerging concern that has received attention at an international level is the status of pathology services in developing countries that also includes the practice of breast pathology. Currently, there is significant variation in the practice of breast pathology at the global level. There are important differences in infrastructures, tissue sampling and processing, interpretation of pathology findings, and analysis of breast samples for biomarkers. Contributing factors for these differences include financial constraints and variation in the level and extent of training of pathology personnel in breast pathology services globally. Implementation of breast pathology guidelines in countries with limited resources

is a significant challenge. Availability of pathology laboratories with the adequate infrastructure, with trained personnel and pathologists is a major obstacle that requires attention. There are still regions of the world that have no/limited access to pathology diagnosis, and often mastectomies are performed based on clinical presentation of a palpable mass or other abnormalities. Development of collaborative relationship among laboratories in different regions of the world may provide an effective alternative.

A qualified pathologist requires international partnering and collaboration. Aside from the allocation of financial resources, the training of qualified personnel involved in handling, processing, and interpreting pathological findings is the most critical step in this process. This may be achieved by the implementation of low-cost interventions that can make a difference. In addition, provisions should be made to educate government officials, healthcare leaders, administrators, physicians, scientists, healthcare providers, nurses, social workers, industry, and religious leaders about the value of accurate pathology diagnosis for the delivery of optimal breast care. It should be understood that proper diagnosis of a breast lesion by a qualified pathologist minimizes over- and underdiagnosis as well as the burden of under- and overtreatment. Measures such as the use of fine-needle aspiration biopsy as the initial diagnostic procedure, the establishment of regional laboratories that can provide interpretation of cytology/pathology slides, and the use of telepathology for diagnosis and training of personnel and local physicians/pathologists are effective initiatives to consider. Despite resource limitation in low- and middle-income countries, appropriate pathology reporting, tumour staging, quality measures, and the availability of prognostic/predictive information are essential factors for the design of personalized therapy and follow-up management. It should be also recognized that the financial burden of establishing or providing access to breast pathology services is counterbalanced by the cost savings from inappropriate use of resources that result from poor pathology practice. The practice of breast pathology is complex and requires integration of morphology with clinical presentations, risk factors, breast imaging, and the status of biomarkers in order to provide meaningful contribution to patient care.

Ultimately, partnership between resource-rich and resource-limited countries is essential to overcome the current barriers in the delivery of optimal breast pathology services around the globe. To improve access to quality breast pathology practice, there are important caveats to be recognized by those combatting breast cancer. For pathologists, however, this requires a cultural change. To actively participate in this process, pathologists not only need to strive for excellence in breast pathology, but they also need to change from being isolated morphologists to being real-time clinician-scientists who eventually even may see patients. As patient advocates, pathologists can lead educational efforts directed towards the public, physicians, leaders in the healthcare community, and the government. As a pathologist-clinician, more pathologists can become familiar with the performance of minimally invasive procedures. As a pathologist-scientist, a pathologist can better understand the biology of breast cancer and recognize the morphological and biological alterations observed within the spectrum of high-risk proliferative breast disease and premalignant and malignant lesions. In order to achieve these goals, it is critically important to create a worldwide excellence in breast pathology programmes encouraging international collaboration among interested pathologists to form the building blocks for a voluntary breast pathology educational programme. The 'International Society of Breast Pathology', founded in 1998 by S. Masood mention as primary purpose to foster an improvement of training programmes to promote standardization and to create a forum for communication for those interested in breast pathology.

**Table 13.1** Use of cytology

| Method                                                                                                | Method result                                                                                                                                                                                                          | Clinical use and key messages                                                                                                                                                                                                                                                                                   |
|-------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| FNA cytology of solid lesion or cyst                                                                  | Detection of malignant tumour cells or mixture of benign cells (further details possible)                                                                                                                              | Less used today because of the need for predictive tumour characterization of CNB prior to surgery or primary systemic therapy.<br>Useful in low-resource settings.                                                                                                                                             |
| FNA cytology of a clinically suspect lymph node                                                       | Detection of malignant tumour cells                                                                                                                                                                                    | Guiding extent of lymph node dissection, especially if primary systemic therapy is intended without prior sentinel node biopsy                                                                                                                                                                                  |
| Touch imprint cytology of core needle biopsies                                                        | Representativeness of biopsy.<br>Detection of malignant tumour cells without further discrimination between <i>in-situ</i> or invasive tumour cells without further discrimination between <i>in situ</i> or invasive. | Immediate feedback allows possibility of repeating CNB.<br>Enables clinicians to counsel patients and plan the appropriate treatment.(1) Can also be used to immediately order immunohistochemistry for the next morning (this allows being able to provide a full histochemistry and IHC report within 24 h).  |
| Touch imprint cytology of resection margins in breast-conserving therapy or nipple-sparing mastectomy | Detection of malignant tumour cells.<br>No need for differentiation between <i>in-situ</i> or invasive tumour cells.                                                                                                   | Larger areas can be examined compared to pure macroscopic or frozen section examination.<br>Immediate further resection avoiding secondary surgery is possible.                                                                                                                                                 |
| Touch imprint cytology of nipple secretion                                                            | Occasional detection of intraductal epithelial cell proliferation (papilloma, ductal hyperplasia, <i>in-situ</i> carcinoma).                                                                                           | Any (single-sided) nipple secretion outside of lactation is abnormal and should be examined cytologically. Detection rate of atypical epithelial cells is scarce in such materials and most often dyshormonal regulation is the cause. Nipple secretion cytology has a low sensitivity, but a high specificity. |

FNA, fine-needle aspiration; CNB, core needle biopsy; IHC, immunohistochemistry

## Essentials/requirements of the practice of breast cytology

Cytology has been used less often in recent years than in previous decades, when primary diagnoses of breast cancer were performed using fine-needle aspirates (FNA), and at a time when the characterization of tumour receptors was less important. Nowadays, cytology has mostly been replaced by core needle biopsies (CNB), but it still has value in special situations, such as when a less invasive method is preferred to guide further clinical decisions (Table 13.1). Furthermore, in low-resource settings, cytology might be used as an appropriate tool to distinguish benign from malignant processes.

## Interpretation of cytology

Clinical information is necessary: age, location (retro-areolar or peripheral or axillary tail, etc.), clinical appearance (e.g. palpable, microcalcification).

People reading cytology, generally pathologists, must be well-experienced in order to avoid misinterpretation. Profound knowledge of the histological morphology is important and probably most helpful for the correct interpretation of cytological breast specimens. High-grade breast carcinomas are most often highly cellular and show obvious atypia. However, low-grade carcinomas are more difficult to recognize. Here, the lack of myoepithelial cells within epithelial cell clusters is a hallmark.

The usefulness of FNA is limited in the diagnosis of *in-situ* carcinoma, lobular carcinoma, tubular carcinoma, and small non-palpable tumours, and it is also not effective in the evaluation of microcalcifications.

Regarding specimen adequacy, initially the amount of evaluable epithelial cells should be noted. Reasons for inadequacy may be hypocellularity, error in aspiration, spreading or staining, or excessive blood.

Depending on the clinical question, cellularity may already be an important result. For example, if a touch imprint of a CNB harbours no or only a very small number of epithelial cells, the probability of a carcinoma is low, except in cases of lobular carcinomas, which can demonstrate a low cellularity.

The cytological result may be given as either three-tiered (negative, suspicious, or positive) or by the five-tiered C-classification: C1, unsatisfactory; C2, benign; C3, atypia probably benign; C4, suspicious of malignancy; C5, malignant.

## Quality control

Whenever possible, the cytological results should be correlated with further histological results. This enables an easy way to calculate sensitivity and specificity of the method, if the B-classification is used for reporting CNB or with further histology of resections.

The accuracy of FNA depends on three main factors:

1. a sample that is adequate and representative of the lesion;
2. suitable processing and staining without artefacts;
3. accurate interpretation of the cytological material with a clear report conveyed to the rest of the clinical team.

The procedure can fail at any of the stages of preparation (aspiration, spreading, and staining) even before diagnostic interpretation. The confidence and experience of the aspirator are vital for obtaining a satisfactory sample. This part of the procedure, like other parts, should not be delegated to novices. For FNA, a sensitivity of >70% and a specificity of >90% should be reached. For C5-lesions, a positive predictive value of 99% should be reached. Calculations are according to the European Guidelines.

## Establishment of breast pathology guidelines in low- and middle-income countries by the breast pathology focus group of the Global Breast Health Initiative (BHGI)

In response to the need for attention to the significance of access to optimal pathology laboratory facilities in 2005, the leadership of BHGI assembled a panel of interested

pathologists, breast cancer clinician specialists, and patient advocates to assess the status of the practice of breast pathology in countries of limited resources and to develop resource-stratified guidelines which emphasized the necessity for accurate pathology diagnosis of breast cancer worldwide. Considering the relative necessity, therapeutic benefit, and cost, four levels were suggested: basic, limited, enhanced, and maximum. The 2005 panel also acknowledged the appropriateness of fine-needle aspiration biopsy (FNAB) as the most economic method for the initial diagnosis and emphasized the necessity of access to optimal cytologic interpretation. In addition, the availability of resources necessary to provide prognostic and predictive factors as well as assessment of the status of axillary lymph nodes were emphasized at different levels within these guidelines. The next step was to determine how to adapt these guidelines into real-time implementation in countries of limited resources and how to identify system changes necessary for this implementation (3). In 2023, the GBCI of the WHO identified criteria for quality pathology examination on a global scale (see Box 13.2) (see Chapter 40).

## Considerations for breast conservation and sentinel lymph node biopsies

Table 13.2 summarizes the guidelines, process, and quality indicators related to the possibility of offering breast conservation in countries of limited resources. As previously indicated, detailed information about the tumour, as well as the status of surgical margins and sentinel lymph nodes are essential to the report (4).

### Box 13.2 Key recommendations of the GBCI—WHO/2023

- Poor-quality pathology reports result in inappropriate care, which negatively impacts outcomes
- Pathology laboratory has to determine at least oestrogen receptor, as well as the human-epidermal-growth-factor receptor (HER2), in all countries
- Centralizing fast-tracking biomarker testing improves quality, reducing cost through high-volume testing, although it can exacerbate systematic delays
- Utilizing point-of-care testing for biomarker evaluation will shorten time to diagnosis especially in low- and middle-income countries (LMIC)
- Secondary-level hospitals may be the best location for breast diagnostic services in LMIC, being more geographically accessible
- A balance between centralized and decentralized diagnostic services is required
- A laboratory serving a population of 1 million people should process 10,000 specimens per year (40 samples per working day) to efficiently utilize its resources
- High quality diagnostic services require radiology and pathology teams to work close together, assessing the concordant or discordant results

Source: data from Global Breast Cancer Initiative <https://www.who.int/initiatives/global-breast-cancer-initiative>



**Table 13.2** Special considerations for breast conservation and sentinel lymph node biopsy

| Guideline                                                                                                                           | Process                                                                                                                                                                                                    | Quality indicator                                                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| Pathology report should include the status of margins, the presence and extent of DCIS, and the presence of lymphovascular invasion | Adopt standardized methods of orienting specimen, and inking and sampling the surgical margins                                                                                                             | % of pathology reports include margin status, DCIS, and lymphovascular invasion                            |
| Measures in place to provide intraoperative evaluation of sentinel lymph nodes                                                      | Adopt standardized methods for determination of the presence and quantification of DCIS and lymphovascular invasion<br><br>Adopt standardized methods for processing and reporting of sentinel lymph nodes | % of diagnostic discordance between intraoperative and final pathologic diagnosis for sentinel lymph nodes |

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## Accreditation

During the last several years, international breast cancer organizations have focused on the establishment of guidelines that promote an organized approach to providing quality care. Various quality metrics have been developed, and it has become a serious expectation that those engaged in providing breast healthcare follow the established guidelines. The National Accreditation Programme for Breast Centres, the International Senologic Society, and the European Society of Breast Cancer Specialists have adapted guidelines for breast pathology reporting focused on the previously discussed emphasis to assure access to the high quality of breast pathology reporting that our patients deserve. In addition, during the last several years, the practice of breast pathology has changed. Pathologists are no longer required to differentiate between benign and malignant disease, but they are required to recognize the spectrum of borderline breast disease in small tumour samples and provide comprehensive information about the biology of each pathologic entity. These challenges are more conspicuous in countries with limited resources, inadequate number of staff and pathologists, and differences in the stage of breast cancer presentation, making international collaboration key.

## Current challenges associated with the practice of breast pathology

One of the most important obstacles in the practice of breast pathology is the limited understanding of the public about the role that pathologists play in their care and outcome. To some extent, the significance of the role of pathologists has remained under-recognized among the medical community. The issue of pathology becomes real when the patients become aware of a mistake in the diagnosis of their pathology during a review process, or there is a significant



discrepancy between the clinical presentation, breast imaging, and the pathology diagnosis. Breast pathology is complex, and there are several look-alikes that are easy to misdiagnose as cancer if the pathologist is inexperienced. These difficult-to-diagnose cases include a variety of atypical proliferative lesions, atypical ductal hyperplasia (ADH) versus low-grade ductal carcinoma *in situ* (DCIS), lobular neoplasia, papillary lesions, atypical sclerotic lesions, fibroepithelial tumours, mucinous lesions, and the status of microinvasion (see Box 13.3).

## Quality assurance and patient safety in the practice of breast pathology

Currently, there are no uniform guidelines in place to effectively measure the rate of diagnostic errors in everyday practice of breast pathology. In addition, the fear of disclosure and medicolegal issues are limiting factors in the reporting of diagnostic errors in breast pathology (see Chapter 34). Therefore, the establishment of quality measures and the monitoring of the status of compliance are critical steps in improving the quality of practice of breast pathology.

### Box 13.3 ‘Prone to error: earliest steps to find cancer’

In this article published in the *New York Times*, patients who were misdiagnosed as suffering from DCIS and who had undergone unnecessary treatment for cancer were profiled, and they shared their stories. One patient recounted having been misdiagnosed with invasive breast cancer, and, when faced with the prospect of a mastectomy, she sought a second opinion. Once her case had been reviewed by three separate expert breast pathologists, they all agreed that there was no evidence of invasive cancer. However, three different diagnoses were given by the three pathologists. One pathologist diagnosed DCIS, with the others diagnosing her case as ADH and apocrine adenosis. Due to the complexity of her case and the differing opinions of the three pathologists, the patient ultimately decided to remain under surveillance, but to postpone any treatment or surgical procedures. After eight years, the patient still had no evidence of cancer.

Errors in breast pathology are not uncommon. Most times, these errors occur when cases are sent to other medical centres for review, or when a patient requests a second opinion. Once a misdiagnosis is realized, there can be significant changes to treatment planning, and this can cause both relief and anxiety for patients and their families. In some cases, a misdiagnosis can cause years of anxiety. In one case, a patient came for advice on what to do as a high-risk patient, since her mother was a breast cancer survivor, who had been diagnosed at age 35 years while she was eight months pregnant. After the birth of her daughter, her mother had undergone a mastectomy and axillary dissection. Upon reviewing her mother’s case, it was determined that there was no clear evidence of cancer, and that her mother had undergone these procedures unnecessarily. Although there was nothing that could be done to reverse what had been done to her mother, the patient was relieved that she was no longer considered high risk for breast cancer.

### Box 13.4 Suggestions for quality measures in breast pathology

Establishment of quality assurance programmes

- Internal quality measures
  - Consensus slide conference
  - Mandatory second review of difficult cancer cases
  - Mandatory adherence to established guidelines

Second opinion

- The review of outside pathology slides and reports by a local pathologist before the initiation of cancer therapy

Involvement in external quality assurance programmes

These quality indicators range from pre-analytic factors, such as fixation and processing of the tissue samples, to analytical factors that begin when the pathologist receives the glass slides, interprets the findings, and renders a diagnosis. The post-analytical factors involve the correlation of the pathology diagnosis with clinical presentation and imaging findings.

Recognition of difficult-to-diagnose cases in breast pathology uses all of the available measures to find the correct answer for every case in breast pathology and is essential in securing the safety of our patients with different breast diseases. Attempts should also be taken to consider accreditation of breast pathology fellowships in recognition of the significance of additional training in a multidisciplinary integrated environment of care.

Ultimately, every breast pathology practice should establish its own quality assurance programmes that include internal and external quality measures and second opinions (Box 13.4).

## Future perspective

### Challenge of modern breast pathology reporting

Post neo-adjuvant systemic treatment reporting of breast cancer specimen (5) is becoming important. Identification of patients with residual disease predicts a worse outcome than a pathologic complete response. The calculation of the residual cancer burden (RCB) provides an assessment of residual risk informing the value of additional treatment.

The reporting of the RCB classification can be done with the help of the RCB Calculator taking into account:

1. Primary tumour bed
  - area in mm
  - % cancer cellularity of area
  - % *in-situ* cancer

2. Lymph nodes
  - number + LN
  - mm largest metastasis

Three RCB classes are defined giving each relevant information.

In addition, the US College of American Pathologists suggest repeating biomarker retesting in cases showing negative results as pre-treatment, as positive conversion may occur.

## Challenges of precision medicine be delivered sustainably and affordably?

Clinical studies have shown that mutational lesions and/or gene expression changes within tumours affecting the protein target of a drug may be predictive of the efficacy of that drug. Examples of such predictive biomarkers include classical activating mutations of epidermal growth factor receptor (EGFR) in non-small cell lung cancer, which confer exquisite sensitivity to EGFR tyrosine kinase inhibitors (TKIs), amplification of ERBB2 and/or high-level expression of the encoded receptor tyrosine-protein kinase erbB-2 (HER2) in advanced breast cancer, which are predictive biomarkers for the HER2 antibody, trastuzumab, and BRAF V600E mutations in malignant melanoma in relation to the selection of patients suitable for treatment with the serine/threonine-protein kinase B-raf inhibitors, vemurafenib, and dabrafenib. In addition, tumours with activating mutations in genes encoding downstream components of specific signalling pathways may be insensitive to drugs targeting upstream components, as exemplified by KRAS mutations and the lack of activity of cetuximab and panitumumab in the treatment of metastatic colorectal cancer. The adoption of such biomarkers into routine clinical practice has clearly shown the potential of precision medicine in relation to the identification of subpopulations of patients more likely to benefit from treatment with a targeted agent.

## The bumpy road to biomarker discovery and drug development

This wider concept of precision medicine envisages that multiagent therapies can be customized according to the individual complex genomic signature of a tumour with all the caveats about data quality and processing, but without the normal rigorous clinical testing of efficacy and safety of such combinations to guide physician recommendations. The presumed promise of such individualized customized therapy is that because it is more precise it will be more effective. However, this raises several key questions: if therapy is increasingly individualized, how can it be evidence-based; how can the safety of hundreds of different possible combinations be assessed; how can a predictive biomarker be validated and appropriate cut-offs defined if it is used in hundreds of different contexts to make hundreds of different decisions; how can payees evaluate the value of each individualized treatment plan; and, in an era of precision medicine, how will hospitals or governments budget for a far wider range of treatment plans?

So, while comprehensive molecular profiling of tumours and the collection of corresponding clinical outcome data from patients will lead to substantial research opportunities, and while such profiling may be useful in enrolling patients into adaptive clinical trials, such approaches cannot, at the current time, be used to deliver effective precision medicine according to this wider context. Whether this will be possible in the future remains an open question. Indeed, on a technical level, the issue of tumour heterogeneity is a potentially serious confounding factor in relation to achieving this goal, because if a particular detected mutational event is present in only a minor subclone of tumour cells, targeted therapy against the encoded product is likely to have only marginal effects on the overall viability of the tumour. It may be that multiple agents could be used to target multiple subclones of a patient's tumour, but this would require the derivation of information on appropriate doses of targeted drugs when administered in a huge number of different possible combinations across different settings. In addition, such an approach would most likely carry substantial cost implications for payers, yielding, perhaps, little or no real-world patient benefit in many cases, and creating a situation which might be disastrous for self-funding individual patients faced with difficult treatment decisions at a time when they are at their most vulnerable. The high cost would also essentially restrict precision medicine treatment strategies to high-income individuals in resource-rich countries.

So, although progress will inevitably continue to be made in relation to the development of new drugs, and although new biomarker assays will continue to be developed to predict the efficacy of those drugs, it is difficult to envisage a situation developing in routine practice, in the foreseeable future, where complex genomic profiles will be used to customize multiagent targeted therapy on an individual patient basis.

## Can we afford precision medicine?

Since precision medicine approaches may result in considerably increased treatment costs, are there strategies for current implementation that would mitigate those projected costs? In relation to biomarker test development, regulatory standards should be tightened, so that there is increased confidence that, as new assays are introduced into clinical practice, they deliver what they are intended to deliver with respect to clinical utility. Trial designs for new drugs should also be aimed at the delivery of clinically meaningful outcomes, so that we move away from the situation where drug approvals are based on large phase III trials which deliver marginal statistically significant improvements in outcome, but which are of minimal value to patients. A further way to constrain costs and minimize variations in care is to employ evidence-based clinical pathways that are regularly updated. Although the use of such pathways may be viewed as running counter to a precision medicine approach, they can be adapted to include predictive assays that are highly evidence-based. One further way to constrain the costs of highly priced targeted drugs will be to rigorously explore indication-specific and value-based pricing.

One other aspect that should be considered in relation to the clinical use of genome-level data in a precision medicine context is that physicians will need to have sufficient training in clinical genomics, associated analysis techniques, and risk assessment to enable them to effectively support patients in making informed decisions on possible treatment alternatives (6). This requirement will represent a significant educational challenge (see Chapter 9).

## Are we ready to use next-generation sequencing (NGS) in daily practice?

The currently lower cost and wider availability of NGS technology raise the debate on the use of NGS in clinical routine, as in breast cancer. However, some proposed treatments based on NGS data are not always evidence-based.

Today, clinicians can choose between large varieties of targeted gene panels offered by gene sequencing companies. Several companies allow the identification of genetic variants based on the sequencing of 200–400 genes, whereas other companies provide restricted gene panels of 3–50 genes for different tumour types. Moreover, oncologists and pathologists do not always have the same point of view regarding the choice of the genes that should be analysed, to say the least.

Targeted gene panels can be separated into two groups: a limited targeted gene panel mainly containing genes with strong scientific evidence for their clinical utility, usually six to 50 genes, or a broad targeted gene panel that also contains genes with weaker scientific evidence for clinical utility, usually more than 50 genes. Several grading approaches exist to define these levels of evidence (OncoKb, CEBM).

For breast tumours, only a few genes currently have scientific evidence for their clinical utility. *BRCA* gene mutation offered the first drug-targeted therapy (PARP inhibition). In addition, *PIK3CA* mutation suggests the use of a PIK3CA inhibitor (Alpelisib), and *ESR1* gene mutation in circulating tumour DNA suggests the use of an oral selective oestrogen receptor degrader in hormone-receptor-positive breast cancer (Elacestrant). However, other molecular tests have enabled improvement in diagnosis and treatment. For example, OncoTypeDX and MammaPrint, which allow separation of breast patients into low and high risk, thus enabling a change in the clinical management of these patients. NGS gene panels can also be used on the blood to detect germline mutations and predict cancer susceptibility (see Chapter 21).

Until now, clinical trials have revealed only some benefits of NGS. A recent European study about real-world data of the implication of NGS-based analysis in metastatic breast cancer showed 9% of the study population had their therapy modified based on the results of NGS. Perspective suggests that NGS analysis could be implemented in clinical practice, particularly where a molecular tumour board (MTB) is active (7).

## Technologies as an enabler for globally accessible molecular diagnostics

### The rise of molecular diagnostics

The world population is expected to grow towards 10 billion by 2050. Rising healthcare costs and budget constraints today push us towards a more intelligent, proactive approach, where diagnostics provide clinicians with more and better information, leading to better treatment outcomes. Healthcare policymakers, governments, insurers, and other payers are already implementing price control systems that favour early diagnosis, better screening and monitoring, and cost-effective therapies.

The global *in-vitro* diagnostics market was valued at US\$85.2 billion in 2024 and is expected to grow at a compound annual growth rate of 6.9% during the forecast period (2024–2029) to reach US\$119.4 billion by 2029. The largest medical diagnostic segment in 2023 was infectious diseases, followed by oncology, endocrinology, cardiology, blood screening, genetic testing, and others (<https://www.marketsandmarkets.com/Market-Reports/ivd-in-vitro-diagnostics-market-703.html>).

The global oncology-based molecular diagnostics market is expected to reach US\$6.0 billion by 2030, according to a new report by Grand View Research Inc (8). The global breast cancer diagnostic market size, being the largest oncology market, was valued at USD 4.3 billion in 2022 and is expected to grow at a compound annual growth rate of 7.4% from 2023 to 2030. Increasing geriatric population, shift to point-of-care testing with automated analysers, and growing awareness of early diagnosis in emerging economies will further increase this tendency.

## Bridging the technology divide in molecular diagnostics

There is an increasing divide between the speed of development of new technologies and the access to these technologies. Looking at hospital settings in 2014, the American College of Surgeons reported that more than 80% of cancer patients are treated locally. This is in distinct contrast with up to 90% of molecular diagnostic tests which are today being sent to an external laboratory, since local testing capabilities are unavailable. Today, due to the technical complexity of molecular diagnostic testing and the fact that most current systems rely on batch-based testing (meaning that a large number of samples requiring the same test are tested in parallel), medical diagnostic testing is currently centralized in specialized molecular laboratories. Consequently, smaller hospitals (lacking the volume of tests for which batch-based systems are designed), or laboratories that are not specialized in medical diagnostic testing, typically send out their samples for analysis by external reference centres. However, this system is being challenged by companies such as Biocartis, which are bringing highly reliable molecular information from virtually any biological sample, in virtually any setting, enabling fast and effective treatment selection in a global world (9) (see Box 13.5).

## The emerging opportunities for digital pathology and artificial intelligence-applications in low- to middle-income countries

Given the increasingly complex nature of biomarkers and the need for assays that can rapidly and correctly identify the optimal patients for individual biologic therapies, there has been a recognized need for the development of analytically validated, robust, accurate, and reproducible tests, a need which historically drove the regulatory recommendation for the development of drug-specific diagnostic tests.

At present, in most cancers, clinico-pathological risk stratification is performed using a limited set of features such as tumour size and lymph node status. Very large adjuvant trials have illustrated the key problem with the current scheme—it does not stratify patients with sufficient granularity to permit optimal selection for clinical trials. This selection is mostly based

### **Box 13.5 Molecular pathology for breast cancer in Pakistan: challenges and threats**

Cancer care disparities persist among the medically underserved patients with cancer in Pakistan. About 30–40% received optimal basic chemotherapy for breast cancer. Most of the investigations are undertaken in the private diagnostic facility centres outside the hospitals due to multiple factors (i.e. out-of-order machines, poor quality of reports, delayed report results etc.). Insurance and public assistance are largely unavailable, patients must sell assets, use limited savings, borrow from relatives and friends, and/or seek loans from informal sources to pay treatment-related expenses. Molecular pathology has revolutionized cancer diagnostics by integrating molecular signatures with traditional morphological assessment. In this context, Pakistan faces unique challenges and threats related to molecular pathology in breast cancer management.

The Lancet Commission on Diagnostics' conclusion in 2021 was that just under half (47%) of the world's population have little to no access to diagnostics. This holds true for Pakistan where basic breast histopathology is only available in large, urban, tertiary healthcare facilities. There is also inconsistency in the routine IHC markers that are tested, there is no standard available because we have yet to determine key diagnostic indicators that must be tested. Although molecular pathology services have been available in Pakistan for over two decades they are still only offered by a handful of laboratories, cost remains high even when subsidized and currently there are weak regulatory and quality requirements. As many healthcare facilities lack the necessary technology and expertise for molecular testing, access barriers prevent timely diagnosis and personalized treatment planning. Patients often face delays due to reliance on international laboratories. Disparities in access exacerbate health inequities. Urban-rural gaps and regional disparities affect patient care. The lack of specialized centres limits comprehensive management.

Addressing these challenges and mitigating threats is crucial. Pakistan must invest in healthcare infrastructure, enhance training for healthcare professionals, and raise public awareness. By bridging the gap between ideal and actual availability, we can improve breast cancer outcomes and empower patients through molecular pathology. However, the continuous cycles of economic crisis take us further away from achieving our development goals for health. Health and economics are the two chains of national DNA as well as individual genomic profiles that determines the outcome of breast cancer for a woman in Pakistan. Until and unless we recognize that we cannot address one without the other we will not be able to achieve sustainable programmes required to make a real difference.

*Source:* data from Aziz Z, Naseer H, Altaf A. Challenges in Access to New Therapeutic Agents: Marginalized Patients With Cancer in Pakistan and the Need for New Guidelines. JCO Glob Oncol. 2022 Feb;8: e2100132.

on quantitative and qualitative parameters and is subject to error influenced by training and experience. The current scheme also takes the approach of placing patients on a continuum of risk. This is at odds with results from high-throughput technologies such as gene expression profiling and genomic assays, which focus on identifying subgroups with particular clinical behaviour. Several results in this area have identified genomic/transcriptomic or proteomic features which in hindsight are associated with particular histological features (10).



This suggests that the histological appearance of a tumour represents a useful cancer phenotype which can be further explored and contribute to staging and stratification.

Artificial Intelligence (AI) refers to a data-driven general computational approach whereby algorithms are used to develop predictive models. These models are finely tuned to optimize accuracy and generalizability as applied to new data. Although AI has existed for some time, more recently, advances in algorithm development and hardware infrastructure have enabled 'deep learning' approaches. Deep learning was originally designed to mimic the neural architecture of the human brain and conceptually uses modular architectures implementing multiple nonlinear transformations estimated by training procedures. Neural nets have the ability to learn rich representations of complex data, which may contain hierarchical and non-linear relationships. These abilities make neural nets ideally suited to image classification. They have exhibited spectacular results in this area, often matching or exceeding human performance, and even exceeding expert performance in image classification (11). Notably, deep learning has overcome ad hoc pattern recognition methods in the analysis of medical images (MI), getting close to expert accuracy in the diagnosis of skin lesions (12) or classification of colon polyps (13) and expanding diagnostic options in radiomics (14).

The transformative nature of this technology is that it holds the promise of an accurate specialist diagnosis regardless of an individual patient's access to world-class experts in their field, and this includes also access to biomarker assessment using AI methods. AI methods provide a toolkit with many applications in pathology. They can assist the pathologist in time-consuming and complex tasks as the quantification of histological and immunohistochemical features, such as PDL1, which have been fraught with interpersonal reproducibility issues. On one level, the robust performance and training characteristics of AI allow us to develop accurate automated computer-aided diagnosis (CAD)-tools for pathological features such as PDL1-stains. These have the potential to be 'learn once, apply everywhere' solutions.

However, most if not all existing AI methods are focused on accelerating or replacing a human task. Is this the right approach?

Each cancer is unique, will develop a unique resistance to therapy, evolve to become more lethal, escape immune watch, and invade other organs. Therefore, it is essential to engineer AI by anticipating each individual cancer's ability to evolve drug resistance; and ultimately, prevent it before it happens. Moreover, emerging evidence indicates that spatial tumour ecology is a key driver in cancer evolution, and remarkably, this feature is often ignored in contemporary AI-developments.

It is therefore of interest to engaging with key cancer hospitals across several countries at a global scale where real-world problems affect the most unfortunate patients: existing tests are ineffective and too expensive when identifying high-risk patients leading to unnecessary systemic chemotherapy/increased toxicity & costs; clinicians struggle in stratifying patients most likely to benefit from adjuvant therapies; existing and once again too expensive assays add delays and additional workload, while not offering personalized biomarkers.

These issues can be addressed with AI technology in a short period of time, and the non-profit deployment of AI technologies in key international sites to maximize reach to as many cancer patients as possible is still largely unexplored. A platform is needed that only requires routinely collected samples, potentially making it suitable for every tissue cancer in the world, with no to limited additional local laboratory work needed.



**Table 13.3** Current problems, suggested solutions, and added value of AI technologies in low- to middle-income countries, leading to the operational model described in Figure 13.4

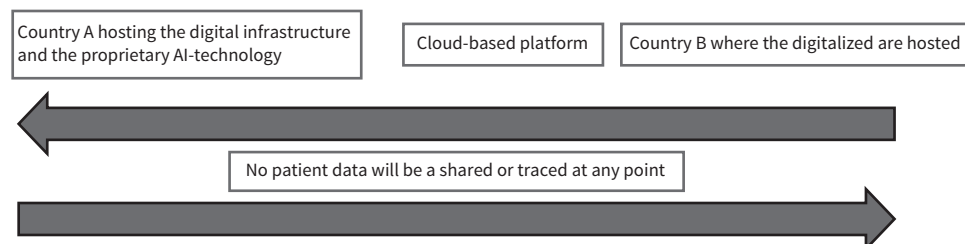
| Problem                                                                                                                                                                                         | Solution                                                                                                                              | Added Value                                                                                                                               |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| Existing technology is ineffective when identifying high-risk patients (e.g. in TNBC, nearly all patients receive systemic chemotherapy)                                                        | Pan-cancer AI technology to predict risk of relapse as well as immunotherapy response – no other technology in the market can do both | Patients: Prevent unnecessary toxicity and lost opportunities to pursue more effective treatments in the most crucial time of their lives |
| Doctors struggle in stratifying patients most likely to benefit from adjuvant therapies                                                                                                         | Enables tailored therapies, reduces overtreatment                                                                                     | Healthcare providers: Save tremendous costs on potentially ineffective treatments/biomarkers                                              |
| Existing assays add additional workload on labs, while not offering personalized biomarkers (e.g. in non-small cell lung cancer, only 50% of patients are predicted accurately for IO response) | Relies only on routine clinical samples—rapid AI SAAS based delivery—no additional lab work required by hospitals                     | Clinicians: Efficient precision oncology by enabling them to offer personalized treatments                                                |
| Delays in traditional labs are logistical; digitization offers reduced turnaround time, increased workflow efficiency                                                                           | Fully developed and trained system, extensive validation on external cancer cohorts                                                   |                                                                                                                                           |

The operational model characteristics are described in Table 13.3 and detailed further in Figure 13.4.

What are the necessities? A digital infrastructure to automate the scanning of, for example, diagnostic slides that the pathologist uses to make a diagnosis on; a cloud-based solution and AI vendors that may be situated in other continents (Figure 13.4).

The importance of this model is that all technology used should be in compliance with the local regulatory framework (e.g. GDPR) and respect patient data privacy guidelines.

An illustrative example is tumour-infiltrating lymphocytes (TILs). TILs are immune cells and are emerging as a very promising biomarker in solid tumours, and therefore, ongoing efforts for the assessment of TILs by AI methods. There are AI methods for TIL-assessment that may be ready to be introduced into clinical trials and daily practice (15). TILs have been shown to be a reliable and reproducible marker of tumour immunogenicity in breast cancer. It is clear that higher levels of TILs are associated with improved prognosis in early stage TNBC and HER2-positive breast cancer, are predictive to chemotherapy as well as immunotherapy, as well as a higher probability of achieving pCR in

**Figure 13.4** Operational model for advanced AI model deployment.

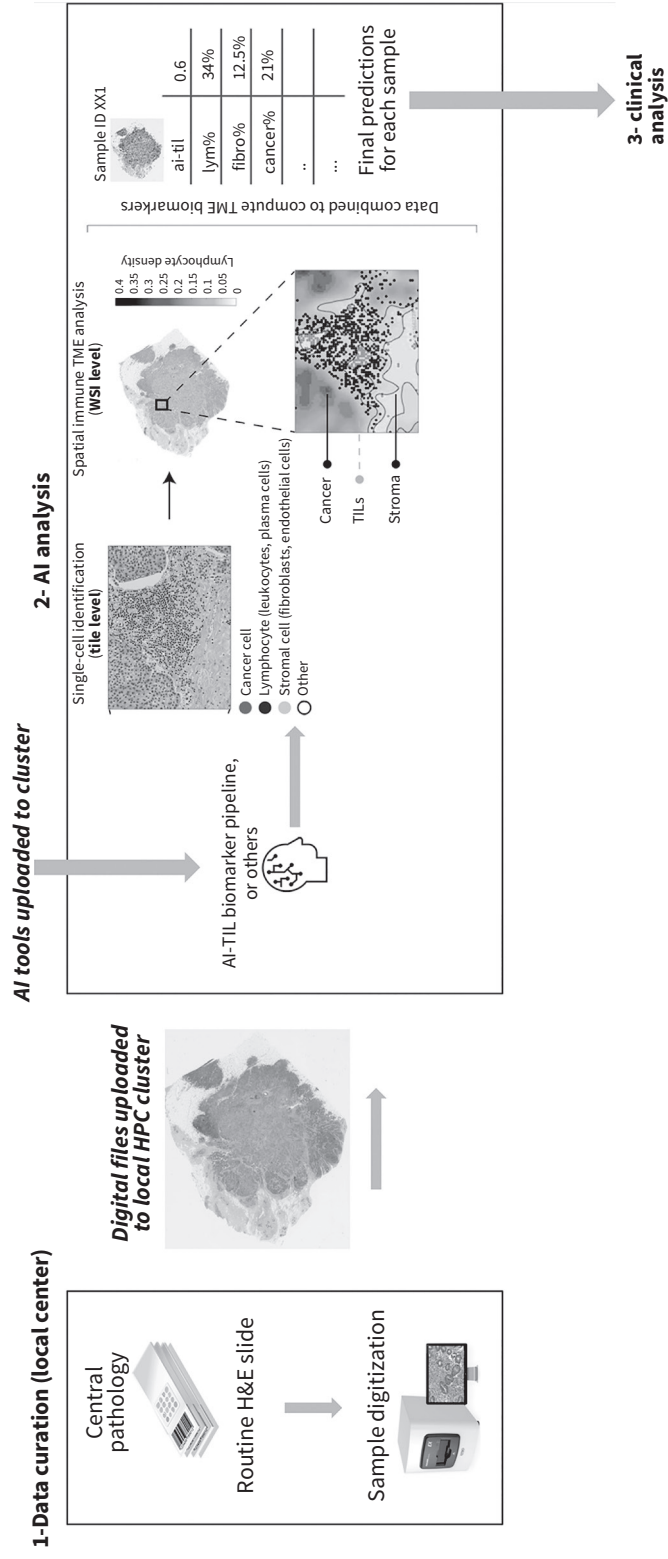


**Figure 13.5** Operational flow of determining TILs in daily practices through integration of AI within the workflow of anatomic pathology laboratories globally.

the neoadjuvant setting. Analysis of TILs in residual disease specimens after neoadjuvant therapy has also been shown to have prognostic value. The evaluation of TILs as a biomarker in breast cancer is expected to be extended from the research domain to the clinical setting in the very near future. The assessment of TILs by digital image analysis will be useful for standardization in the future, since this approach has the potential, for example, to determine the number of TILs per mm<sup>2</sup> stromal tissue as an exact measurement contrary to the approximate semi-quantitative evaluation suggested at this moment (Figure 13.5).

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## Breast cancer surgery

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### Introduction

Breast cancer was first described by ancient Egyptians and was considered an incurable disease. The first recorded attempt to amputate a breast is attributed to Leonides of Alexandria in the second century AD. by the 1600s. Axillary lymph node dissection (ALND) was first reported as part of the tumour eradication philosophy in 1882 by William Banks, and in 1894 William S. Halsted (Baltimore, MD, USA) reported his radical mastectomy, which included the entire breast, the axillary lymph nodes, and the pectoralis muscles and became the standard of care until the 1970s. Gradually, a less aggressive surgical trend emerged beginning with modified radical mastectomy sparing the pectoralis muscles, then followed by breast-conserving surgery (BCS) preserving the breast. These evolutions were possible due to breakthroughs in the understanding of tumour biology, the introduction of radiation treatment, and the advent of adjuvant systemic therapy. Sentinel lymph node mapping was then introduced reducing the extent of axillary dissection. Finally, oncoplastic surgical techniques emerged to enable breast contour preservation and improved mastectomy techniques such as skin or nipple-sparing mastectomy to facilitate breast reconstruction (1).

Standard and effective breast surgery does not require complex or expensive technology. It can be performed all over the world in a facility equipped with a surgical theatre, a radiology department taking care of marking non-palpable lesions and a pathology department. The current key to successful breast cancer treatment is a multidisciplinary approach in which the breast surgeon collaborates closely with other involved breast cancer specialists. The technical aspects of breast surgery are relatively easy to learn. However, a common mistake is to define a breast surgeon simply as someone capable of performing sentinel node biopsy, nipple-sparing mastectomies, and cosmetically acceptable breast conservation procedures which would be a concept that certainly falls short.

The current concept of a breast surgeon comprises a deep knowledge not only of surgical technical details, but also of tumour biology, disease staging, prognosis, mastery of reconstructive techniques, and leadership to interact with a multidisciplinary team. A breast surgeon must master the ever-changing decision-making algorithm for the optimal treatment of breast cancer that takes into account the timing of systemic therapies (neoadjuvant or adjuvant) and bidirectional implications of radiotherapy and surgery. The surgeon must even be aware of historical aspects to understand where we stand today and to help elucidate new questions through research to lead the future direction of the discipline. It is likely that the demand for breast surgical oncologists will increase in step with the ageing population.

## Surgery of the breast

Surgical removal of the tumour is the cornerstone for treating early-stage breast cancer. There are two options for breast surgery: mastectomy involving removal of the entire glandular breast and BCS removing just the tumour and a small amount of surrounding normal tissue to ensure negative margins. In the 1970s, pioneering trials demonstrated equivalent long-term survival rates for patients with early-stage invasive breast cancer treated with mastectomy or BCS combined with adjuvant radiotherapy (RT), and the superiority of BCS with radiation compared to BCS alone (2). The emergence of adjuvant therapy made possible a less radical surgical approach of breast cancer. After BCS, if cancer cells are found at the edges of the specimen, additional surgery may be necessary as positive margins are related to a higher local recurrence rate. A margin width of 2–10 mm was considered necessary in the past, but the current definition of a negative margin is ‘no ink on tumour’ for invasive lesions and at least 2 mm for ductal carcinoma *in situ*. Re-excision may be necessary to achieve adequate margins. If a large amount of tissue has been removed and margins are still involved, mastectomy may be recommended. On average, about two-thirds of patients are treated with BCS and one-third with mastectomy. Factors that favour mastectomy over breast-conserving therapy (BCT) include large tumour size, multiple tumours, extensive ductal carcinoma *in situ*, small breasts precluding adequate resection with an acceptable aesthetic result, and contraindications for RT (e.g. pregnancy, connective tissue disorders, or previous RT on the ipsilateral breast). Large tumours, some tumour subtypes (HER2-positive or triple-negative), or more advanced disease (clinically or biopsy-proven positive axilla) may be candidates for neoadjuvant treatment (before surgery) with chemotherapy, targeted immunotherapy, or endocrine therapy. In cases where the tumour area remains large, oncoplastic breast-conserving approaches may be warranted to obtain an acceptable cosmetic outcome. Well informed candidates for breast conservation may choose mastectomy based on individual preference. When mastectomy is indicated or desired, some patients will opt to also have a contralateral mastectomy of the normal breast. This is especially the case in pathogenic genetic variant carriers with increased risk of breast cancer, or in those with strong family history (family clusters), or with documented high-risk proliferative lesions.

There are different types of mastectomy. A total or simple mastectomy involves removing the entire breast with most of the skin without reconstruction ending with a flat chest, often called an aesthetic flat closure (AFC). To aid reconstruction, skin-sparing procedures preserve most of the skin resulting in a skin-sparing mastectomy. Keeping the whole skin envelope will result in a nipple-sparing mastectomy. The latter procedure has been adopted in more recent years as we learned that the retroareolar area rarely includes terminal duct lobular units where most carcinomas arise and a negative margin enables its preservation. Skin or nipple-sparing mastectomy allows for better immediate reconstruction.

Oncoplastic and reconstructive procedures have revolutionized breast cancer surgery considerably in recent decades, and reconstruction of the breast is an important option for women who undergo mastectomy (3, 4, 5). There are several options for reconstruction, and women planning to undergo mastectomy should be evaluated by a plastic surgeon or a breast surgeon with formal training in reconstruction to discuss these options before surgery. Replacement of the breast volume can be performed with the use of either implants or autogenous tissues. The choice of technique is dictated by a variety of factors that include

the size and shape of the native breast, tumour location, and involvement of adjacent structures, the availability of remaining tissues around the breast and at other sites, the patient's age and comorbidities, and the type of planned adjuvant therapy. Patient's preference plays an important role in the final decision. Timing for reconstruction may be either immediate or delayed. With current techniques most cases are candidates for immediate reconstruction. Neither implant-based nor autogenous tissue-based reconstruction have any effect on the incidence or detection of cancer recurrence. The preservation of body image, femininity, and sexuality through immediate breast reconstruction can have psychological benefits and considerably reduce postoperative emotional stress. A more detailed review of breast reconstruction and oncoplastic surgery is presented in Chapter 15.

## Management of the axillary lymph nodes

Sentinel lymph node biopsy (SLNB) is a reliable method for staging the axilla in most breast cancer cases and axillary recurrence is a rare event in patients with a positive sentinel node who undergo ALND (6).

ALND involves removing most of the lymph nodes in the axilla, typically described as level I and II nodes. This operation was commonly performed for all women with invasive breast cancer in the past and is associated with complications such as pain and arm swelling (lymphedema). ALND is now usually performed only in the presence of multiple cancerous lymph nodes in the axilla.

The sentinel lymph node basin is the first lymph node or group of nodes that receive lymphatic drainage from the breast and it is usually located in the axilla. In rare cases, it may be near the sternum between the ribs (internal mammary chain lymph nodes). In regions with population breast cancer screening most patients do not have cancer in their sentinel lymph nodes.

SLNB is performed to stage the axilla and to spare patients an ALND when the biopsy is negative. It is based upon the finding that if the sentinel node does not contain cancer cells, the likelihood that other lymph nodes in the axilla contain cancer cells is very small. To identify the sentinel lymph node, blue dye, a radioactive material, indocyanine green, or a combination of two agents are injected into the breast. The dyes or radioactive material enter the lymphatic channels and flow to the sentinel lymph node. This allows the surgeon to identify and remove the appropriate lymph nodes. The sentinel nodes are subsequently examined under the microscope by a pathologist.

## Management of the axilla in the scenario of upfront surgery

Data from randomized controlled trials (RCT) have provided practice-changing recommendations for the indication of ALND. The Z0011 trial from the American College of Surgeons Oncology Group (ACOSOG), included patients with T1-2 ( $\leq 5$  cm) lesions who were candidates for BCS with whole breast radiotherapy, had not received neoadjuvant chemotherapy, and had one or two positive sentinel nodes (micro or macroscopic disease). A total of 446 patients were randomized to no further surgical treatment of the axilla (SLNB-only) and 445 cases to ALND. With a median follow-up of 9.25 years, the 10-year cumulative

locoregional recurrence, the 10-year overall survival (OS), and the 10-year disease-free survival (DFS) were similar in both arms, showing non-inferiority for the omission of ALND (7).

The AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery?) trial from the EORTC (European Organization for Research and Treatment of Cancer) presented a similar design to the Z0011 including cases with T1-2 lesions with positive sentinel node (micro or macroscopic disease), but this trial also included patients treated with mastectomy (18% of cases) and randomized cases to ALND (n = 744) or axillary radiotherapy (ART; n = 681). After a median follow-up of 10 years, there were no significant differences in 10 y-axillary recurrence rate and 10 y-OS between the two groups. ALND was associated with a higher lymphedema rate in updated five-year analyses. Quality-of-life scales did not differ by treatment through five years (8).

What seems clear from older trials and confirmed by the recent studies described here is that lymph node metastases are indicators but not governors of survival (9). Based on these studies, most guidelines have been modified to consider no further axillary surgery in patients who meet all Z0011 selection criteria: T1-2 lesions cN0, one or two positive sentinel lymph nodes (SLNs), candidates for BCT, and no neoadjuvant chemotherapy.

## Omission of axillary surgery/staging

De-escalation of axillary surgery in patients with one or two positive SLNs has raised the question of whether selected breast cancer patients may even forgo axillary surgery or staging. A recent RCT carried out in the era of SLNB, the SOUND trial (Sentinel node vs. Observation after axillary Ultrasound) included patients of any age, with tumours up to 2 cm in size (cT1) and a clinically negative axilla (cN0) who were candidates for BCS with whole-brain radiation therapy (WBRT) (BCT) and randomized to SLNB or no further axillary surgery (BCT-only). The study included 1405 women in the intention-to-treat analysis, 708 in the SLNB group and 697 in the BCT-only group. Median tumour size was 1.1 cm and 88% were ER+/HER2-negative. In the SLNB group, 97 patients (13.7%) had positive axillary nodes. After a median follow-up of 5.7 years, the five-year distant DFS (DDFS) was 97.7% in the SLNB group and 98.0% in the BCT-only group (log-rank  $P = 0.67$ ). The five-year OS was 98.2% in the SLNB group and 98.4% in the BCT-only group (log-rank  $P = 0.72$ ). The five-year cumulative incidence of axillary recurrences was 0.4% in both groups (Gray  $P = 0.91$ ) (10).

A similar study, the INSEMA (Intergroup Sentinel Mamma) trial included patients of any age, with T1-2 lesions (up to 5 cm), cN0 and planned BCS with WBRT and randomized either to no further axillary surgery or SLNB in a 1:4 allocation. Patients with a positive SLN underwent a second randomization in a 1:1 ratio to completion ALND or no ALND. The per-protocol population comprised 4858 patients, 3896 in the SLNB group and 962 in the BCT-only group. Median preoperative tumour size was 11 mm, with 79.4% of tumours  $\leq 2$  cm (pT1) and 95% HR+/HER2-negative. In the SLNB group, 15% had positive axillary nodes. After a median follow-up of 73.6 months, omission of axillary surgery was non-inferior to SLNB (HR 0.91; 95% CI 0.73–1.14) (11).

In an era of systemic therapies based more on tumour biology than lymph node status, these studies paved the way to widen indications for omission of axillary surgery/staging, not only in elderly patients with ER+/HER2-neg cN0 disease. According to the ASCO Guideline Update (2025) for SLNB in Early-Stage Breast Cancer, clinicians should not recommend



routine SLNB in select patients who are postmenopausal,  $\geq 50$  y/o, with a clinically negative axilla (cN0, including negative axillary ultrasound), Grade 1–2, small ( $\leq 2$  cm) lesions, HR+/HER2-negative, who undergo upfront BCS + WBRT (12).

## Management of the axilla in the scenario of neoadjuvant therapy

Early reports of SLNB in patients after neoadjuvant chemotherapy (NAC) showed increased false negative rates (FNR) (~12% or higher) compared to upfront surgery (~5–8%), generating controversy about the technique in this scenario.

More recent and detailed prospective studies have shown FNRs ranging from 7 to 13%. The SENTINA study included 1,737 patients with clinically negative or positive axilla (cN0 or cN1–2) receiving NAC. SLNB was performed in different timings (before or after chemo), and two groups had backup ALND, allowing for calculation of FNRs. The most concerning group, patients with cN1–2 at presentation who became ycN0 after primary systemic treatment, showed a FNR of 14.2%. Removal of 3 SLNs reduced the FNR to 7.3% and combined blue dye and radiolabeled colloid increased the detection rate and number of nodes detected (13).

With the aim to further decrease the FNR in this setting, Caudle and colleagues explored targeted axillary dissection (TAD) by retrieving the sentinel node/s and clipped biopsy-proven node/s with a reduced FNR of 2.4% (14). Other alternatives to increase detection rates and decrease the FNR include marking axillary lymph nodes with radioactive iodine seeds (MARI procedure) and superparamagnetic iron nanoparticles guided surgery.

Prospective experience reported from MSKCC performs SLNB in patients with initially positive axilla (biopsy-proven) who become clinically negative (ycN0) with dual tracer technique (blue and radiolabeled colloid) and pursue to remove at least 3 SLNs without marking or clipping biopsy-proven node/s (no TAD). Of 234 patients with these characteristics with a negative SLNB and a median follow-up of 40 months, only one axillary recurrence (0.4%) has been observed (15). However, experience from large centres performing single-tracer (radiolabeled colloid) SLNB question the need to adopt dual tracer technique with ‘at-least-three-SLNs-policy’ or the need of any TAD. Galimberti and colleagues report 123 cases with negative SLNB out of 222 cases cN1–2 who became ycN0. No more than 2 SLNs were retrieved in 74% of cases. With a median follow-up of 9.2 years, only 2 (1.6%) axillary recurrences have been observed with no difference in 10-year cumulative incidence of distant events compared to cases with initial cN0 (16).

Based on current evidence and reported experience, recommendations for SLNB in the neoadjuvant setting may include:

- Preferably perform SLNB after neoadjuvant chemotherapy (NAC).
- Perform SLNB only in patients with clinically negative axilla (ycN0) after NAC.
- In cases with clinically negative axilla at presentation (before NAC), standard SLNB technique (as per each institution) should suffice.
- In patients with initially positive axilla (cN+) who become clinically negative (ycN0), consider the adoption of:
  - dual tracer SLNB technique with removal of  $\geq 3$  LNs.



- or
  - TAD technique.
- Keep a low threshold for proceeding to ALND (i.e. suspicious nodes during surgery, difficulty with SLNB technique).

Again, the development of clinical guidelines is always a work in progress, so recommendations are expected to be subject to modifications.

## **Surgery after neoadjuvant systemic therapy (NAC)**

Historically, neoadjuvant systemic therapy (NAC) was primarily employed to transform inoperable locally advanced breast cancer to operable disease. Subsequently, its use has expanded to tumour reduction, preservation of breast and axillary contents, and evaluation of treatment response.

The decision for mastectomy or breast conservation depends on factors such as the feasibility of obtaining clear margins while maintaining an acceptable cosmetic outcome, the presence of multifocal carcinoma, extensive microcalcifications on mammography, or contraindications to radiotherapy. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 clinical trial demonstrated that neoadjuvant therapy did not show superiority over adjuvant chemotherapy regarding primary endpoints like DFS or OS. However, it did exhibit an inclination towards facilitating more breast-conserving surgeries (17).

A systematic review and meta-analysis to assess the axilla after NAC showed an overall axillary pathologic complete response rate of 37% for patients who were initially node-positive (18). Consequently, axillary dissection may overtreat 37% of patients who could have benefited from SLNB after NAC. Management of the axilla in this scenario is described here.

A new role assigned to NAC is assessing the response to systemic therapy, particularly in breast cancers characterized by HER2 overexpression and the triple-negative subtype. The current most effective regimen for achieving a pathological complete response (pCR) in triple-negative breast cancer involves the addition of a PD-1 inhibitor along with platinum based chemotherapy (19). Furthermore, the pCR rate in neoadjuvant dual-target therapy for HER2-positive breast cancer surpasses that of single therapy (20). Subsequent adjuvant systemic therapy can be customized based on the response post-NAC, with an excellent prognosis achieved if a pCR is attained.

Looking to the future, there is a growing interest in identifying a subgroup of patients who achieve pCR in both the breast and axillary lymph nodes, potentially eliminating the need for surgery altogether (21). This reflects the evolving landscape of breast cancer treatment, where personalized and minimally invasive approaches are becoming increasingly important.

## **Multidisciplinary management of locally advanced breast cancer**

Locally advanced breast cancer (LABC) encompasses tumours displaying specific characteristics, including a size of 5 cm or larger, involvement of the skin or underlying chest muscle, presence of more than three affected lymph nodes, or inflammatory breast cancer. LABC

is distinguished by its advanced stage and propensity for widespread metastasis. However, through a combination of systemic therapies like chemotherapy and endocrine treatment, along with locoregional approaches such as surgery and radiotherapy, LABC can be effectively treated, offering prospects of cure.

At the heart of managing LABC lies the collaboration among various specialists, including oncologists, surgeons, radiation oncologists, pathologists, and radiologists. This multidisciplinary team conducts a thorough evaluation of each case, considering factors such as tumour size, lymph node involvement, hormone receptor status, HER2 expression, and patient preferences. By engaging in shared decision-making, customized treatment plans are devised to cater to the individual needs of each patient (22).

While some patients may initially be considered for primary surgery, those with locally advanced disease face a significantly elevated risk of local recurrence and distant metastases. As a result, the general recommendation is to treat LABC with neoadjuvant chemotherapy (NAC) first. However, exceptions may arise, particularly in cases where immediate relief is necessary due to factors such as fungating or bleeding tumour, which may be more common in regions with limited resources.

With the development of new targeted agents, such as the anti-HER2 therapy, CDK4/6 inhibitors, and immunotherapy, which can be used together with chemotherapy, excellent responses to NAC can be obtained, enabling breast conservation to be carried out. However, mastectomy may still be required in many cases, particularly in inflammatory breast cancer (22). MRI is the most accurate modality to demonstrate response to therapy and to help ensure accurate presurgical planning (23). Surgery is often followed by radiation therapy, with further systemic therapy in the adjuvant setting dependent on the histopathological outcome (whether complete or partial pathological response) and the molecular markers to inform further systemic therapy (hormone therapy, targeted therapy, or chemotherapy) (24).

## **Advancements in surgical management for metastatic breast cancer**

Metastatic breast cancer (MBC) presents a significant clinical challenge, with diagnosis rates varying from 5% in high-income countries to 25% in low-income countries. Despite its incurable nature, survival rates have seen improvement due to the development of newer therapeutic agents. Historically, surgical intervention in MBC primarily aimed at palliating symptoms to enhance quality of life rather than seeking curative outcomes. However, ongoing research and advancements in surgical techniques, coupled with a deeper understanding of the disease biology, have prompted a reevaluation of surgery's role in managing MBC.

The question arises: Is there a benefit in removing the primary tumour when cancer has already spread beyond the breast and axilla? Traditionally, surgery in MBC focused on alleviating symptoms related to local tumour burden, such as pain, ulceration, or bleeding. While these interventions remain crucial in select cases, surgery's role in MBC has expanded to encompass broader therapeutic objectives, including disease control, prolonged survival, and even potential cure in carefully chosen patients.

Literature presents conflicting data regarding surgery's impact on survival in MBC. Retrospective studies suggest a survival advantage with primary tumour surgery, particularly in cases with free surgical margins and specific types or numbers of metastatic sites. For

instance, women with bone-only metastases showed improved survival post-surgery (25). Conversely, prospective randomized trials have failed to demonstrate an OS benefit from primary tumour removal. While surgery improved locoregional control, it did not enhance quality of life or OS (26). Notably, the only prospective study reporting an OS benefit was from the MF07-01 Study group, which found a 14% higher chance of survival after a 10-year follow-up among patients with de novo MBC who underwent surgery followed by systemic treatment (27).

Challenges persist in the surgical management of MBC, including the risk of perioperative complications, potential delays in systemic therapy, and the need for careful patient selection to optimize outcomes. The decision to pursue surgical intervention in MBC must be carefully individualized, considering factors such as the extent and location of metastatic disease, tumour biology, patient performance status, and treatment goals. Multidisciplinary collaboration among oncologists, surgeons, radiation oncologists, and other specialists is crucial in evaluating each case comprehensively and formulating personalized treatment plans tailored to the unique needs of the patient.

## Breast centre certification and its impact on surgery

Some evidence suggests that patients with breast cancer treated in high-volume centres (i.e. more than 150 primary breast cancer surgeries per year) and by specialized surgeons (operating on more than 50 new cases per year) may have improved outcomes. This is not just related to surgery but also to a multidisciplinary approach involving specialized radiologists, oncologists, pathologists, etc. A well-structured organizational approach may also optimize costs and reduce waiting lists.

Current data show that the use of quality indicators (QIs) for breast cancer care, regular internal and external audit of performance of breast centres, and benchmarking are effective means to improve the quality of care (28). Adherence to guidelines markedly improves the quality of care, notably regarding adjuvant treatments, likely resulting in better outcomes. Since quality assurance benefits patients, it will be a challenge for the medical and hospital community to develop affordable quality control systems. The European Society of Breast Cancer Specialists (EUSOMA [formerly European Society of Mastology]) started in 2003 a voluntary certification process in an attempt to improve the clinical performance of dedicated European breast centres. An essential element to ensure and improve high standards of care is quality control based on structured QIs defined at local, national or international level with the main objective of setting benchmarks to reduce diagnostic and therapeutic variability and to improve outcomes. The EUSOMA QIs are an essential part of the voluntary European certification process (29) (Table 14.1).

## Look to the future

It is undeniable that the role of the surgeon in the management breast diseases is the subject of continuous evolution moving from the cancer-extirpative surgeon to a deeply informed surgical leader who interacts in a multidisciplinary setting and encompasses tasks for risk assessment, genetic counselling, new diagnostic approaches, and breast reconstruction. It is

**Table 14.1** Recently updated QIs that have an impact on surgery (29)

|     |                                                                                                                                                                                                                                                                                                                                                                                               |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1.  | Time from neoadjuvant chemotherapy treatment (NAC) to surgery. Definition: Proportion of patients with non-metastatic invasive BC who underwent surgery within 6 weeks from the end of NAC. Time interval from the end of NAC to surgery ideally up to 6 weeks or maximum within 8 weeks. Minimum standard: 80%. Target: 90%.                                                                 |
| 2.  | Time from surgery to adjuvant chemotherapy. Definition: Proportion of patients with non-metastatic invasive BC that start adjuvant chemotherapy within 6 weeks interval from the date of surgery to the start of adjuvant chemotherapy. Time interval from surgery to the start of adjuvant chemotherapy ideally up to 6 weeks or maximum within 8 weeks. Minimum standard: 80%. Target: 90%. |
| 3.  | Time from surgery to radiation therapy (RT). Definition: Proportion of patients with non-metastatic invasive BC and ductal carcinoma <i>in situ</i> (DCIS) who started postoperative RT within 20 weeks after surgery (excluding those receiving adjuvant chemotherapy). The time interval from surgery to the start of RT is ideally up to 8 weeks. Minimum standard: 80%. Target: 90%.      |
| 4.  | Rate of surgically excised benign lesions. Definition: Proportion of benign lesions undergoing surgical excision compared to all diagnosed lesions based on the definitive pathology report (surgical specimen only, fine needle sampling, or core needle biopsy excluded). Minimum standard: 10%. Target: 5%.                                                                                |
| 5.  | Breast conservative surgery (BCS) in DCIS patients. Definition: Proportion of patients with DCIS, not greater than 2 cm, who underwent BCS, excluding carriers of BRCA1/2 and other high-susceptibility gene mutations. Minimum standard: 90%. Target: 95%.                                                                                                                                   |
| 6.  | Single operation in DCIS patients. Definition: Proportion of patients with DCIS only who received a single operation for breast primary disease, excluding reconstruction. Minimum standard: 70%. Target: 90%.                                                                                                                                                                                |
| 7.  | BCS in patients with invasive BC. Definition: Proportion of patients with invasive BC not greater than 3 cm (total size, including DCIS component) who underwent BCS as primary treatment, excluding BRCA 1/2 mutation carriers and other high-susceptibility gene mutations. Minimum standard: 85%. Target: 95%.                                                                             |
| 8.  | BCS after NAC. Definition: Proportion of patients with invasive BC no greater than 3 cm after NAC, treated with BCS with or without oncoplastic techniques, (excluding BRCA 1/2 mutation carriers and other high-susceptibility gene mutations and inflammatory BC). Minimum standard: 85%. Target: 95%.                                                                                      |
| 9.  | Single operation in patients with invasive BC. Definition: Proportion of patients with invasive BC who received a single operation for primary BC (excluding reconstruction procedures and axillary procedures). Minimum standard: 80%. Target: 90%.                                                                                                                                          |
| 10. | No sentinel lymph node biopsy (SLNB) in DCIS patients. Definition: Proportion of patients with a preoperative diagnosis of DCIS, who underwent BCS without SLNB. Minimum standard: 80%. Target: 90%.                                                                                                                                                                                          |
| 11. | SLNB in patients with invasive BC and clinically negative axilla. Definition: Proportion of patients with invasive BC and clinically negative axilla (i.e. negative at clinical examination by palpation and axillary ultrasound, cN0) who underwent SLNB, (excluding patients who received NAC). Minimum standard: 90%. Target: 95%.                                                         |
| 12. | Number of axillary lymph nodes (LNs) excised for SLNB in patients with invasive BC. Definition: Proportion of patients with invasive BC who underwent upfront SLNB with no more than five nodes removed. Minimum standard: 90%. Target: 95%.                                                                                                                                                  |
| 13. | No ALND in cN0, in upfront surgery BCS and $\leq 2$ positive SLNs. Definition: Proportion of patients with early-stage BC (cT1–2) and cN0 who underwent BCS and had $\leq 2$ positive SLNs, with no further axillary surgery (no ALND). Minimum standard: 90%. Target: 95%.                                                                                                                   |

Table 14.1 Continued

|     |                                                                                                                                                                                                                                                                                                                  |
|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 14. | SLNB after NAC in cN0. Definition: Proportion of patients with invasive BC and a clinically negative axilla cN0 (i.e. negative at clinical examination and axillary ultrasound) before NAC who underwent SLNB after NAC. Minimum standard: 90%. Target: 95%.                                                     |
| 15. | SLNB in cN1 after conversion to ycN0 after NAC. Definition: Proportion of cN1 patients treated with NAC, who have converted to ycN0 that underwent axillary staging after NAC other than ALND, [including SLNB (minimum three nodes) or targeted axillary dissection (TAD)]. Minimum standard: 50%. Target: 90%. |
| 16. | Immediate breast reconstruction. Definition: Proportion of patients undergoing mastectomy receiving immediate breast reconstruction, excluding patients with inflammatory BC and those requiring postmastectomy radiation therapy (PMRT). Minimum standard: 40%. Target: 60%.                                    |
| 17. | Immediate breast reconstruction in patients with PMRT. Definition: Proportion of patients with PMRT, who received immediate breast reconstruction, excluding patients with inflammatory BC. Minimum standard: 20%. Target: 40%.                                                                                  |

Source: data from Biganzoli, Laura et al. Quality indicators in breast cancer care: An update from the EUSOMA working group. *European Journal of Cancer*, Volume 86, 59–81

also conceivable that further in the future we may identify a subset of tumours that could be managed by some type of non-surgical ablation. However, it is likely this will apply only to a small subset of cases. For the moment, surgery remains the most important intervention with a full curative attempt.

## Key messages

- The current concept the breast surgeon comprises a deep knowledge of surgical technical details, tumour biology, disease staging, prognosis, mastery of reconstructive techniques, and leadership to interact with a multidisciplinary team.
- A breast surgeon must master the ever-changing decision-making algorithm for the optimal treatment of breast cancer that takes into account the timing of systemic therapies and bidirectional implications of radiotherapy and surgery.
- In general, two-thirds of early breast cancer patients can be treated with breast conservation.
- Practice-changing recommendations in the management of the axilla are still ongoing towards a more conservative approach.
- Surgical removal of the tumour currently still represents the most important intervention with a curative attempt for early-stage breast cancer.
- Development of clinical guidelines is always a work in progress, so recommendations are expected to be subject to modifications.

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## **Oncoplastic and reconstructive breast surgery**

*Pankaj G. Roy, Maurício Magalhães Costa, and Cary S. Kaufman*

### **Introduction**

Surgery for breast cancer has evolved dramatically over the years, from Halsted's radical mastectomy to the development and acceptance of breast-conserving surgery (BCS) as the standard of care. BCS followed by radiotherapy has been found to be equivalent in disease-free and overall survival when compared with mastectomy and hence has become the standard of care for early-stage breast cancer. For patients with a large tumour to breast size ratio, wide local excision (WLE) may result in poor cosmetic outcomes or the need for mastectomy. The introduction of oncoplastic breast surgery techniques in the last couple of decades have made it possible to reshape the breast aesthetically in these patients. Still many patients require mastectomy, who have the option of total breast reconstruction using either implants or autologous tissue—either at the same time as the mastectomy (immediate) or as a separate operation (delayed).

Oncoplastic and reconstructive surgery may be performed by the oncological or the plastic surgeon depending on local protocols. In most countries and in most large breast centres, a multidisciplinary approach with both oncological and plastic surgeons working together is the reference standard for the reconstructive cases. But the scenario is variable and depends on many different factors. Many oncologic breast surgeons are learning basic or intermediate oncoplastic techniques to provide aesthetic as well as oncologic breast care. To facilitate wider adoption of oncoplastic breast surgery, some countries have created a model of training super-specialist oncoplastic breast surgeons, who are dually qualified in cancer and reconstructive surgery. Many centres in the UK and Europe are offering oncoplastic breast surgery fellowships to overseas candidates to help widen the adoption and training of oncoplastic breast surgeons.

### **Oncoplastic breast surgery**

The primary goal of all oncological surgery is cancer resection. In the past, the secondary goal of returning the patient to look as normal as possible was not addressed. There is increasing awareness of the need for good aesthetic outcomes from these procedures (1). Most breast cancer patients will live their normal lives and should carry with them the least amount of deformity possible. Good aesthetic outcomes have been linked with significant improvements



in patient satisfaction and quality of life (2, 3). Oncoplastic breast surgery utilizes the benefits of plastic surgical techniques at the time of cancer resection rather than to be used later to repair poor results.

The oncoplastic breast surgery (4) includes the following components:

- Surgery to treat cancer.
- Partial reconstruction for WLE defects.
- Access to total reconstruction for mastectomy (Immediate or delayed).
- Symmetrization surgery.

## Oncoplastic breast conservation surgery

‘Oncoplastic breast conservation surgery’ involves combining oncological resection with plastic surgery reconstruction techniques (1, 5, 6, 7, 8) and is indicated if the expected volume loss after tumour resection is greater than 20% of the breast volume. For volume loss less than 20%, standard WLE or level 1 techniques, such as batwing/doughnut resections without involving extensive resections or breast re-alignment, are usually sufficient. Oncoplastic BCS can be broadly divided into two fundamentally different groups:

1. Volume displacement using glandular or dermo glandular redistribution of breast tissue into the resection site (therapeutic mammoplasty) (Figure 15.1).
2. Volume replacement using autologous tissues from an extramammary site to compensate for volume loss after tumour resection, the commonly used being chest wall perforator flaps (Figure 15.2).

These techniques extend the indications for breast conservation surgery, and there is now data from several centres establishing the oncological safety of these procedures in addition to low re-excision rates (9, 15).

The individual therapeutic procedure is worked out and planned together with the patient, considering the tumour size and location relative to breast size, patient preferences, comorbidities, and tumour biology. The use of neoadjuvant systemic therapy, particularly

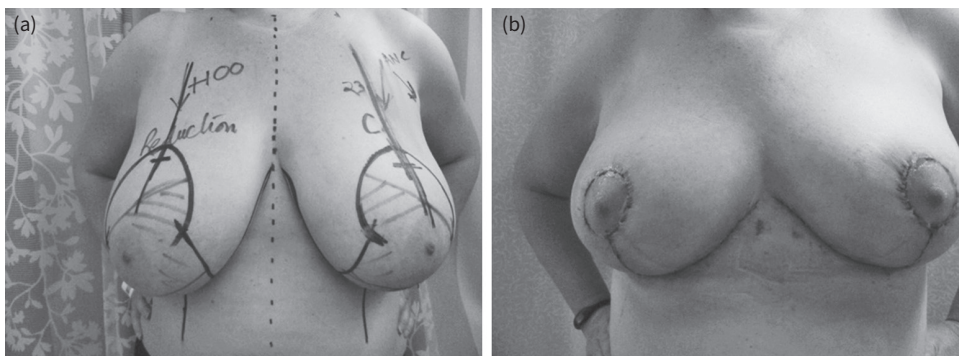


**Figure 15.1** Therapeutic mammoplasty left breast and simultaneous right breast reduction for 4 cm cancer in the left lower central breast. (a) Pre-op photo; (b) Post-op photo.



**Figure 15.2** Right breast conservation surgery with wide local excision and immediate partial breast reconstruction for lateral chest wall perforator flap for 27 mm cancer in the upper outer quadrant of right breast in a B-cup breast. (a) Pre-op photo, (b) Pre-op photo with drawings for the flap and perforator mapping, (c) post-surgery photo.

in triple-negative and Her-2-positive tumours has a significant potential to downsize the tumour to allow breast conservation. The surgical approach ought to be balanced with oncological safety.

The oncoplastic BCS has the following advantages over mastectomy with breast reconstruction:

1. Shorter procedures, so lesser hospital stays.
2. Quicker recovery.
3. Fewer complications.
4. Maintenance of sensation.
5. Financial viability for the healthcare system.
6. Positive psychosocial impact for the patient.
7. Quicker return to routine activities.

A recent Cochrane review (10) shows that the oncological outcomes are similar with potentially improved aesthetic results and reduced re-excision rates when the oncoplastic techniques are compared to standard WLE but there seems to be a higher risk of complications with oncoplastic techniques. Similarly low certainty of evidence in favour of oncoplastic breast surgery was concluded by an independent published study (11). There however remains support for oncoplastic breast conservation surgical techniques from the experts due to the intended benefits as highlighted above. Moreover, long-term data have shown that breast conservation surgery shows a trend for improved survival over mastectomy for the treatment of breast cancer (21), favouring breast conservation surgery where safe and feasible.

## Mastectomy and total breast reconstruction

There is a wide variation in women choosing breast reconstruction after mastectomy despite the evidence that there is a clear benefit on patients' quality of life. This may be due to various factors including sociodemographic, ethnic backgrounds, medical conditions, and access to reconstruction services, of which the latter has become more apparent after the COVID pandemic due to the strain on the healthcare services globally. The decision is personal and is

made according to the patient's perspective of her body image, sexuality, and self-esteem. Patient education is the key, and all suitable reconstructive options should be discussed.

The reconstruction audit in the UK showed that the rate of mastectomy and reconstruction varied from 23% to 75%, while immediate reconstruction varied from 8% to 43% (12).

The eligibility for immediate vs. delayed reconstruction should be established by the surgical team early on, to manage patient expectations and the expected timelines for the cancer pathway. Mastectomy with immediate breast reconstruction may protect breast cancer patients from a period of psychosocial distress, poor body image, and diminished sexual well-being compared with those waiting for delayed breast reconstruction (13).

As a disadvantage, immediate breast reconstruction may be a larger, more complex surgery requiring a longer recovery time. Also, if the patient experiences any kind of complication (wound dehiscence, haematoma, tissue loss), it may postpone adjuvant therapy. A patient may wish to delay reconstruction until after all treatments have been completed. Many women feel that delaying reconstruction gives them time to focus on treatments and research the type of reconstruction that best suits their needs.

## Simple (or total) mastectomy

It is important that patients undergoing mastectomy without reconstruction (either as a choice or due to clinical reasons) are left with a neat scar that is typically placed along the inframammary fold with a flat chest wall and minimal redundant folds to allow easy hygiene and prosthetic fitting (Figure 15.3). This is often called an aesthetic flat closure (AFC). This closure should avoid redundant folds and visible scars that often compromise quality of life, causing stress and inconvenience.

## Total breast reconstruction for mastectomy

Candidates for immediate breast reconstruction include skin- and nipple-sparing mastectomy for early invasive or *in situ* disease and prophylactic mastectomies (Figure 15.4).

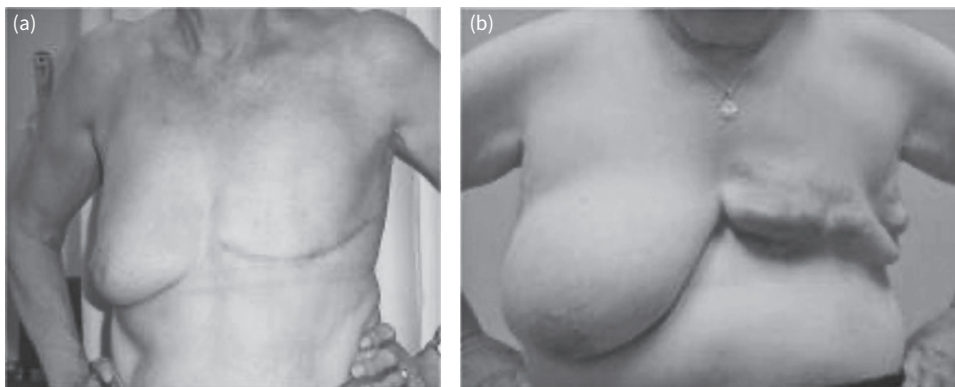


**Figure 15.3** Scars after simple mastectomy. (a) Preferred scar i.e. placed low down on the chest wall with no redundant folds. (b) Such scars should be avoided.

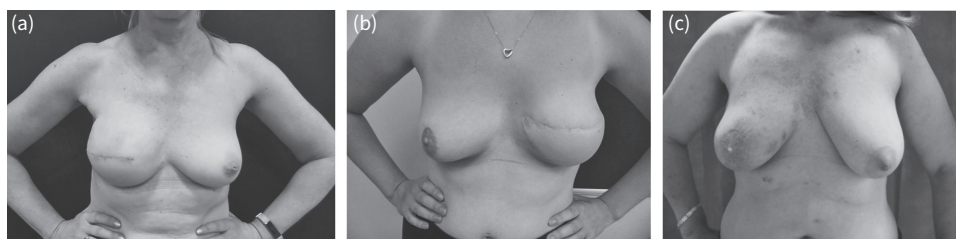


**Figure 15.4** Photographs showing mastectomy with total breast reconstruction. (a) Immediate reconstruction with pre-pectoral implant assisted with commercially available dermal matrix. (b) Delayed reconstruction with abdominal free flap. (c) Immediate reconstruction with LD (*latissimus dorsi*) flap.

Immediate breast reconstruction is often performed with an expander or an implant. The rate of immediate breast reconstruction with implant or tissue expander has seen an increase with the adoption of pre-pectoral implant reconstruction, which facilitates quicker recovery. There is an ongoing debate about whether meshes/matrices derived from animal skin should be used to cover the implant. Emerging data indicate that post-radiotherapy capsular contracture rates are low with prepectoral implant reconstruction as compared with subpectoral implant reconstruction.

Lipomodelling/fat transfer has shown a promising role as an adjunct in all types of breast reconstruction. The fat transfer procedure involves removing fat from other parts of the body with excess fat by process of liposuction. The retrieved fat is then processed and transferred by injecting at the recipient site. This is commonly offered after prepectoral implant reconstruction that results in implant visibility and rippling due to a lack of muscular cover. The concerns associated with fat transfer about the potential risk of cancer recurrence have been allayed by studies with long-term follow-up (14). Fat transfer can also be used to correct focal defects after breast conservation surgery.

Autologous reconstruction using abdominal free flap is still the gold standard although the uptake can vary depending on the availability of the expertise and resources needed to support the free flap service. Viable tissue flap reconstruction may be performed either as immediate or delayed reconstruction of the mastectomy site. Tissue flaps and free flaps are complex procedures performed at facilities equipped with close postoperative monitoring. These tissue flaps move a section of skin and underlying fat from one location in the body towards the missing breast area while maintaining the blood supply to the flap (15). The blood supply source may remain from its original location by rotating the flap into the breast area. Alternatively, the blood supply to the flap may be disconnected from its origin and reattached to local blood vessels at the new breast location. The reconstruction using Latissimus dorsi flap (with/without implant) has seen a significant decline in parallel to the rising popularity of the implant alone reconstruction over the last decade. Certainly, these are complex procedures and require specialized training, skills, and experience.

## **Patient-reported outcomes and health-related quality of life with breast reconstruction**

Patients who have the opportunity to receive breast reconstruction after mastectomy can significantly improve health-related quality of life (HRQoL). Factors associated with HRQoL

include satisfaction with appearance, psychological well-being, and physical function. In patients with breast cancer, some studies have shown that aesthetic outcome also influences HRQoL (16).

Multiple questionnaires have been used to measure patient-reported outcomes (PROs) after breast surgery for patients with breast cancer. However, until the turn of the century, few instruments had sufficient evidence for specific use in these patients due to limitations in certain areas, including aesthetics and body perception. In 2009, the BREAST-Q questionnaire was developed to meet this need, as a validated PRO measurement specific to breast surgery (17). Since its release, the BREAST-Q has greatly improved studies of satisfaction with breast surgery from the patient's perspective. The three BREAST-Q domains are: 'Satisfaction with breasts', 'Psychosocial well-being', and 'Physical well-being'. Each domain score was obtained by transforming the scale item responses with the Q-score software program. The transformed scores range from 0 to 100, and higher scores indicate greater satisfaction or quality of life.

The BREAST-Q score for 'physical well-being' in different studies, was maintained at 5 years after breast reconstruction, and breast reconstruction procedures were better than mastectomy for 'Satisfaction with breasts' and 'Psychosocial well-being' (18, 19, 20).

A comparative study on breast reconstruction with prosthesis or autologous tissue should ideally be conducted in every country due to cultural issues, and to have data from all countries regarding this type of surgery. Cultural influences are important and play a central role in the perception of the body (21). Furthermore, the use of BREAST-Q with all its modules needs to have as much feedback as possible for the cultural adaptation of the translation.

## Surgical training

Oncoplastic breast surgery is an essential factor in maintaining quality of care, and calls for an integrated training programme to meet the growing demand for expertise in the field.

Oncoplastic surgery has four levels of competence:

- **Level 1:** Unilateral and displacement techniques, aesthetic skin incisions, de-epithelialization of areola margins, glandular mobilization, and reshaping techniques; these may include crescent mammaplasty, round block or doughnut mammaplasty, and AFC.
- **Level 2:** Therapeutic mammaplasty, breast reduction, mastopexy, Grisotti flap, and nipple and areolar reconstruction, volume replacement techniques for breast conservation;
- **Level 3:** Expander and implant techniques, immediate breast reconstruction with temporary expanders or implants, and contralateral symmetry with breast augmentation;
- **Level 4:** Autologous flaps, either pedicle or free tissue transfer, or a combination of both techniques.

Specialist surgeons dealing with breast cancer should be prepared to work with a minimum of levels 1 and 2, but the ideal is to have a team with people equipped to cover all aspects of training to manage the full spectrum.

As the demand for breast reconstruction steadily increases and the key to optimizing care is the multidisciplinary approach, an interspecialty training programme with plastic and

breast surgeons developed to equip surgeons with the combined skills of oncological and reconstructive techniques would be an excellent development, similar to the Training Interface Group (TIG) fellowships in oncoplastic breast surgery in the UK. For surgeons in practice, there are multiple oncoplastic surgery course options for education and validation of skills.

## Future perspectives

The future of breast reconstruction may be associated with new technologies and advances in regenerative medicine. With the studies on fat grafting and its regenerative potential mediated by stem cells, fat is a promising entity for full breast reconstruction. The development of three-dimensional (3D) printing and tissue engineering is also promising for surgeons. New implant materials, textures, and shapes may diminish the rate of capsular contracture and complications in implant-based reconstructions.

Virtual reality and 3D imaging for preoperative planning are already a reality in some breast centres. These technologies may be useful for patient education at the preoperative consultation. There is need to intensify the global efforts so that oncoplastic surgical techniques become essential to the basic practice of versatile breast cancer surgeons, and all the women with breast cancer have the opportunity to choose surgery with improved aesthetic results along with better oncological outcomes.

The binomial of oncological safety and cosmesis is currently the regent for successful surgical treatment. Quality control in breast reconstruction is difficult to quantify, but great quality care lies in a multidisciplinary team, a well-trained surgeon, and an educated patient.

## Key messages

- Oncoplastic breast cancer surgery includes a series of techniques that can be combined with cancer resection to provide patients with improved outcomes.
- Oncoplastic surgical treatment of breast cancer requires safe and adequate cancer resection but includes leaving the patient with an aesthetically acceptable breast or reconstruction.
- When mastectomy is necessary to treat breast cancer, it is important to consider the options for immediate or delayed breast reconstruction, which results in a variety of long-term benefits for the patient.
- It is important that surgeons treating breast cancer become familiar with the variety of techniques of oncoplastic breast cancer surgery to provide high-quality clinical care.

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## Radiation therapy

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### Introduction

Radiation therapy (RT) is a cornerstone of the treatment in the post-lumpectomy breast and post-mastectomy settings. Over the last few decades, there have been several advances in clinical areas (e.g. more accurate patient selection based on tumour- and patient-related characteristics and more accurate treatment volume delineation) as well as in the field of technology (e.g. treatment planning and delivery). More recently, biological factors are entering clinical practice. Using evidence-based estimates from the literature, the number of patients receiving RT for breast cancer is expected to increase in Europe by approximately 16% over a decade (1).

Postoperative RT is applied to reduce the probability of local-regional recurrences of breast cancer following surgery. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analyses of prospective randomized trials demonstrated that postoperative RT improves local control, disease-free survival, and overall survival for patients with early-stage breast cancer in the case of lymph node involvement and/or in the framework of breast-conserving therapy (2, 3, 4). In view of the impressive improvement of the outcome after diagnosis and treatment that was obtained over the last decades, current research also focuses on de-escalation of treatments for low-risk patients (5, 6).

RT reduces the risk of all types of recurrences, and the greatest effect is observed for local and regional control. While the risk for distant metastases is also reduced, the competing risks for recurrences outside of the irradiated volumes limits the impact that local RT can have on overall survival. With the increasing use and effectiveness of adjuvant systemic therapy, the potential for improvements in local-regional control to improve overall survival might further increase (7).

Side effects of treatments, related to comorbidity and age-related disease conditions, have a well-demonstrated influence on patient outcomes. Their reported rates are confounded by insufficient standardized reporting and the interaction with surgery and systemic treatments. In early-stage, low-risk, node-negative breast cancer patients, this may, for example, lead to a possible choice between radiation or endocrine therapy based on the risk for side effects rather than based on the expected efficacy. Therefore, in all circumstances, the full range of factors that contribute to the risks related to tumour progression as well as to the occurrence of side effects should be individually discussed with every patient. In this, the personal scope of the patient, including her expectations for her future life, should be considered as possible decisive factors in this shared decision-making process.



To de-escalate the use of RT, a critical appraisal is required of not just patient selection, but even more of target volume selection, target volume size, and dose (7). While a boost to the primary tumour bed can be indicated for patients with a high risk of local recurrence, accelerated partial breast irradiation might be offered to low-risk patients as an attractive low-burden treatment approach. With the decreasing surgical approach towards the axillary lymph nodes, combined with the encouraging results from the recent regional nodal RT trials, de-escalation of the total treatment includes a selective substitution of surgery by RT to the lymph node regions.

## Minimal and optimal requirements

In general, patients with cancer, and patients with breast cancer in particular, often have several treatment options and need to be evaluated by a multidisciplinary team before final treatment recommendations are made. Treatment recommendations should take into consideration patient-related factors (e.g. age and comorbidities), disease-related factors (e.g. pathology features and stage), and the patient's own preferences (8). RT, being an integral part of the treatment of most non-metastatic breast cancer patients and contributing to the management in the metastatic setting (e.g. palliation, pain relief), requires a broad understanding by the entire breast team of the indications for RT for breast cancer patients.

Technological advances, such as patient setup imaging and correction before and during treatment, immobilization, target volume definition, improved treatment plans, and respiratory control during treatment have led to more accurate treatment planning and delivery techniques to deliver therapeutic radiation doses more precisely to the target tissues while reducing the doses (and subsequent risks) to the surrounding normal tissues and thereby improving the therapeutic ratio of RT (see Box 16.1). Similarly, progress in our understanding of the optimization of radiation fractionation regimens and target volumes definition have reduced the treatment burden for breast cancer patients, for example, by shortening radiation courses and introducing partial breast irradiation (PBI). However, many of these advances tend to *increase* the complexity of treatment and thus might increase the risk of an error (9). Consequently, a comprehensive understanding of the utility and hazards of these advances and an open collaborative relationship between the members of the

### **Box 16.1 The proper sequence for treatment preparation highlights that the technique itself is a tool to fulfill pre-set requirements**

- Defining the indication for radiation therapy
- Defining the target volumes
- Prescribing the dose
- Setting the dose objectives for the target volumes and the dose constraints for the organs at risk
- Target and organ at risk volume delineation
- Treatment planning

multidisciplinary radiation oncology team (i.e. radiation oncologist, medical physicist, radiation therapist, technician, nurses, etc.), are required to ensure a high treatment quality. All members of the radiation oncology team need to have appropriate training and support peer review, standardization, incident reporting, and on-going quality assurance as a means to enhance the culture of safety and quality of care. These concepts are particularly important as we embrace new technologies (10).

## Equipment, personnel, and patient load

Cancer is a growing global problem and is not restricted to high-income countries. Therefore, there are several on-going global initiatives to assure treatment availability and quality, and these include task forces specialized for breast cancer. The Global Task Force on Radiation Therapy for Cancer Control (GTFRCC) defined the role of, and the global needs for, RT (11). Several countries and study groups defined minimum criteria for the infrastructure and staffing of a radiation oncology department as well as their participation in clinical studies (12, 13) (Table 16.1).

**Table 16.1** Requirements for infrastructure, staffing, and workload, as defined by the Radiation Oncology Group of the European Organization for Research and Treatment of Cancer

| EORTC ROC requirements for infrastructure, staffing, and workload |              |              |
|-------------------------------------------------------------------|--------------|--------------|
|                                                                   | Before 2009  | Since 2009   |
| <i>Human resources: workload</i>                                  |              |              |
| ETE radiation oncologists per department                          | Minimum 2.5  | Minimum 3    |
| Patients treated per year/FTE radiation oncologist                | Maximum 100  | Maximum 250  |
| FTE qualified radiation physicists per department                 | Minimum 1.3  | Minimum 2    |
| Patients treated per year/FTE radiation physicist                 | Maximum 500  | Maximum 500  |
| Radiation technologists per treatment unit                        | Minimum 2    | Minimum 2    |
| <i>Equipment: numbers</i>                                         |              |              |
| Simulator (classical and/or CT scanner)                           | Minimum 1    | Minimum 1*   |
| Megavoltage treatment units**                                     | Minimum 2    | Minimum 2    |
| <i>Equipment: workload<sup>a</sup></i>                            |              |              |
| Patients per year/megavoltage unit                                | Maximum 700  | Maximum 600  |
| Patients per year/conventional simulator                          | Maximum 1500 | Maximum 1200 |
| Patients per year/CT simulator                                    | –            | Maximum 2400 |

*Abbreviations:* CT, computed tomography; FTE, full-time equivalent.

\*Including access to a CT scanner

\*\* Preferably <10 years old.

<sup>a</sup> Based on normal waking hours.

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The needs for RT in Europe are estimated to rise over a decade by 16% with a variation of less than 5% to more than 30% among European countries. The expected relative increase by 2025 for breast cancer is 10% (14). However, readily accessible radiation facilities for the treatment of breast cancer are not universal. Despite radiation being an essential and cost-effective tool for cancer treatment, it has a low uptake on the African continent, and access is not well distributed relative to the needs. Within Africa,  $\approx 90\%$  of radiotherapy facilities are concentrated in Northern and Southern regions (15), with a large strain placed on oncologists treating in these areas. At the time of writing,  $\approx 26$  African countries have *no* radiotherapy facilities, and in most countries where radiation services are available, access is limited due to poorly maintained tertiary centres, or being unaffordable in the private sector (15). Wait times for RT are often  $>3$ –6 months. Further, the limited RT facilities in Africa are centrally located in developed cities; and the financial toxicity and logistical challenges associated with daily transport are substantial. Overall, poor access to RT facilities has become a limiting factor to breast conservation surgery in many countries in Africa.

The optimal timing of RT after breast-conserving surgery has not been well-defined, but there is a fair amount of data to guide us. Clinical trials that reported the benefit of postoperative radiation after breast-conserving surgery typically restricted the maximum interval between surgery and the start of RT to 6–8 weeks (in the absence of adjuvant pre-RT chemotherapy). In settings where access to RT is limited, the resulting longer wait times may lessen the utility of post-lumpectomy RT and hinder breast conservation. While there is not much data about the minimal acceptable time from surgery to the beginning of external beam radiation, three to four weeks following surgery to initiate RT should allow for adequate healing of the breast and axillary area and for the patient to have adequate arm mobility to facilitate treatment planning. A further reduction seems feasible in view of the decreasing use of axillary surgery and as demonstrated to be feasible by the intraoperative (partial breast) irradiation studies. The skew of patients to higher stages at presentation in some under-resourced settings (e.g. in Africa [16]) also lessens the use of breast-conserving surgery plus RT.

## Best practice

### General

In high-income countries, the mortality/incidence ratio of breast cancer decreased from about 40% in the 1970s to about 15% 35 years later, while worldwide this ratio remains about 30% (17). This can be attributed to a combination of earlier (and perhaps increased) diagnoses and improved treatment, which are, however, not universally accessible. Alongside improving outcomes, we have to re-think some of the conventional treatment paradigms and also consider the interaction between local-regional and systemic treatments. In low-risk patients with a very good outcome after one of both treatment options, parameters such as side effects and quality of life should be used to assist the patient in making an individualized treatment choice. In contrast, high-risk patients will benefit most from a positive interaction between both treatment modalities by individualizing their combination. Thanks to advances in both our knowledge of the biology of breast cancer and RT techniques, the

occurrence and the severity of late side effects have been sharply reduced. Many factors, several of which might be modulated, may influence RT-induced morbidity.

## Radiation therapy fractionation schedules

There are a number of fractionation schedules for whole breast irradiation that were used in randomized clinical trials, ranging from a total of 40 Gy in 16 daily fractions to 54 Gy in 30 daily fractions (with or without a boost to the tumour bed). Historically, a very common conventional fractionation schedule used for the whole breast was 50 Gy in 25 fractions.

Several randomized trials evaluated shorter courses of radiation (e.g. 15 to 16 fractions of 2.66 or 2.67 Gy in 3 weeks; often termed moderate hypofractionation) mainly in patients undergoing breast-conserving surgery (without nodal RT) (19). These studies report similar disease control rates compared to conventional fractionation at a follow-up of around 10 years. No significant differences in regard to toxicities such as cardiac disease were noted, while cosmesis was even better for the hypofractionation protocols compared to conventional fractionation in the START A/B trials. A tumour bed boost was not consistently used in these clinical trials. Further reduction of the treatment duration was tested, to evaluate late side effects, in the FAST randomized trial, which compared two ultra hypofractionated schemes (28.5 Gy in 5 fractions and 30 Gy in 5 fractions, both over 5 weeks) versus a conventional regimen (50 Gy in 25 fractions over 5 weeks) for node-negative patients older than 50 years with tumours <3 cm. At 10 years of follow-up, the 28.5 Gy schedule was equivalent to the conventional fractionation in regard to breast appearance and normal tissue effects, but normal tissue effects (shrinkage, induration, oedema, telangiectasia) were greater with the 30 Gy schedule (20). Subsequently, the FAST-FORWARD trial compared three whole breast RT schedules: 27 Gy in 5 fractions, 26 Gy in 5 fractions (both over 1 week), and 40 Gy in 15 fractions over 3 weeks (i.e. moderate vs. marked hypofractionation). At  $\approx$  5 years of follow-up, the local tumour control was essentially equivalent across all arms, but normal tissue effects were worse in the 27 Gy arm vs. the other two (21). After including over 4000 patients, a sub-study of this trial evaluated the same fractionation schedules for regional nodal irradiation, as well.

Initially, not as much published data regarding hypofractionation to the chest wall was available, although some patients were included in the above-mentioned trials (for example, 15% of the patients participating in the START A/B trials with moderate hypofractionation). In the meantime, the study from Wang et al. confirmed similar outcomes, independent of fractionation, for the chest wall, including node irradiation (22). No specific adverse effects were noted with radiation in the post-mastectomy group. None of the patients underwent breast reconstruction prior to irradiation, and results from the recently closed RT-CHARM trial comparing hypofractionated post-mastectomy radiation to conventional radiation in the setting of reconstruction also confirmed similar toxicity outcomes with hypofractionated vs conventional post-mastectomy RT (24).

Prospective data about hypofractionation for elective nodal irradiation is now sufficiently abundant, though, with all studies reporting similar recurrence or complication rates compared to the standard fractionation.

Older RT techniques have resulted in relatively heterogeneous doses with 'hot spots', where the delivered dose exceeded the prescription dose (often by  $\approx$  15%). With the

higher prescribed doses per fraction used with hypofractionation, the delivered doses to these areas of 'hot spots' could be even higher. Modern RT techniques are better able to deliver homogenous doses, reduce the size/magnitude of 'hot spots' of higher doses, and thus likely increase the safety of hypofractionation. Therefore, hypofractionated schedules are being increasingly adapted for broader indications and target volumes (5). Pending data from a subset of patients on the FAST-Forward trial who also received nodal RT will further inform with question. Recently ESTRO published that moderately hypofractionated radiotherapy can be offered for all indications for whole as well partial breast, chest wall (with or without reconstruction) and nodal volumes (23). The RT CHARM Trial in women with breast reconstruction concluded also that moderately hypofractionated PMRT (Post-Mastectomy Radiation Therapy) appears safe and effective (24).

## Total dose

Since most local recurrences occur in the same quadrant of the primary tumour, the concept of a 'boost' dose to that region after whole breast irradiation was introduced. Several trials demonstrate that a boost reduces the risk of local recurrences by about 40% at long-term follow-up (25), but does not improve overall survival, and it can worsen cosmetic outcomes. As the absolute rates of local-regional recurrences decline (likely following better diagnostic tools, patient selection, systemic therapies, surgery, and whole breast RT approaches), the role of the boost may decline, but it will likely remain clinically relevant, especially for high-risk and younger patients (26)

## Partial breast irradiation (PBI)

PBI has been introduced as an alternative treatment to conventional whole breast radiation in selected patients with early-stage low-risk breast cancer. A major advantage of PBI is the shorter treatment time (as it usually implies an accelerated schedule) compared with the standard fractionation and less exposure of dose to normal tissues. The concept of PBI is supported by the observation that the majority of in-breast tumour recurrences following lumpectomy without whole breast irradiation occur at or near the initial tumour bed. The RT techniques used to deliver PBI include interstitial brachytherapy (e.g. via multiple interstitial catheters), intracavitary brachytherapy (e.g. via a single or multi-catheter balloon placed inside the lumpectomy cavity), intraoperative radiation (e.g. via megavoltage electrons or low energy photons), and external beam radiotherapy (e.g. via electrons or photons). Typical regimens include the delivery of 34.5–38.5 Gy in 10 fractions or 30 Gy in 5 daily fractions, both in 1 week for fractionated schedules and 20–21Gy in one fraction for intraoperative treatments.

Most studies evaluating the role of PBI in low-risk breast cancer patients reported good local control rates of 3–4% at 10 years for well-selected patients, and these are similar to local control rates following whole breast irradiation (27).

Cosmetic results after PBI vary between studies, and this points to the particular importance of details regarding techniques and doses for partial breast irradiation.

Possible explanations for this variation are that the volume of the breast receiving a significant proportion of the prescribed dose should be more restricted and that the twice-daily schedule does not allow for complete interfraction recovery (thereby increasing the relative biological effect). In the Florence study, which used a once-a-day fractionation schedule for PBI (with fractions delivered every other day) and limited the dose to the non-target parts of the breast with intensity-modulated radiation therapy, cosmetic results were very favourable (27). Outside of clinical trials, patients who fulfil ESTRO and ASTRO recommendations for PBI (23, 28) could be offered this time-sparing approach.

## Simultaneous integrated boost

New radiation treatment planning and delivery techniques allow for ‘dose painting’ as a means to deliver higher radiation doses to the tumour bed *concurrently* with whole breast irradiation (i.e. not subsequent to whole breast irradiation as is conventionally done and as was done in the major boost trials). Such a ‘concurrent boost’, introduced in the framework of a clinical trial around 2005, offers dosimetric, as well as overall treatment duration, advantages (5). Clinical results are encouraging, with data from prospective randomized trials (e.g. RTOG 1005 and IMPORT-HIGH) showing similar efficacy, cosmetic outcomes, and toxicity with a simultaneous boost as compared to a sequential boost, provided that good quality radiation oncology, including the use of small boost volumes, is practised (29, 30). In all groups, five-year ipsilateral breast tumour recurrence (IBTR) incidence was lower than the 5% originally expected, regardless of boost sequencing. Moreover, dose escalation is not advantageous. Of importance, this fractionation schedule also reduces the number of patient visits.

## Proton radiation therapy

*Photon* beams (i.e. X-rays) deposit dose throughout their entire trajectory through the patient (i.e. upstream and downstream from the target). Conversely, *proton* beams deliver dose in a more defined range of depths (i.e. only upstream of the target, and there is essentially no ‘exit’ dose). Tissues at specific depths are targeted by careful selection of the proton beam energy, and of specific target thicknesses treated by varying that energy (i.e. ‘spreading out the Bragg peak’). Theoretically, there are potential advantages for the proton beam over conventional photons for many tumour sites, including the breast. However, there has been only a limited study of proton beam therapy in patients with breast cancer. Further, proton therapy is not widely available, and it is associated with expensive infrastructure and operating costs. In addition, since the uncertainties with protons are generally larger than with photons, it is possible that they may even result in worse outcomes. Therefore, proton beam treatment should currently be reserved for limited and well-defined indications (e.g. very challenging geometry and resultant clear cardiac risks, as well as, possibly, re-treatments) or on trial. There are several technical and clinical issues that need to be better addressed before this approach can be routinely applied for patients with breast cancer (31).

## Regional differences in the applicability of the previous discussion

Many of the approaches described earlier require modern RT equipment and trained/experienced personnel (e.g. to avoid 'hot spots' during hypofractionation, integrated boost, protons), and thus are not possible in under-resourced areas. For example, in the 28 (of 54) countries in Africa that have RT services, 3D conformal RT is available in only 60% of the facilities, and Cobalt is still being used in  $\approx 42\%$  of the facilities (16). As a result, there has been a low uptake of hypofractionation in Africa (16, 26). Patients in Africa also often tend to present with later-stage and aggressive disease with higher mortality rates that vary widely by country (18). This wide range of survival can be attributed to the disparities in health infrastructure and Africa's diverse socio-economic groups that exist around the continent. Unfortunately, none have population-based screening as resources are constrained with insurmountable backlogs. In addition, limited awareness of the various cancer treatment modalities has led to misinformation and fear of RT treatment (15). Financial and social burdens of black women have resulted in many patients being unable to complete their treatment, contributing to a higher mortality rate.

## A glimpse at the future for radiation therapy in breast cancer

RT has evolved into a very effective and increasingly less-toxic modality. Additional expected advances include the following:

- Multidisciplinary patient- and tumour-based selection of an individualized combination of local and systemic treatments, including the sequence and the extent.
- Individualized risk-adapted target volume selection: whole breast or partial breast; which part of the regional lymph nodes; boost to the primary tumour bed or to other high-risk zones; dose limitation to low-risk volumes.
- Individualized anatomy-based target volume delineation.
- Delineation of organs at risk based on international standards and on actual risks for side effects.
- Improvements in individualized treatment-planning procedures based on dose objectives for target volumes and dose constraints for organs at risk.
- Further alterations in fractionation schemes, including fraction size as well as risk-based dose adaptation.
- Generalization of improved patient positioning including respiratory control such as gating and breath hold.
- Improvements in set-up verification during treatment delivery and leading, also, to adaptive treatment strategies.
- Registration of treatment outcomes for all treated patients and analysis of this 'big data'.
- Personalizing the fractionation and total dose based on assessments of tumour and normal tissue responses defined on tissue samples obtained before or during the early phase of RT.



- Understanding of the differing side effects by race (including increased skin reaction among black patients).
- Increased representation of different races into clinical studies, which may improve symptom detection to reduce the gap in radiation therapy experience and outcomes
- Studies are evaluating if the degree of response to initial chemotherapy (as assessed by subsequent surgery) can be used as an indicator for the degree of impact of subsequent local/regional RT (with the hypothesis being that those patients with a complete response to chemotherapy may either derive less, or on the contrary more benefits from the addition of RT).
- There are mounting data that some newer less-extensive surgical approaches (e.g. skin/nipple-sparing mastectomy) may leave more 'tissues at risk local recurrence' (e.g. thicker skin flaps), and this may increase the utility of RT in the post-op setting.
- The increasing use of artificial intelligence in repetitive tasks such as volume contouring and treatment planning.
- A 'One-Week Breast RT' programme (1WB) was recently successfully implemented in the clinic. This 1WB combines same-day consultation, treatment planning, first-fraction delivery, and same-week completion of radiation therapy, integrating the FAST-Forward regimen, AI-based contouring and scripted dosimetry (33).

## Key messages

- The radiation oncologist actively contributes as a member of the multidisciplinary team, evaluating and treating breast cancer patients from the initial phase of the diagnostic-therapeutic pathway.
- Postoperative RT decreases local-regional recurrence in both the post-lumpectomy and the post-mastectomy settings by 75–85%; patients at a higher risk for local recurrences experience a greater absolute benefit.
- Postoperative RT in the post-lumpectomy and post-mastectomy settings decreases any/all-site recurrences, breast-cancer related, and overall mortality.
- Generally, postoperative RT is recommended in the post-lumpectomy setting for axillary node-negative and node-positive patients to decrease all forms of recurrences, breast-cancer related, and overall mortality.
- Generally, postoperative RT is recommended in the post-mastectomy setting for axillary node-positive patients (and node-negative patients with large primary tumours or other high-risk features) to decrease all forms of recurrences, breast-cancer related, and overall mortality.
- Modern RT starts with careful consideration of treatment positioning/immobilization, target volume delineation, and treatment volume-based prescription. The available treatment techniques serve the goal of optimizing dose distributions, but its use is not an objective by itself.
- Patients treated in trials starting after 1989 have no increased treatment-related mortality at 15 years. With contemporary radiation techniques, short- and long-term side effects are expected to be further reduced.



- The interaction between local-regional and systemic treatments is complex. Most of the benefit of RT on survival is expected for low-risk patients, who do not receive systemic therapy, and high-risk patients who receive effective systemic therapy, as in both cases the risk of distant metastases is low/reduced. As the efficacy of systemic therapies increases, the ability of local-regional therapy to improve survival may *increase*.
- Lowering the burden of RT can be done via reducing the total dose, the number of fractions, and/or the size of the target volumes in combination with optimized treatment techniques. Additionally, the use of ultra-hypofractionated regimens—such as five fractions of partial or whole breast radiation—should be increasingly considered, particularly in settings where resources, time, or other constraints are limiting factors. These regimens are associated with similar efficacy and toxicity as moderately hypofractionated treatments and in the setting of five fraction partial breast radiation, better quality of life.
- While RT might be omitted for low-risk patients receiving endocrine therapy, the administration of 1 week of radiation instead of several years of endocrine therapy is being evaluated in prospective clinical trials (32).
- Surgical treatment to the axilla is essentially a diagnostic procedure, and even in node-positive patients ‘less surgical therapy’ could be adequate for the axilla. However, recent studies confirm that regional nodal irradiation improves outcomes, so reductions in planned nodal therapy should be done carefully.
- Access to RT and associated advanced technologies vary across the globe. Developing national standardized protocols from local clinical research based on available resources in each country may be an effective way to manage breast cancer in variable environments.

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## Systemic therapy

*Didier Verhoeven, Agnes Jager, Boudewijn Dullens, Lien van Walle, Tanja Cufer, and Helena Earl*

### Introduction

Systemic treatment is defined as the use of drugs, e.g. chemotherapy, endocrine therapy, targeted therapy, and immunotherapy. Evidence for the efficacy and safety of these treatments is obtained through clinical trials, which usually start at advanced stages of the disease. The available literature concerning quality indicators for systemic treatment of breast cancer is limited. Although population-level studies focusing on quality of care of systemic therapy have been reported, a lot of questions remain, and further studies are warranted (1).

Before 2005, underuse of chemotherapy, non-evidence-based schedules, and variability in dose intensity were the most common findings. More recently the overuse of chemotherapy and unnecessary associated costs have created more acute problems. To try and improve this the American Board of Internal Medicine (ABIM) started the 'Choosing Wisely' initiative hoping to avoid unnecessary tests, treatments and procedures ([www.choosingwisely.org](http://www.choosingwisely.org)).

Importantly more attention is being paid to patient-reported outcomes. By involving physician leaders, outcomes researchers, and patient advocates, standard sets of health outcomes for breast cancer have now been defined (see Chapter 8).

The median age of patients receiving a diagnosis of breast cancer is 62 years, and 42% of all patients are 70 years or older at the time of diagnosis. Where necessary a geriatric assessment is needed to fine-tune and adjust care to the health status of individual patients (2). However, only 24% of patients included in clinical trials are 65 years or older, and when older patients are enrolled in clinical trials, they have fewer comorbid conditions than the average older patients in clinical practice. For each patient with breast cancer, a multidisciplinary specialized team with a lead oncology specialist responsible for coordinating treatment modalities is necessary. Depending on the stage of the disease and the local protocols, the breast surgeon or oncologist will be in the lead.

In a Canadian study the quality improvement priorities for women receiving systemic therapy for early breast cancer were analysed. Computerized electronic order entry for chemotherapy, emergency room visits, hospitalizations during chemotherapy, and timely receipt of the treatment were identified as the most important quality measures with the largest potential for improvement (3).

Recently, based on new systemic treatment modalities, EUSOMA identified additional indicators of systemic treatment (see Chapter 5) for early breast cancer (4). These indicators

were identified by a panel of European experts. Moreover, EUSOMA joined efforts with the advanced breast cancer (ABC) Global Alliance to identify nine additional QIs for metastatic breast cancer (5). Some of these QIs, especially in the adjuvant setting were based on PFS, rather than overall survival (OS) results, which makes them debatable in a global perspective. Although many of these QIs are only recommended in countries where the medication is reimbursed, we do not support some of them because they encourage overuse e.g. MRI breast before treatment in 90% of early breast cancer patients and neoadjuvant treatment with pembrolizumab in 70% of TNBC patients. In the US, the Quality Oncology Practice Initiative (QOPI) is a voluntary quality programme launched by ASCO and designed for outpatient-oncology practices to foster a culture of self-assessment and improvement. They published their measures for the quality of oncological care in 2008 with a recent update in 2013 (6).

A recent review highlighted the significant lack of research on systemic anticancer therapy quality indicators, particularly for resource-constrained settings (7), i.e. only one study was conducted in a middle-income country, South Africa (8). In China, QIs for systemic treatment were developed by Han Bao based on existing US indicators. However, a recent update demonstrated a wide gap between optimal recommended care and actual practice using the ASCO indicator set. For example, there was a large variation between healthcare providers for the use of anthracycline-containing adjuvant chemotherapy with the lowest percentage of only 12%. In another Chinese study, a difference of 42% in the use of adjuvant endocrine therapy between Chinese centres was observed using a radar chart (9). Shortage of trained staff and lack of integrated multidisciplinary pathways of care were suggested as the main reasons for failure to achieve goals such as optimal use of neoadjuvant chemotherapy. A study in Nepal showed a very low rate of neoadjuvant chemotherapy because of the patients' anxiety not to delay surgery, the lack of an MDT and because of logistics. In the same study, only one of 21 patients with HER2-positive breast cancer received trastuzumab (10). Finally, a recent partnership between the ASCO and the WHO aims to standardize global quality through appropriate indicators and their goal is to develop a summary of the initial key findings in 2024.

## Defining quality indicators of systemic treatment

To increase the quality of care, QIs are defined for the clinical care pathway, patient satisfaction and outcome (see Chapter 4). Most countries have not yet established an integrated breast cancer care process to achieve excellent care and there is a need for harmonization of quality indicators for breast cancer care (11). Three types of QI are considered essential.

### Structure indicators

#### Education: a global curriculum

The best way to improve the quality of systemic treatment use for breast cancer is education and the promotion of medical and clinical oncology as recognized specialties in as

many countries as possible. Based on a global survey in 2019, performed by the ESMO/ASCO Global Curriculum working group, medical oncology was recognized as a stand-alone specialty or subspecialty in a vast majority of countries. In 2023, a new edition of the ESMO/ASCO Global Curriculum in Medical Oncology was published (12) to provide recommendations for the training and to establish educational standards. Free movement of medical oncologists is encouraged, thus spreading best practice and improving the quality of cancer care worldwide. The fundamental pillar is five-years' education with a minimum two years of internal medicine and two years of medical oncology (see Chapter 9). The new edition also includes chapters on genetic and genomic testing with counselling, nutritional support, and survivorship. An entirely new chapter is dedicated to cancer control principles, aiming to ensure that medical oncologists can identify and implement sustainable and equitable cancer care, tailored to local needs and resources. Medical oncologists must be able to understand major disparities in cancer-related survival outcomes and the principal determinants for delivering equitable and sustainable cancer care worldwide. They must understand the challenges of providing cancer treatment in countries with limited human and/or financial resources and the opportunity for value-driven priority setting. In developing countries, in the absence of a medical oncologist, systemic treatment could be given by other specialists with at least two years of training in systemic treatment. However, every effort must be made to train medical oncologists, since they are the healthcare providers who can coordinate all aspects of multimodal drug treatment. They must have an in-depth understanding of systemic therapy. They must be able to perform specialized assessment, treatment, and counselling; including conducting/participating in clinical trials, deploying and assessing genetic testing. They need to pay attention to prevention, early detection, and screening as well as long-term survivorship. In addition, the oncologist must be aware of the psycho-social support that patients require and be able to provide adequate palliative care.

### **Day clinic facilities**

Delivery of chemotherapy continues to shift from the inpatient setting to ambulatory day services. Rapid access to treatment in an oncology unit dedicated to the administration of systemic treatment is required. Trained oncology nurses and patient navigators are necessary and staffing of chemotherapy nurses is a top priority for cancer centres, although no optimal nurse: patient ratio is available (see Chapter 20). The concept of 'value-based healthcare' emphasizes the investigation of new healthcare models that provide individualized treatment in a cost-efficient way. Oncology Home Hospitalization is such a model in which cancer drug(s) and comedication are administered at home (13). At least 10% of the commonly used drugs are applicable, mostly those that can be administered subcutaneously and intramuscular (e.g. trastuzumab, pertuzumab, fulvestrant, denosumab, pegfilgastrim, GnRH agonist, immunotherapy). Adopting this model requires a good management framework and can offer opportunities to create capacity in the oncology ward.

### **Dedicated pharmacy facilities**

Close collaboration of the oncology department with a dedicated pharmacy facility is required. The oncology pharmacy plays a critical role in discussing pharmaceutical treatment

and supervising the preparation of oncological drugs. Experience in interactions with other drugs and dose adjustments according to age, liver-, and kidney functions is necessary. In Europe, pharmacy facilities must comply with the European QuapoS guidelines (European Society of Oncology Pharmacy, [www.esop.eu](http://www.esop.eu)). Cytostatic and other oncological drugs must be handled and prepared in a designated area. The handling must take place under the supervision of an oncology pharmacist in accordance with the Ljubljana Declaration of 2006. In 2022 the International Society of Oncology Pharmacy Practitioners (ISOPP) updated the standards for the safe handling of cytotoxic drugs (14).

### **Electronic prescribing system**

Use of a computerized provider order entry system must become standard. All prescribers of systemic treatments and hospital pharmacists must be familiar with the prescribing systems including their weaknesses. Each patient must be treated according to an authorized, digitally recorded treatment protocol (15).

## **Process indicators (see Boxes 17.1 to 17.3)**

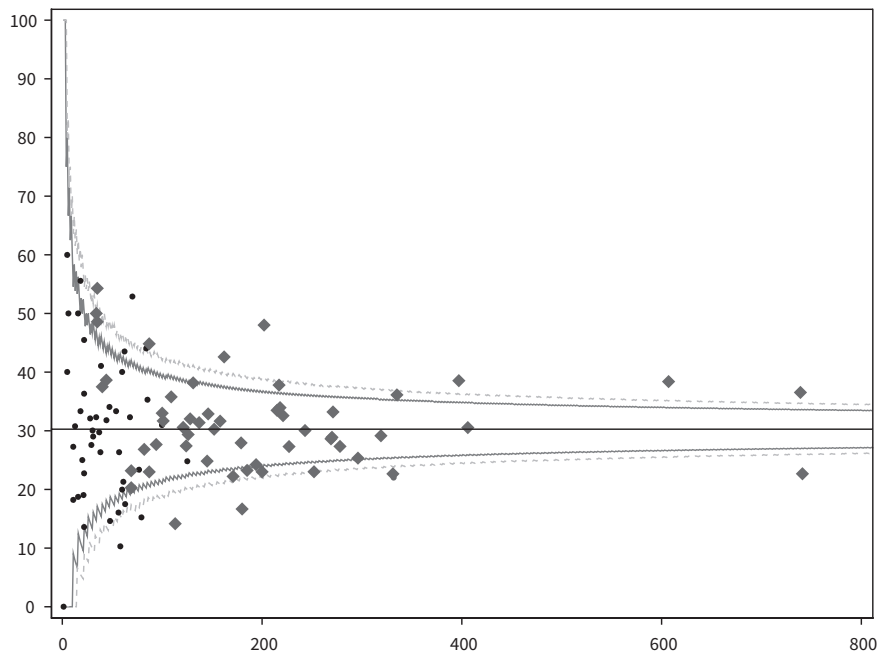
### **Timely access to appropriate advice from experts in systemic treatment, guideline adherence, and monitoring of practice**

The time between the diagnosis of breast cancer and the start of anti-cancer treatment is important for patients to ensure efficacy and avoid anxiety. The maximum delay between the patient's first appointment in the system and the start of treatment must be between four and eight weeks.

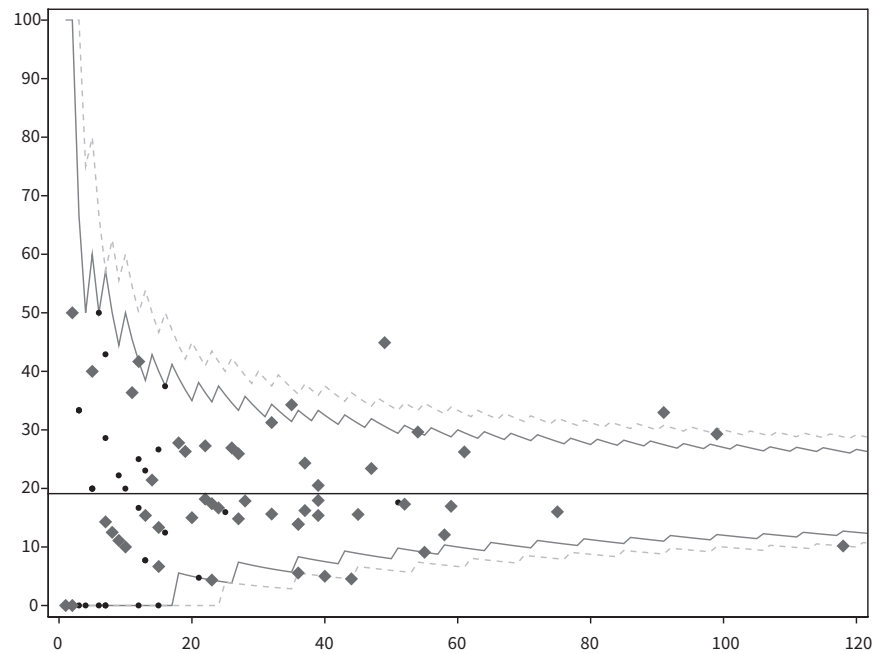
According to (inter)national guidelines, the reporting on the treatment delivery is crucial for quality control. Insight into the treatment, and the applied schedule is required. Ideally, a database is present in each breast cancer centre. First, the proportion of the total breast cancer population of the individual centre that receives chemotherapy, endocrine therapy, or targeted treatment must be registered to provide insights into the prescription pattern of the individual centre. In addition, this information should be documented according to the stage, the age and the different molecular subgroups: triple-negative, HER2-positive, and oestrogen receptor (ER)-positive/HER2-negative breast cancer. As an example, Figure 17.1 shows the administration of chemotherapy in Belgian hospitals for the period 2010-2014. Substantial variation is seen for the use of chemotherapy, even when selecting the favourable patients with clinical stage I ER-positive HER2-negative breast cancer (Figure 17.1b) (16) and the elderly patients (Figure 17.1c).

Importantly, reimbursement schemes that are implemented in a country can influence the use of treatments. Thereby overuse of certain treatment modalities and underuse of others can be induced, for example by the restriction of reimbursement to intravenous administrations only. These observations stress the importance of documenting the use of ambulatory versus inpatient treatments, including their administration schedule (oral, subcutaneous, or intravenous) in a detailed way.

(a)



(b)





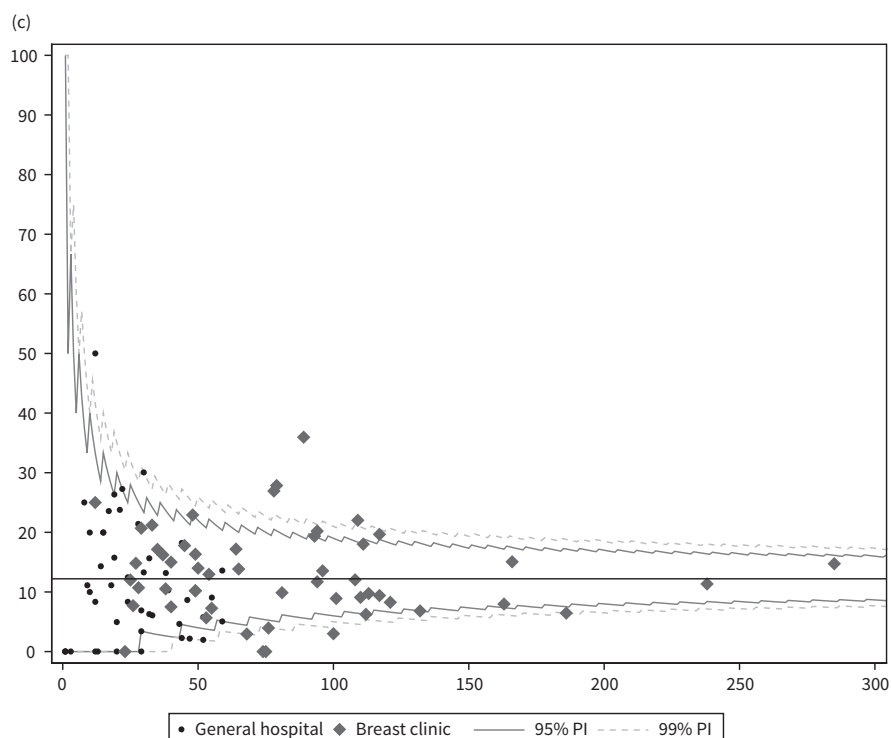


**Figure 17.1** Proportion of patients with breast cancer who received neo/ adjuvant chemotherapy within 4 months after surgery in Belgian hospitals. (a) Patients with breast cancer younger than 70 years who received neo/ adjuvant chemotherapy in cStage I. (b) Patients with breast cancer younger than 70 years who received neo/ adjuvant chemotherapy in cStage I luminal A/ B- like HER2- negative breast cancer. (c) Patients with cStage I–III breast cancer aged 75 years or older who received neo/ adjuvant chemotherapy within 4 months after surgery

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### Treatment planning, multidisciplinary, and use of supportive medicines

A documentation of patient's body-surface area, planned and prescribed dose, and informed consent must be considered as good clinical practice.

### Equity in systemic treatment

Equity in access to systemic treatment with respect to confounding factors such as race, socioeconomic status, income, and geographical location, must be recognized as an important aspect of quality. Analysis of breast cancer mortality in the US based on SEER data has repeatedly shown important differences between Caucasian, African-American, Asian, and

Hispanic patients, partly due to ethnic considerations, but also due to socioeconomic resources, barriers to care, and many other factors (17). A racial/ethnic disparity was also identified in adjuvant endocrine therapy adherence and was explained by socioeconomic status and out-of-pocket medication costs (18).

## Outcome indicators: ‘fulfilling the purpose’

Different ways of looking at the final results of our treatments are possible, depending on the patients’ and doctors’ visions. Although OS remains the keystone, cancer-free survival is also important, and today there is more attention on quality, as well as length of life. We still do not have simple ways of measuring quality of life and toxicity of treatment that can be integrated with the more easily quantified cancer-free life and OS. Improvement could potentially be achieved within clinical trials by using generalized pairwise comparisons as a statistical method (19).

### Overall survival

Overall survival (OS) remains the gold standard as an endpoint for breast cancer treatments. However, increasingly effective treatment means that the direct positive relationship between relapse-free and OS may become less clear. Keeping OS as an ultimate goal is important since it also informs us of the potential harms of treatment for both early and metastatic disease. For example, the long-term cardiac consequences of treatment increases the older the patient gets. Cross-linking data from cancer registries with individuals in the wider population may help to obtain survival data within a country, but is subject to legal approval by national authorities and does not happen in all countries. Nevertheless, OS data can be misleading when comparing individual hospitals, because of the difficulties recognizing all factors which could influence outcome (see Chapter 4). Real-world trends in OS of patients with metastatic breast cancer remain difficult to obtain due to the lack of reliable data in most national cancer registries (20). For 2/3 subtypes, the median OS is approaching 5 years, with many patients living >10 years, turning breast cancer soon into a chronic disease. The data of the SONABRE Registry in the Netherlands are suggesting a median overall survival of 38 months in ER-positive/Her2-negative breast cancer, after the introduction of CDK4/6 inhibitors (21).

### Cancer-free survival

Cancer-free survival could be a better term to describe event-free, relapse-free survival, and progression-free survival, which all have different definitions (22). From the patient’s point of view, being cancer-free is important. Cancer-free survival is an increasingly important endpoint and in subtypes with high risk of recurrence (HER2-positive and triple-negative breast cancer) can be read out early and thus help to speed up the licensing of new treatments. The biology of the disease is such that the risk of recurrence for these patients decreases markedly after 3 to 5 years from diagnosis. Paradoxically, the patients with luminal cancers/prognostically good tumours continue to experience some risk—albeit small—of recurrence year after year, for decades after diagnosis. Finally, response rate as such is

almost always a secondary endpoint in clinical studies since the relation of response rate and survival is unclear (23).

## Safety

The number and diversity of systemic treatments is rising and the introduction of new effective treatment groups such as immunotherapy, has increased the frequency, range, and severity of complications. Most cytotoxic drugs have a narrow therapeutic range, and effective doses have predictable and sometimes severe side effects. Dose adjustments are often needed. However, most of the immune-checkpoint inhibitors (ICIs) have been licensed at maximum tolerated rather than minimally effective doses. There are now a plethora of side effects of these agents, some of which could probably be avoided by using more optimal doses. In addition, some of the most severe side effects of ICI (e.g. pancolitis, myocarditis, and myasthenia gravis) are rare and therefore—unlike the side effects of cytotoxic therapies—oncologists and their teams are not practised at dealing with them. Side effects of ICIs may be lifelong (e.g. endocrine failure) and although hypothyroidism once recognized is relatively easy to treat with replacement, this is not the case for adrenal or pituitary failure.

Treatment delivery is a multi-step process, each step being a potential source of error. Recent studies have shown about 3% to 10% of potentially harmful errors with systemic anti-cancer treatments, even with the use of computerized physician order entry systems. The ASHP (American Society of Health-System Pharmacists; [www.ashp.org](http://www.ashp.org)) defined guidelines on preventing medication errors with chemotherapy and biological response modifiers.

Sometimes errors are due to high patient load and inattention of the prescribers to omissions in prescription:

- incorrect dose
- abbreviations
- incorrect instructions
- incorrect drug
- no signatures

To develop a system that reduces errors, the following measures can be taken (ISOPP publication):

- Recognize that human errors will occur, and these need to be reported routinely and reviewed regularly for education purposes
- Create a culture with coworkers to reduce errors
- Maintain accurate records of chemotherapy and other systemic treatment
- Systems for training which recognize the need for improvement using continued professional development courses for all staff
- Reliable patient identification
- Focus on pharmacy concerns

## Toxicity

Patients receiving treatment for cancer can experience many side effects, of which clinicians should be aware. Future challenges are identifying the appropriate dosing of cytotoxic agents to maximize therapeutic efficacy while limiting both acute and long-term side effects. Some important toxicities to monitor are listed.

- Infection or thrombosis of an intravascular device.
- Hospitalization due to acute toxicity of treatment (e.g. febrile neutropenia).
- Long-term toxicities in survivors (e.g. leukaemia after anthracycline use, cardiac failure after trastuzumab, neuropathy after taxanes, and platinum).

## Health-related quality of life

Health-related quality of life (HRQoL) constitutes an additional endpoint which ensures earlier assessment of direct clinical benefit for the patient (24). Patient-reported outcome measurements (PROMs) capture a patient's perception of their health (symptoms, anxiety, unmet needs), patient-reported experience measurements (PREMs) capture a patient's perception of their experience with healthcare or services (integrated care, waiting times, communication, etc.) (see Chapter 8) and lastly patient-reported safety incidents (PRIMs) identify safety issues. Recent advances in technology provide possibilities for collecting PROMs, PREMs, and PRIMs electronically using simple questionnaires and these could play a major role in shared decision-making. Nevertheless, technological problems, reimbursement barriers, and standardization have prevented, thus far, the widespread use of these methods. Although the introduction of dual HER blockade and CDK4/6 inhibitors have significantly improved survival for many patients with metastatic HER2-positive and ER-positive disease respectively, maintaining a good QoL remains important in this setting given the more limited survival generally. However, HRQoL assessment is more studied in early stages. Specific measurements were developed by various research groups, such as the EORTC QLQC-30 scale ([www.eortc.org/tools](http://www.eortc.org/tools)). This questionnaire consists of multi-item and single scales. It includes functional scales (physical, emotional, social, and cognitive), symptom scales (fatigue, nausea, and pain), global health status and other items (dyspnoea, insomnia, appetite, constipation, diarrhoea, and financial toxicity). This tool is currently being updated to become a breast cancer questionnaire of 45 items (BR45). Other QoL scales are available, such as the World Health Organization Quality of life (WHOQOL-100) developed by the WHOQOL Group with 15 international field centres, aiming to develop a QoL assessment that would be applicable across different cultures. Few specific tools for QoL measurements in the metastatic setting exist, leading to very limited evaluation of the impact on QoL for many interventions. Nevertheless, recently a patient-centred core outcome set for assessing HRQoL has been developed for metastatic breast cancer patients (25). Focus needs to be not only on physical, but also on functional, social, psychological, and spiritual domains. In addition, few quality-of-life measurements for end-of-life care are available. All patients with advanced breast cancer should receive dedicated palliative care services early enough in the disease course, i.e. concurrent with active treatment, in order not to be implemented too

late and, thereby lead to feelings of abandonment and loss. An optimal collaboration with interdisciplinary palliative care services must be established. Palliative care means patient and family-centred care that optimizes QoL by anticipating, preventing, and treating suffering. Of note, such a policy will also cause a reduction in direct breast cancer costs (see Chapter 19).

## Minimal and ideal requirements

### WHO essential medicines list (EML)

See Chapter 30.

## Multidisciplinary discussion

All decisions related to systemic therapy should be taken in a multidisciplinary meeting (MDM) or tumour board. Characteristics of the MDM are discussed in Chapter 11. Effective cancer care demands seamless teamwork of a diverse range of dedicated professionals with a commitment to prioritize the well-being of all patients. The Interact-Europe EU project embarks on providing an interspecialty cancer training across all cancer centres in Europe. [https://health.ec.europa.eu/non-communicable-diseases/cancer/europes-beating-cancer-plan-eu4health-financed-projects/projects/interact-europe\\_en](https://health.ec.europa.eu/non-communicable-diseases/cancer/europes-beating-cancer-plan-eu4health-financed-projects/projects/interact-europe_en).

## Guidelines

Guidelines are evidence-based statements to help deliver high-quality care. Many international and national organizations have defined guidelines for breast cancer care: ESMO, NCCN, NICE, ABC Consensus Guidelines, and St. Gallen Consensus Guidelines. All of these organizations claim that *their* guidelines are widely recognized, are free to consult, and should be used as the standard by clinicians and payers. Ideally, they are regularly updated adding the availability of 'proven' new treatments. They must be based on reliable statistics from phase III clinical trials with clear endpoints. In the case of different results from multiple similar studies, meta-analyses have been helpful, the most influential of which are from the Early Breast Cancer Trialist Collaborative Group (EBCTCG). Pitfalls and usual biases in guidelines come mainly from unpublished data and a lack of QoL reporting. However, regular discussion of the guidelines for most appropriate local implementation, remains essential. Constant efforts should be made to harmonize different guidelines covering the same topics. A consensus meeting, such as the St.Gallen and the ABC Global Alliance Conferences, can help decision-making in cases where no clear guidelines are available (see Chapter 10). A recent EUSOMA-based study revealed important variations in EBC management between European-certified breast centres, indicating the different interpretations of these guidelines. So-called practice indicators, using real-world data, can help monitor,

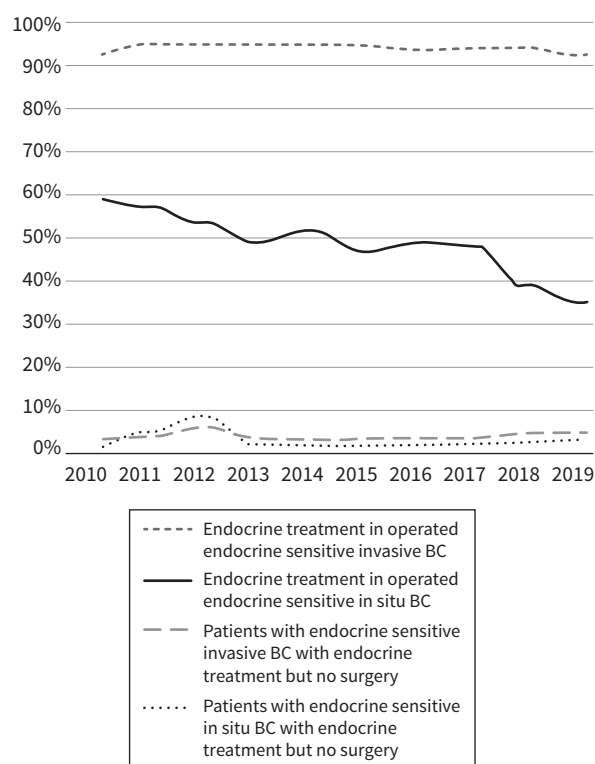


**Figure 17.2** Breast cancer in Europe, EUSOMA data: time trends (2010–2019) of endocrine treatment practice for endocrine sensitive early breast cancer

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evaluate and eventually guide and align good clinical practice in the management of breast cancer (see Figure 17.2) (26).

## High-value, patient-centred care

The International Consortium for Health Outcomes Measurement (ICHOM) takes a unique approach to defining healthcare outcomes. First, they involve patients directly in the process, as the ones who experience health outcomes first-hand. Then, they bring together leading physicians from across the globe who specialize in treating breast cancer. These physicians hold diverse perspectives and are pioneers in their respective countries. Finally, the ICHOM team facilitates physician and patient discussion, to define outcomes that matter most to them (see Chapter 8).

A good example of patient-centred outcomes is ‘number of days spent at home in the last 6 months of life’ which is defined as 180 days minus all days spent in inpatient facilities (including hospice unit).

## Workforce required

A systematic assessment of required workforce is needed as is the determination of the actions required to meet those needs. There is an ongoing joint effort between WHO and ESMO to define workforce needed in Europe and worldwide. The 2017 WHO cancer resolution is a landmark document, calling for the implementation of national cancer plans, population-based cancer registries, a world cancer report, and a well-trained oncology workforce. ASCO has called for an increased use of non-physician practitioners, research in care delivery efficiency, and efforts to recruit new oncologists. Physicians dedicating up to 25% of their time to non-direct patient care activities decrease specialists' availability and add to dissatisfaction and burnout.

## Follow-up

Personalized follow-up is recommended (see Chapter 32) depending on the risk of recurrence, long-term QoL, and side effects issues. Who can be consulted and how frequently must be decided depending on the availability of nurse-practitioners, primary care physicians, medical oncologists, and breast surgeons. No specific examinations are required besides annual or biennial mammography unless treatment is ongoing, or if monitoring and management of side effects are necessary. Supportive and survivorship issues must be addressed. Following tumour markers for the detection of relapse has only limited proven benefit at present. Special attention must focus on new symptoms, and compliance to treatments, especially long-term endocrine therapy (5 to 10 years). Bone density monitoring is important both for aromatase inhibition and ovarian suppression.

## Best practice

### A better use of systemic treatment

#### Optimal use of chemotherapy

Chemotherapy, non-specific anti-cancer drugs, are still the cornerstone of anti-cancer therapy for the treatment of breast cancer. Although targeted therapy, from endocrine to immunotherapy, has attracted much attention recently, many breast cancer patients still receive chemotherapy as an important part of their treatment. Depending on the breast cancer subtype and line of treatment, primary chemotherapy resistance occurs in up to 70% of patients. Unfortunately, there is very limited information available to guide therapy selection. In the neo/adjuvant setting, the choice is mainly determined on the basis of classical prognostic factors (e.g. tumour size, lymph nodes involved, histological grade, hormone receptor status, Her2 status, Ki67 expression). If the prognosis is unfavourable, and the expected absolute benefit of chemotherapy is sufficient, chemotherapy is proposed. Worldwide, a gain in 10-year breast cancer-specific mortality of at least 3% by adding chemotherapy is accepted to

advise this treatment. Mathematical models, based on the results of randomized clinical trials, can estimate the benefit of systemic treatment in breast cancer patients (<https://www.breast.predict.nhs.uk/>). For ER-positive luminal breast cancers, if there is doubt about the added value of neo/adjuvant chemotherapy, a validated gene expression test on tumour tissue can be performed (27). However, these tests are expensive, only useful for ER-positive/Her2-negative breast tumours, not available worldwide, and above all are mainly of prognostic rather than predictive value. Although some gene expression tests and DNA sequencing algorithms have shown some success in predicting response to chemotherapy, these tests are still far from ideal. Validated predictive biomarkers that can guide chemotherapy choices to reduce overtreatment, prevent unnecessary toxicities, improve quality of life, and reduce costs are eagerly awaited.

### To treat or not to treat?

The most experienced oncologists say that one of the most difficult decisions to make with their patients is that of '*to treat or not to treat*'. Importantly, this subject will be covered in the palliative care section (see Chapter 19), but there is also a place in adjuvant breast cancer treatments for discussion. For patients at very low risk of recurrence, the benefit of additional adjuvant anti-oestrogen treatment is much debated and is probably very small. The emergence of prognostic/predictive molecular signatures has prompted testing in randomized clinical trials—TAILORx, RxPONDER, both of which have been reported. The third trial OPTIMA will complete recruitment at the end of 2024. The first two of these trials have gone some way to changing guidelines, advising against unnecessary adjuvant chemotherapy in patients with good prognosis ER-positive breast cancer, in which multi-parameter tests indicate that tumours are likely not to respond to chemotherapy. The OPTIMA trial is testing the whole pathway of care by randomizing higher-risk patients (by staging) to chemotherapy (standard of care) or biomarker-directed adjuvant therapy. While the results from the OPTIMA trial are awaited, it is important to have open and honest conversations with breast cancer patients, to discuss the uncertainties of whether to proceed with adjuvant chemotherapy or not.

### *Tailored therapy*

Tailored oncological therapy aims to treat the patient with a specific breast cancer subtype with the right drug, at the active dose, at the right time. This requires targets on the tumour cell that ideally do not occur on other cells. Starting as a non-selective therapy a century ago and following the identification of ER as a predictive marker, endocrine therapy in breast cancer has been the ultimate targeted, or tailored, cancer therapy since the 1970s. More recently, targeted therapies against HER2-receptor overexpressing breast tumours have revolutionized the field. These tumours represent approximately 15% of all breast tumours and have a poor prognosis, but with the advent of targeted therapies against the HER2-receptor, the prognosis has improved dramatically. Initially, the focus was on the development of monoclonal antibodies directed against the extracellular part of the HER2-receptor, soon followed by antibodies directed against HER3 and tyrosine kinase inhibitors directed against the intracellular part of the HER2-receptor. The so-called antibody-drug conjugates (ADCs), in which chemotherapy is linked to monoclonal antibodies via a linker, are the next ground-breaking group of tailored therapies. Interestingly, ADCs have



been developed against all different subtypes of breast cancer, including the highly aggressive triple-negative breast tumours (sacituzumab govitecan). With the introduction of the PARP inhibitors, there is now also a tailored treatment for patients with *BRCA1* or *BRCA2* mutation-driven breast cancer.

### Safe prescribing of anticancer drugs

Careful treatment of cancer is critical for patient safety. Anticancer drugs present a narrow therapeutic index with potentially lethal adverse events. Many studies have highlighted the benefit of computerized prescriptions in oncology. However, errors can occur in the prescription software, so-called e-iatrogenesis, which can have serious unintended consequences, especially in an area with complex prescriptions such as oncology. Importantly, software upgrades should be performed as regularly as possible and software users should perform audit testing.

### Geriatric oncology

Populations around the world are rapidly ageing. Advancing age is a high-risk factor for cancer in individuals over 65 years. Given the specific features and comorbidities of the geriatric population, personalized treatment is required (see Chapter 32). Recent findings showed the addition of adjuvant chemotherapy to hormone therapy conferred no survival benefit in women aged 70 years and above with a genomic grade index high-risk oestrogen receptor-positive HER2-negative breast cancer, and was associated with more adverse events, providing important data on the benefit-risk balance of adding adjuvant chemotherapy to adjuvant hormone therapy in this older age group (ASTER 70s) (28). To improve the care of older patients, the International Society of Geriatric Oncology (SIOG) was founded in 2000 (<https://siog.org>).

### Value of treatment

The availability of new systemic treatment options in oncology has accelerated rapidly. Recent research has shown that despite this increase in new medications, the added survival benefit is limited. This, together with all the new drugs in development, means that the rise in healthcare costs worldwide is becoming unsustainable and rigorous steps must be taken to address this development.

Two important developments would be a step in the right direction:

Firstly, by broadly embracing the European and US criteria, which describe the standards a new medicine must meet before it can be marketed. To date, the useful ESMO Magnitude of Clinical Benefit Scale and the ASCO conceptual framework are recommendations and not obligations (29). Secondly, the use of effectiveness research at the time of implementation of a new anticancer drug. A concrete example is the SONIA trial (30). This phase-3, randomized, investigator-initiated trial evaluated the efficacy, safety and cost-effectiveness of CDK4/6 inhibitors added to either first- or second-line endocrine therapy in patients with ER+, HER2– advanced breast cancer who have received no prior

therapy for metastatic disease. Evidence of the superiority of first-line over second-line use based on a head-to-head comparison was lacking. Nevertheless, most international guidelines advise first-line use, despite prolonged toxicity and a steep increase in costs compared to use in second line. The results of the SONIA trial showed that first-line use of CDK4/6i did not provide statistically significant, nor clinically meaningful PFS benefit compared to second-line use. However, first-line use prolonged the time on CDK4/6i by 16.6 months and increased toxicity and costs. This trial showed that second-line use may thus be a preferred option for the majority of patients, preventing unnecessary toxicity, and reducing costs.

## Clinical trial participation

The percentage of patients enrolled in clinical trials is sometimes considered a quality indicator (EUSOMA), depending on the hospital environment. The accepted opinion in the oncological community is, that patients are better off when treated within the context of a clinical trial. Arguments in favour are improved access to innovative medication and adherence to state-of-the-art guidelines. One report showed that recurrence-free survival was significantly better in patients included in clinical trials. Clinical trials guarantee appropriate care with optimal endpoints, but there is little unbiased evidence of outcome improvement. Possible reasons for better outcomes are experimental treatment effects, participation effect, a prognostically favourable subset, the method of data gathering, publication bias, and the fact that these studies are mostly performed by motivated experts.

All breast centres must have the opportunity to collaborate in some kind of research. Not only early phase studies and registration trials are needed. It is also interesting to evaluate long-term effects and the value of treatments in daily practice. In addition, the participation of all centres in providing data to cancer registries and the evaluation of 'big data' is extremely valuable. The ASCO Cancer LinQ initiative wants to learn from the 97% of patients not in research studies in order to enhance cancer diagnosis and treatment ([www.cancerlinq.org](http://www.cancerlinq.org)). The aim is to empower the oncology community and improve quality of care and patients' outcomes through transformational data analytics (see Chapter 24).

## Emerging modalities

The paradigm for treating breast cancer has changed rather dramatically over the last two decades. An evolving knowledge of the underlying biology that drives malignant progression and metastasis in breast cancer has led to multiple new therapies. Therapies targeting ER, HER2, PI3K/mTOR, CDK4/6, ESR1, AKT1 mutation or PTEN inactivation, PARP, and TROP2, as well as immunotherapies, have been integrated into daily clinical care in HICs. Tumour genomic testing includes sequencing for targetable mutations,

accomplished through large panel tumour genomic testing in a certified laboratory, performed on tissue or plasma obtained at the time of progression or from archival tissue. In the absence of direct comparative data and a lack of OS benefit for non-CDK4/6 targeted agents, a balanced discussion of risks and benefits with the patient will guide individual choices (31).

New therapies often lead to further treatment escalation, but they can bring opportunities for treatment de-escalation strategies and trials. Some studies have shown that de-escalation is possible in selected patients.

With new treatments, we encounter new side effects. A deep understanding of how to manage these side effects, e.g. life-threatening lung-toxicity on ADCs or immune-related adverse events triggered by anti-PD1 therapies, is crucial for good clinical practice. Studies evaluating strategies for improved patient selection, for example, biomarker analysis, should be promoted to avoid unnecessary toxicities.

The financial burden on society of new expensive treatments should not be underestimated and could expand disparities in breast cancer care. It is important to evaluate the magnitude of benefit of these treatments before implementing them in daily practice, for example, with the 'ESMO Magnitude of Clinical Benefit Scale' or the 'ASCO Value Framework Net Health Benefit Score'. Broadly embracing the European or American criteria that describe what a new medicine must meet before it is allowed on the market would be a step in the right direction. Until now, these 'ESMO Magnitude of Clinical Benefit Scale' and ASCO's conceptual framework are only recommendations and not obligations. Strict compliance with these criteria worldwide will have the side effect that pharmaceutical registration studies will also adhere to these criteria, where currently much less (survival) gain is the norm. These two tools allow regulators and administrations to prioritize reimbursements in settings with limited resources. Although both tools were recently updated, they display different results, and more harmonization is desirable (29). The recent ESMO Magnitude of Clinical Benefit Scale version 2.0 (ESMO-MCBS v2.0) was published in 2025 (32). The amendments change the scores of 13.6% of evaluated studies (10.5% downregulated, 3.1% upgraded) and add toxicities annotations to 45.5% of the studies in the curative setting, improving their discriminatory capacity and utility.

The revolution of artificial intelligence (AI) has, like in daily life, found its way into medicine and oncology. The potential and opportunities are important, but they will also bring new challenges. Its use has already been reported in many fields of oncology, and the number of new publications is countless. For example, in radiology AI as an independent reader of screening mammography has successfully been reported (33). This has the potential to replace a second reader in LMICs with a shortage of radiologists. But a bias in BI-RADS scoring has been reported (34), and one could imagine harm by overdiagnosis and overtreatment. AI can also be used in radiology to extract hidden parameters in the pixels of medical imaging that are not seen by human eyes, called radiomics. This potentially could lead to more accurate lesion description and reduce the need for invasive procedures (35). In addition, better quantification and tracking of breast density, now recognized to be a risk factor for the development of future breast cancer, could be improved.

The use of AI to analyse the data generated by multi-omics (technologies that generate multi-layer information from the genome, epigenome, transcriptome, proteome, metabolome, and more) could be an important step to help us better understand cancer biology and lead us in the direction of more personalized medicine (36). AI is also used in real-world evidence to help us dissect the crucial information that is generated and work on hypothesis-generation.

The complexity of integrating AI into breast cancer care cannot be underestimated. Many of the developments are still in the early phase, and prospective trials to validate AI use are necessary. For the future to facilitate a sustainable use of AI, it is of the utmost importance that implementation is accompanied by ethical rules of conduct, regulatory and financial frameworks, and guidelines.

## Looking into the future

To optimize the quality of systemic anti-tumour treatment for breast cancer patients worldwide with as equal availability of these medicines as possible, a number of issues are important.

First of all, there needs to be a universal indication. There are European and American guidelines on the minimum efficacy that systemic anti-tumour treatments against (breast) cancer must meet. Pursuing a universal guideline and adhering to it worldwide forces the pharmaceutical industry to design studies that meet these criteria. The aim is to prevent overtreatment worldwide and increase the chance of accessibility of drugs in low-income countries.

Secondly, recognizing differences in the quality of breast cancer care between countries worldwide and therefore also differences in possibilities, wishes, and priorities about how this quality can best be optimized. Establishing a minimum quality that systemic therapy for (breast) cancer must meet worldwide by authoritative bodies could contribute to this. Local healthcare professionals can use this to put pressure on policymakers in their own country where necessary.

Thirdly, the goal should be to implement 'value-based healthcare' worldwide. This form of care enables individualized treatment in a cost-efficient manner. This can be done by increasing the efficiency of the treatment (e.g. through better selection of patients and thus less 'overtreatment') or by reducing costs (e.g. the development of biosimilars and the search for optimal instead of maximum doses of drugs). Preference is given to finding applicable selection methods that can also be used in low-income countries, and then rolled out globally.

Fourthly, researchers have shown that genetic changes normally found through a biopsy can also be detected in a blood sample. Several types of these 'liquid biopsies' are likely to become game-changing by evaluating circulating tumour cells, circulating DNA or RNA, and exosomes. As a simple blood draw is much less invasive than a tissue biopsy, liquid biopsies are becoming a tool to be applied in many steps of breast cancer management. Cost-effectiveness has to be proven, but a paradigm shift in the care of metastatic breast cancer is expected from regular blood testing, revealing that treatments stop working and allow intervention sooner when tumour burden is low, with a better chance of a good outcome (37). Next-generation sequencing will also likely become standard for breast cancer, making molecular tumour boards critical for interpretation.

Fifthly, the creation of networks is needed to better organize treatments and the usage of resources. Since the 1990s, the model of the cancer networks has spread out as a best practice for organizing and delivering high-quality care for patients. Cancer networks have been developed across European countries, at the local and regional level, as well as at the international level for rare cancers.

Finally, it is important to further investigate the most important developments that exist for optimizing the quality of (systemic breast) cancer care for patients. If we want to make a difference globally in the long term, three developments are of particular importance. First, to use the patient as a source of clinically relevant information by measuring PROMS. Second, to optimize global research based on real-world data, and finally, the use of AI in daily clinical practice.

## Key messages

- Overuse of systemic treatment can burden patients with unnecessary toxicity and society with unnecessary costs.
- Structure indicators are education, day clinic, pharmacy facilities, electronic prescribing system, and the existence of specialized breast units.
- Uniform guidelines are necessary to identify reliable process indicators.
- PROMs, PREMs and PRIMs with participation of patient advocates are necessary to increase patients' satisfaction and better match their expectations and concerns.
- Systemic treatment is a high-risk process with many potential side effects.
- Long-term OS remains the gold standard outcome endpoint in breast cancer, with QoL gaining importance.
- The WHO provides a list of essential cancer medicines for all patients worldwide.
- Tailored therapy can provide personalized, high-quality care for older patients. Implementation of a geriatric assessment into clinical practice and incorporation of geriatric assessment measures in clinical trials is mandatory.
- Value-based clinical benefit of systemic treatment and cost are among the biggest issues in breast cancer care today. ESMO and ASCO frameworks of value are important and valuable tools.
- Precision medicine and AI will help provide the best care for every breast cancer patient in the future.

## Ideas for the identification of process quality indicators for systemic treatment

Suggested by the authors, to be adapted according to local guidelines and registration possibilities. EUSOMA suggested a lot of new quality indicators to be accomplished in countries where these molecules are reimbursed (marked with asterisk). In a global perspective most of these cannot be supported.

### **Box 17.1 Organizational aspects treatment early and metastatic breast cancer patients**

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#### **Documented plan for systemic treatment/chemotherapy**

- 1.1 Dose-route-time interval
- 1.2 Height-weight-BSA
- 1.3 Availability of histological diagnosis, TNM classification with determination of grade, hormonal receptors status, HER2 status (before decision of systemic treatment)
- 1.4 Serotonin antagonist (5HT3 receptor antagonist) and corticosteroids with HEC (highly emetic chemotherapy)
- 1.5 Staging: % PET—CT if stage I or II (negative indicator)
- 1.6 % patients (early and metastatic) discussed at least once at the multidisciplinary tumour board

#### **Signed informed consent**

- 2.1 Discussing also fertility preservation with patients in reproductive age before starting therapy
- 2.2 Genetic counselling if high increased risk of hereditary cancer

#### **Well-being, QoL**

- 3.1 QoL standardized assessed during treatment
- 3.2 % complications of chemotherapy resulting in hospitalization
- 3.3 % of patients dying in known location versus hospice—hospital
- 3.4 % of patients administered chemotherapy in the last two weeks of life
- 3.5 % of intravascular device infections
- 3.6 % of patients returning to normal activity of daily living, one year after neo/adjuvant treatment for primary breast cancer
- 3.7 % of patients maintaining professional activity during and after treatment

### **Box 17.2 Early BC patient receiving optimal therapy by patients under 70 years, stage 1 (T1c) to 3, within 4 months of diagnosis/ 1 year after diagnosis**

- 4.1 % of chemotherapy: All patients with primary breast cancer
  - % patients with triple-negative primary T >2 cm BC
  - % patients with TNBC receiving neoadjuvant CT and pembrolizumab \*
  - % patients receiving adjuvant capecitabine after non-pCR with neoadjuvant chemotherapy\*
  - % patients receiving adjuvant PARP inhibitor in TNBC and a germline BRCA mutation \*
- 4.2 % trastuzumab if HER2 positive/in general/and if T1a (the last one is a negative indicator)
  - % patients receiving NACT and trastuzumab \*
  - % patients receiving NACT: trastuzumab and pertuzumab if LN + \*
  - % patients receiving adjuvant T-DM1 with non-pCR post-neoadjuvant therapy and post-surgery \*
- 4.3 % endocrine therapy if ER-positive within 1 year of diagnosis
  - adjuvant bisphosphonates in postmenopausal patients with ER-positive BC \*
  - % receiving at least 5 years of adjuvant endocrine therapy
  - % patients receiving adjuvant abemaciclib, 2 years in high risk, LN +, ER-positive/ Her2-negative breast cancer\*
- 4.4 % of patients receiving adjuvant chemo if T1a, ER-positive/HER2-negative (negative indicator)

### **Geriatric patients (>70 years)**

- 5.1 % geriatric patients with geriatric screening
- 5.2 % geriatric patients (>75 years) with documented geriatric assessment (if screening is positive)
- 5.3 % receiving adjuvant chemotherapy if ER-positive breast cancer
- 5.4 % receiving adjuvant chemotherapy if triple-negative breast cancer
- 5.5 % of patients receiving trastuzumab in adjuvant setting without chemotherapy (negative indicator)
- 5.6 % of patients receiving the whole duration of treatment as planned, in adjuvant setting

**Box 17.3 Optimal systemic treatment for metastatic patients**

- 6.1 % of ER + breast cancer patients whose first-line therapy is endocrine treatment (with or without CDK4/6 inhibition) versus chemotherapy
- 6.2 % of geriatric patients who need dose adjustment in the 3 months after the start of chemotherapy and/or targeted treatments
- 6.3 % IV bisphosphonate or denosumab for multiple bone metastases
- 6.4 % patients with HER2-positive breast cancer receiving first-line trastuzumab-based therapy \*
  - % patients receiving trastuzumab-pertuzumab in first line \*
  - % patients receiving trastuzumab-based treatment in second line \*
- 6.5 % patients TNBC with CPS >10% receiving ICIs in first-line setting \*
  - % patients with germline BRCA mutation receiving PARP inhibitor\*

**Locally advanced and inflammatory breast cancer**

% patients who received multidisciplinary treatment with primary neoadjuvant chemotherapy if inflammatory breast cancer

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## Primary care

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and Haireen Abdul Hadi*

### Introduction

Primary care is defined by the World Health Organization (WHO) as a model of care that supports first-contact, accessible, continuous, comprehensive and coordinated person-focused care (1). It aims to optimize population health and reduce disparities across the population by ensuring that subgroups have equal access to services.

Typically, primary care is provided by clinicians who are generalists, as distinct from specialists with expertise in a specific area of clinical practice. Most high-income countries have some form of primary care embedded in their healthcare systems, although its role may vary. In some countries, all inhabitants are registered with a primary care physician (PCP) such as a general practitioner that acts as a gatekeeper to specialty care services. In other countries this gatekeeping role is not part of PCP care. Regardless of the difference in organization and function between countries, PCPs have long standing relations with their patients and their families, know their environment and context, and together with multidisciplinary teams consisting of nurses, pharmacists, physical therapists, and many others provide continuous care for chronic conditions such as diabetes, chronic pulmonary diseases, perform cardiovascular risk management, and psychological and psychosocial support.

Breast cancer care in low- to middle-income countries (LMICs) can vary significantly and faces challenges related to resource limitations, healthcare access, healthcare infrastructure variations, financial toxicity, alternative treatments, societal values, and cultural norms (2). PCPs in LMICs manage acute issues in the community, lacking networks with tertiary referral centre, continuity of care and little regulatory oversight (3). In LMICs, primary care infrastructures were historically built to address communicable diseases, nutritional deficiencies, and maternal-child health (4). Thus, the present dual endemic of communicable and non-communicable diseases (NCD) is challenging. Among investments in NCD, cardiovascular diseases, the usual leading cause of premature mortality, are seen as more urgent compared to cancer, as the nature of the presentation of the illness is often more acute and needs immediate medical attention compared to cancer.

The most significant challenge in LMICs is to reduce the burden of advanced-stage disease via context-specific strategies at the individual, health system, and population levels (5). Medical specialization in cancer care in LMICs was prioritized to address the immediate lack of cancer treatment capacity rather than focus on the root cause of cancer challenges in LMIC, like improving health literacy and screening for early detection in the community. Furthermore, low PCP capacity in acute community practice has led more to specialization

in acute primary care diseases like asthma, diabetes mellitus, and hypertension or remain as general practitioners, thus neglecting cancer screening. Therefore, the generalist approach is to reorient and enhance the primary healthcare vision for cancer control (6).

Evidently, primary care plays a varying, but essential role in the care for patients with cancer in general, and patients with breast cancer in particular. PCPs are involved in prevention and screening, diagnosis, care during treatment, follow-up and survivorship care, and palliative and end-of-life care (7). PCPs also guide the caregiver, who plays an important role in looking after their family members through treatment and their social welfare.

In this chapter, we will discuss the role of the PCP in the care for breast cancer in all these phases of breast cancer (BC).

## Prevention and screening

Universal prevention, which entails promoting health advice to individuals without complaints (who typically have not yet consulted a PCP), falls more within the domain of governments and local authorities. However, there is a gradual scale to this, as patients who wish to quit smoking and do not yet have smoking-related conditions can still receive support in primary care. Primary-care-based brief interventions can reduce alcohol consumption, widely acknowledged as a risk factor for BC. PCPs, along with practice assistants, often provide preventive care for patients at increased risk for cardiovascular diseases. Risk factors for cardiovascular diseases overlap with risk factors for BC (8). Preventive care for these patients may therefore also be preventive for BC.

Prevention or early detection through screening is possible for relatives of patients with hereditary BC or patients otherwise at risk for cancer. PCPs can offer women at moderate or high risk of breast cancer risk-reducing medication or enhanced breast screening/surveillance (9).

Many high-income countries have adopted screening programmes for breast cancer. In some countries, these programmes are nationwide screening programmes, performed by separate screening organizations, in which PCPs are informed about the diagnosis and play a varying role in referral to treatment facilities. In other countries, screening is performed on an individual basis and often initiated by the patient or the caring PCP (opportunistic screening). However, it is well-established that PCPs play an important role in cancer screening, regardless of their formal role. They are essential for providing balanced information about screening, possibly improving uptake, and in providing advice and support about and after screening tests (10).

## Diagnosis

The majority of women with BC are diagnosed outside of regular screening programmes, in many cases after presenting to a PCP with symptoms (11). PCPs are typically the first point of contact when symptoms such as a breast lump, changes in breast shape, skin dimpling, nipple discharge, or pain occur. The role of the PCP includes conducting a thorough (family) history and physical examination, ordering initial diagnostic tests such as mammography, and

referring patients to specialists for further evaluation and treatment. Early detection of BC by PCPs can significantly impact the prognosis and treatment outcomes for patients.

## Treatment

The role of the PCP starts during treatment decisions (12). PCPs are trained to enhance patient participation in shared decision-making, taking into account both the medical and contextual background of the patient. Because PCPs often have a longer history of acquaintance with the patient and their context, they can provide information about the context, treatment goals, and preferences to specialists in the hospital, which can subsequently be considered when weighing different treatment options.

Once treatment has commenced, PCPs remain involved in the care for other (pre-existing) conditions (13). Patients with cancer, especially older patients, often have chronic comorbid conditions (14). These conditions may worsen due to oncological treatments. It is important for the PCP to actively collaborate with the specialist to identify and address potential interactions between oncological treatments and pre-existing conditions. Additionally, the PCP is the treating physician for acute illnesses. Thus, the PCP plays a direct co-treating role in conditions resulting from cancer treatment. This role becomes more evident in the treatment of effects of chemotherapy or radiotherapy, such as skin conditions, neuropathies, and pain.

Furthermore, PCPs play a clarifying role during or immediately after treatment. Information provided in the hospital may sometimes be difficult to understand, or patients may have questions later on. Patients consult their PCP with questions about treatment effects, side effects, or lifestyle. Patients may seek alternative therapies, and PCPs need to provide balanced information and ensure that these choices do not interfere with conventional treatments. Educating patients about the evidence-based benefits and potential risks of alternative therapies is crucial for informed decision-making. Additionally, PCPs have provide psychosocial support to cancer patients by listening to their problems, putting them in perspective, and referring them to specialized psychological help if necessary. In many cases, the PCP is also the PCP of family members of the patient with cancer; the PCP is also their provider of (psychological) support.

Effective communication and coordination between PCPs and oncology specialists is essential for the optimal management of breast cancer patients. This includes sharing information about the patient's treatment history, ongoing symptoms, and any new or possible future health concerns (15). Integrated care models where PCPs and specialists work closely can enhance patient outcomes by ensuring that all aspects of a patient's health are addressed comprehensively.

## Survivorship care

While most follow-up care aimed at recurrence detection is performed in hospitals, PCPs continue to play an important role for patients with BC during this phase. They remain the first point of contact for care in between scheduled follow-up, and their roles may include explaining self-examinations, performing physical examinations, and requesting additional diagnostics such as mammography. In the past decade, debate about the most effective form

of BC follow-up has spiked (16). In some countries, performing BC follow-up in primary care has been suggested as a viable alternative to hospital follow-up, which is shown to be equally effective and appears to be accepted (17).

Next to that, PCPs remain the treating physician for comorbidities and other health problems, for both patients and their families. Research has shown that PCPs are consulted frequently by BC patients and their partners and appear to be involved in psychosocial support and supporting patients and partners with returning to their pre-cancer lives (18). COVID-19 has shown telemedicine can play a role in cancer patient's follow-up between their PCP and oncologists and can be a medium to provide education resources to patients, remote monitoring and reminder of their medical care (19).

After end hospital-based follow-up, PCPs are the primary physician for most BC patients. Yet, many patients with cancer can experience a plethora of persistent health problems related to their BC or its treatment. Research has shown that even after 10 years patients still experience psychosocial problems, with approximately 25% of patients experiencing fatigue (20). Moreover, PCPs need to remain vigilant for late effects of BC treatments, such as cardiac and cardiovascular problems (21).

In the US primary care involvement in survivorship care delivery remains low even more than 5 years after completing treatment. Confidence in the PCP ability to manage survivorship may represent an opportunity to foster transition to primary care-led survivorship care delivery (22).

In light of these, PCPs also play a role in promoting a healthy lifestyle to reduce the risk of recurrence, long-term effects, and improve overall health. This can involve advising on diet, exercise, and mental healthcare, as well as monitoring for late effects of cancer treatment. Their holistic approach ensures that breast cancer survivors receive the support they need to maintain their health and well-being long after their initial treatment has concluded.

## Palliative and end-of-life care

When breast cancer progresses to an advanced stage, PCPs are knowledgeable in providing palliative and end-of-life care. This includes managing pain and other symptoms, providing emotional support, coordinating care with other healthcare providers, and helping patients and their families navigate the complexities of end-of-life decisions. PCPs ensure that patients receive compassionate and holistic care that respects their values and preferences.

## Perspective from LMICs

In LMICs, the role of PCPs in monitoring recurrence and managing long-term effects of breast cancer is crucial but often challenged by limited resources. Access to regular follow-up care, including mammography and other diagnostic tools, may be constrained by financial, geographical, and infrastructural barriers (23). PCPs in these settings must often rely on clinical examinations and patient-reported symptoms to monitor for recurrence.

- **Community health workers:** Community health workers (CHWs) play a significant role in extending the reach of primary care services in LMICs. They can assist in

educating patients about self-examinations, lifestyle modifications, and the importance of regular follow-ups. CHWs can also provide emotional support and help navigate the healthcare system, making it easier for patients to access necessary services.

- **Resource-appropriate interventions:** In LMICs, interventions must be adapted to the available resources. This can include the use of mobile health technologies to follow-up with patients, telemedicine consultations, and community-based screening programmes. These strategies can help overcome some of the barriers to care and ensure that breast cancer survivors receive continuous and comprehensive care.
- **Health literacy:** Low levels of health literacy can hinder patients' understanding of the importance of follow-up care and adherence to recommended lifestyle changes. PCPs play a crucial role in providing culturally appropriate education and support to enhance patients' knowledge and engagement in their care.
- **Traditional and alternative medicine:** In many LMICs, traditional and alternative medicine practices are common. PCPs need to be knowledgeable about these practices and engage in open, non-judgemental conversations with patients. Collaboration with traditional healers and integrating safe, complementary practices into the care plan can improve patient satisfaction and adherence to treatment.
- **Mental health services:** Mental health services are often limited.
- In some LMIC, there is poor communication between the PCP and the specialists in secondary care. A delay in a patient's treatment information to the PCP can affect patients' continuity of care and timely interventions if required (24).
- Primary care providers in LMICs often lack the necessary training and knowledge in oncology. This gap makes it challenging to manage cancer patients effectively, especially regarding the latest treatments, side effect management, and follow-up care (25).

By considering these additional perspectives, the role of primary care in the management of breast cancer can be better understood and optimized, ensuring that all patients, regardless of their geographical location, receive the best possible care.

## Key messages

- Primary care is important in the comprehensive care of breast cancer patients
- Effective communication between PCPs and oncology specialists is essential
- PCP must be involved from prevention and early detection to treatment, survivorship, and palliative care
- PCPs ensure that patients receive compassionate and holistic care that respects their values and preferences
- In LMICs, the role of PCPs is crucial but often challenged by limited resources

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## Supportive, palliative, and end-of-life care

*Christine Langenaeken, John Weru, and Carole Bouleuc*

### Introduction

Palliative care (PC) has historically been associated with hospice and end-of-life (EoL) care. However, a shift in paradigm has occurred with the integration of PC into standard oncological care (SOC) and a focus on patient-centred care.

For the sake of terminology, we refer to the World Health Organization (WHO) definition of PC, i.e. care aiming to prevent and relieve suffering by assessment and treatment of physical, psychosocial, and spiritual problems, and to the Multinational Association of Supportive Care in Cancer (MASCC) definition of supportive care, i.e. the prevention and management of the adverse effects of cancer and its treatment.

From the WHO definition of PC, it follows that this type of care is appropriate at any stage of the disease and can be provided alongside oncological treatment. Yet the word ‘palliative’ may have negative connotations for patients and delay their referral or readiness to accept PC. Nevertheless, consciously putting patients’ holistic needs at the centre of every activity is the cornerstone of supportive and PC. To cover both, the ESMO Supportive and Palliative Care Faculty proposed the use of the term ‘patient-centred care’ (1).

In this chapter, we will discuss patient-centred care with a focus on advanced disease and EoL/terminal phase.

### Minimal requirements

#### Patient-centred care and the multidisciplinary team

In their disease trajectory, patients may have different physical, psychosocial, and spiritual needs, which will evolve over time and may even increase in the palliative and EoL phase. Therefore, patient-centred care cannot be standardized although it should be provided through a standardized framework. To ensure that patients’ concerns and needs are being heard and considered, detailed and routine physical and psychological assessments must be performed, allowing for supportive and palliative interventions to be personalized and integrated in the continuum of care. Patient-reported outcomes (PROs) are an important part of these assessments, informing healthcare professionals (HCP) of patients’ needs and concerns. Tailored approaches are needed to promote patient engagement and improve adherence to ePRO assessments in PC. The multidisciplinary team (MDT) plays a key role in assuring that patient-centred interventions are discussed alongside disease-specific treatments, respecting patient preferences and cultural specificities. The composition of the MDT, its tasks and responsibilities may vary depending on the patient’s needs, resources, and local



settings. Increasing complexity, workload pressures, and resource constraints require effective leadership and chairing in cancer MDTs. By aligning chairing and leadership styles with meeting demands and integrating supportive technologies, MDTs can sustain their pivotal role (2). In case the necessary staff is not available in-house, patients should be referred; the oncologist or other HCP in charge of the patient should coordinate and regularly evaluate these interventions.

The team approach and multidisciplinary of the team are not novel to oncology and PC. As PC has been delivered through primary healthcare providers, dedicated PC nurses, and community healthcare workers, the latter being particularly useful in specific settings such as rural/remote areas or low- and middle-income countries (LMIC), one might even wonder whether an oncologist is necessary or what his role would be. Patients with cancer have complicated illnesses and need multiple individuals to help with the management of their disease all the way. Some aspects of SOC and PC, such as symptom assessment and management, can be managed by supporting members of the team. Other aspects such as informing patients about their disease status, prognosis, implications for ongoing care, and discussing goals of care are better conveyed by direct oncologist-patient interaction (3).

## Education

Education is a key pillar in providing quality PC at every level, ranging from addressing barriers to referral to providing for an educated workforce of HCP, including trained nurses and community health workers.

In the ESMO/ASCO recommendations for a global curriculum in medical oncology edition 2023, supportive, palliative and EoL care are listed among the competencies required (4).

A lack of trained PC providers and insufficient education at various levels have led to different strategies to deliver PC education by developing a wide variety of training programmes. However, the quality of these programmes is varied, often lacking hands-on experience and the level of competencies developed is heterogeneous. The problem of getting high-quality PC training is particularly relevant for LMIC. This could be addressed by providing PC training at high-quality institutions that might also offer mentorship, training, and accreditation to develop PC education programmes in LMIC centres. WHO, State members, and local academic institutions should work as facilitators to overcoming the financial, certification, language and cultural barriers, and promoting academic exchange. Provider training was found to play a central role in implementing resource-stratified guidelines for PC in LMIC. Favouring international collaboration and enhancing academic exchange is an essential step to improve the training of regional PC providers, thereby also enhancing mutual understanding and expanding the knowledge of global PC (5).

## Best practices

### Assessing palliative care needs

To introduce PC in a timely fashion, one needs to identify the ‘palliative’ patient well before the terminal phase and irrespective of the underlying disease. Prognosis of the disease and life expectancy, as well as care needs, must be considered.

Prognostication is a process rather than an event, as prognostic factors may evolve over time. Clinician prediction of survival is the most commonly used approach to estimate prognosis, by asking the ‘surprise question’: ‘Would I be surprised if this patient would die within the coming year?’ This clinical instrument has proven useful and feasible in identifying the ‘palliative’ patient at an early stage. In the Anglo-Saxon world, the Supportive and Palliative Indicator Tool, SPICT, is widely used (6).

Based on the SPICT, the Palliative Indicator Tool, PICT, was developed in Belgium (7). The PICT is a two-level questionnaire tool (1) identifying the ‘palliative’ patient by considering elements of vulnerability and incurability and (2) distinguishing various levels of needs in the palliative population.

Although it is widely acknowledged that screening for PC needs is important, the implementation in daily practice is lagging behind. In a survey of German Comprehensive Cancer Centres (CCC), different validated screening tools were used in different combinations in those CCC that performed screening, but not in all oncology departments performing screening. Both the lack of technical and human resources and structural conditions were identified as barriers to implementation (8).

In the Czech Republic, the NECPAL (Palliative Necessities) tool, based on the EoL care information system, was found to successfully identify PC needs (9). Again, support of the main stakeholders and effective leadership were key factors in implementation and success.

## Referral

Even if PC needs and the ‘palliative patient’ are identified, there are still barriers to referral for PC, related to clinicians, patients, and the healthcare system.

Misconceptions persist among oncologists, reducing or delaying referral for PC: lack of information on local services, belief that PC is incompatible with oncological care, and conviction that it is their role only to provide for PC. Barriers on the patient/family side include lack of knowledge, not seeing the point in seeing another specialist, and misperception that PC is synonymous with ‘giving up’. There may be logistical barriers on the side of the healthcare system too, relating to the availability of an educated workforce and essential drugs.

Addressing these barriers requires an integrated and structured approach to (1) inform both oncologists and HCP involved and raise awareness of the true value and meaning of PC, and (2) ensure continuing education of all actors involved. Education of HCP, patients, and the public is key, as is the availability of essential drugs. Collaborating with nurse care practitioners, trained community workers or alike may be instrumental in lowering barriers to PC in a contextualized way, i.e. adapted to the local circumstances.

In times of pandemic or long travel distances, telephone consults may be helpful. However, a telephone consult was less informative than a face-to-face consult (10).

Different approaches have been used to improve PC and hospice referrals, e.g. the use of standardized criteria for PC consultation, augmented intelligence (AI) tools (11), and machine learning (12).

Although there is a wealth of guidance for specialty PC integration, there still are no agreed-on guidelines for referral. Current clinical guidelines apply a one-size-fits-all framework to often nuanced levels of PC need. Rapid evolution in cancer treatments and the associated dynamic nature of patient outcomes dictate a need for ‘precision PC’, transitioning

away from prognosis- or disease severity-based criteria for specialist PC referral to criteria focusing on patient and caregiver needs and complexity (13), thus highlighting the interrelationship of identifying PC needs and referral issues.

## **Navigating and communicating about serious illness and end-of-life**

Even if the course of the disease and prognostic information have repeatedly been well communicated with the patient and family, in a sensitive way, tailored to their preferences, it is not uncommon for patients to express seemingly unrealistic hopes (14). This is disconcerting for the clinician who wants to understand what matters most for the patient and may fear the patient is ill prepared for EoL and death.

To help patients develop their capacity to cope with the disease and EoL, clinicians need more than just communication skills: they should be able to help cultivate prognostic awareness and existential maturation. This requires recognition of the patient's current understanding of their illness and their capacity to adaptively cope with prognostic information. Prognostic awareness is the patient's ability to integrate the likely illness trajectory both cognitively and emotionally. Partnering with patients to reach this goal is an iterative process that requires multiple conversations over a prolonged period. Cultivating prognostic awareness may lead to the development of coping strategies to manage a more integrated awareness of an uncertain future and is a part of a process of existential maturation (Table 19.1).

## **Advanced care planning**

Patient-centred care becomes even more important for patients and their families when meaningful life-prolonging or disease-stabilizing treatment options have been exhausted and life draws to a close.

Advanced care planning (ACP) can help patients and HCP cope with this transition, navigating through the different stages of the disease and discussing goals of care (GoC).

A patient's ability to cultivate prognostic awareness as part of the existential maturation process is critical when it comes to ACP, when what is most important to the patient is translated into a treatment plan, especially as it relates to EoL care.

Serious illness/EoL conversations and ACP share the common goals of aligning medical care with the patient's goals and values. As these conversations are an interactive process, so is ACP. Trials that have analysed ACP have shown that patient preferences can change and that it is hard for most patients to determine an appropriate medical decision far in advance of the need for that decision. Moreover, patients may change their minds and set new boundaries of what they consider 'acceptable' QoL. ACP should not be considered 'filling out a document' to be archived in the patient's file, but rather a process by which patients come to understand their prognosis, share what matters most to them and iteratively express their preferences for medical care.

ACP conversations must be conducted in an open and culturally sensitive and contextual way. Values are at the heart of ACP, being influenced by culture and religious beliefs.

**Table 19.1** Key clinical points in navigating and communicating about serious illness and end-of-life

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- Partnering with patients as they navigate serious illness requires effectively communicating prognostic information while responding to the emotions generated by the conversation
  - Clinicians should expect, and have the skill, to engage in a continuum of conversations that allow patients to integrate prognostic information cognitively and emotionally
  - Patients oscillate between expressions of intense hopefulness and more realistic aspirations: this is a normal and expected part of the process
  - Facilitating patient exploration of their hopes and worries allows them to grieve, understand their priorities, and build coping skills for living with the disease
  - As patients integrate prognostic information, clinicians should discuss what is most important to the patient given the likely illness trajectory and incorporate these goals and values into a recommendation about medical care, including EoL care
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Source: data from V. Jackson, L. Emmanuel. Navigating and communicating about serious illness and end-of-life. *N Engl J Med* 2024;390:63–9.

Community-based participation can help to identify nuances and realize culturally concordant ACP (15).

## Organization of palliative care in different settings

In **urban and high-resourced settings** PC may be found on-site or ‘siloed’ at an external location. In rural areas accessibility and travel distance are but some of the barriers to PC. Challenges to and specificities of PC in rural and remote areas include being mindful of the local culture, adapting traditional geographically based/local-rooted care delivery models, and using novel PC education delivery methods to increase community-based HCP, layperson, and family PC expertise to account for limited local PC resources (16). Notwithstanding their limitations, rural and remote communities also have strengths and opportunities, including close-knit, committed community practitioners. So, adapting PC models, using culturally appropriate novel care delivery methods, and providing remote education and support to existing community providers are promising advances to install PC. Reformulating health policy and nurturing academic-community partnerships that support best practices are critical components of providing integrated PC not only in rural and remote areas, but also in **low-resource settings**.

**Community-based programmes** have broadened the reach of PC by providing PC beyond the constraints of a hospital or hospice programme, as they meet patients and families in their homes, identify and address gaps in care, stresses of diagnosis and treatment, barriers to treatment compliance, safety concerns, and caregiver burden (17). Interdisciplinary teams collaborating with the patient’s family physician, home care, and oncology team are key to providing quality PC consistent with the patient’s evolving preferences and GoC. Community-based PC is widely applicable, regardless of the setting; however, coordinating care and keeping all actors involved ‘in the loop,’ not letting anyone go astray, is definitely a challenge! Toolkits and digital technologies are useful resources for this purpose.

## Low- and middle-income countries with a focus on Africa

Breast cancer is the most common cancer in Africa and has increasingly become a disease of high morbidity and mortality. While breast cancer patients are relatively young compared to other geographical regions, they also present late with over 80% of patients consulting a doctor for the first time with metastatic disease. Late-stage disease is consistent with delayed identification and diagnosis of breast cancer and is both an access and psychosocial issue. Limited medical literacy by patients and healthcare providers, initial lack of pain, fear of diagnosis and treatment, fear of diminished sexuality and femininity, preference for traditional medicine and spiritual healing, and financial burden all contribute to delayed diagnosis. Common symptoms include pain, fatigue, physical, and psychological effects of a fungating wound and other psychosocial distresses due to the diagnosis (18). Advance care planning and EoL care for breast cancer patients is a significant need across the continent.

Given the increasing incidence of breast cancer in Africa, it is only fair that there is a provision of timely and contextualized PC. However, there are many challenges to meeting this endeavour. There is a general misconception of what PC is, with it being equated to EoL care and thus patients, families, the community, and healthcare providers do not appreciate its worth and avoid it. So cultural attitudes and behaviour are significant barriers to the development and implementation of PC in Africa. This leads to limited community engagement, low public awareness, and few community volunteer workers, who are an important group in advocating for healthcare services. There is a paucity of people trained in PC, which is a relatively new specialty/subspecialty. There is limited research on PC in Africa, which mirrors other LMIC (19). There is a general lack of integration of PC into national healthcare systems. This means that standardization is not possible and therefore evaluation and assessment of its effectiveness and efficiency cannot be done. Other challenges include the high cost of care, distance to care centres, limited human resources, and erratic or no access to opioids. The WHO has integrated key elements for developing PC in the Actionable Indicators Model, a conceptual model for assessing PC development that focuses on identifying gaps in service provision, thus helping define priorities and guiding decisions. In Mexico, this model found items halting PC development that have been identified over and over again: insufficient PC services, lack of a (national) PC authority, limited access to essential drugs and scarce (undergraduate) education (20). The same barriers were identified in a survey on ASCO guideline adherence among HCP in LMIC (21).

A multilevel public health approach is needed to make PC universally available. This includes health policy that supports the integration of PC and investment in systems of healthcare delivery; changes in legislation and regulations that inappropriately restrict access to opioids for patients with life-limiting illnesses; education and training of HCP; development of a methodologically rigorous data and research data base specific to LMIC that encompasses health systems and clinical care, and shifts in societal and HCP attitudes to PC and EoL care. International partnerships are valuable to achieve these goals, particularly in education and research, but leadership and health system stewardship within LMIC are key to driving and implementing change (22).

## Standards, guidelines, and quality measures for PC integration

Advances in methods and procedures to guide integration of specialty PC into SOC have led to a proliferation of standards, guidelines, and quality measures around the globe (23).

Several oncology organizations in the USA and internationally have produced recommendations including the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN) for the USA; the European Society of Medical Oncology (ESMO), and the European Association of Palliative Care (EAPC).

Although there are differences among the various recommendations arising from diverse roles of PC specialists within cancer care, they all share four common themes: the need to guarantee access to specialty PC for all patients with cancer, use of stratification methods to determine referral, focus on informal caregivers alongside the patient, and interdisciplinary composition of the PC team.

Most PC quality measures evaluate processes of care; less commonly structure and outcome measures are used. To assess all the outcomes improved by PC at the individual, system, and population level and identify areas for improvement, an expansion of the classical ‘Structure-Process-Patient health outcome’ pyramid is required to include access, resource use, patient experience and cost, and population health. As there is an increasing number of available PC quality measures, there is an imperative need to prioritize. This effort can be guided by using feasibility and usefulness criteria. Implementation is an important endeavour for the field.

## Emerging modalities

### Telehealth and digital technology

Telephone and video-assisted visits have already been used in the past to supplement in-person visits, particularly in remote areas, and have also proved valuable in LMIC. The practice has greatly increased during the COVID-19 pandemic and is here ‘to stay’.

Lessons learned from programmes that were already developed and implemented prior to the pandemic, and from the accelerated widespread use of telehealth during the pandemic, are the need for planning for all actors involved, ongoing patient support, HCP training, providing care in a culturally responsive way, and cancer health system programmatic considerations, such as reimbursement, software, hardware, and cybersecurity (24).

A number of strategies to improve symptom management and increase the delivery of PC are emerging. These include integrating PROs in the electronic health record (EHR) and using natural language processing (NLP) and clinical decision support (CDS), providing recommendations via the EHR. Integrating PROs may alert members of the team to uncontrolled symptoms, enhance patient-HCP communication, symptom management, QoL, and patient satisfaction, and decrease emergency visits or unplanned admissions. In the future, NLP can supplement PROs by searching the EHR for uncontrolled symptoms; this may be particularly helpful for patients who find it difficult to quantify symptoms.

CDS builds on the information provided by PROs or NLP and, using algorithms developed from accepted national consensus guidelines for symptom assessment and treatment along with patient-specific data, ‘works behind the scenes’ in the EHR to capture, analyse, and make suggestions for assessment and treatment of patients’ pain and other symptoms.

Thus, CDS may facilitate the adoption of guidelines for symptom management by providing patients and HCP with relevant knowledge and/or person-specific information, intelligently filtered or presented at appropriate times. For CDS systems to improve practice, they must be part of the workflow, provide specific recommendations, be present at the time and location of decision-making and be computer-based.

## Art therapy

Art therapy can offer a creative outlet for patients in PC to express emotions, manage distress, and enhance well-being. Integrating art therapy into PC further supports holistic, patient-centred care (25).

## Key messages

- Patient-centred care is a holistic approach covering the continuum of supportive and palliative care
- The multidisciplinary team is key
- Precision palliative care must focus on patient and caregiver needs and the complexity of care
- Advance care planning and EoL communication are iterative processes, creating prognostic awareness and existential maturation
- Organization of palliative care needs to be adapted to the local circumstances
- A multilevel public health approach, international partnerships in education and research, and leadership within LMIC are key to universal PC
- Guidelines and quality measures must include access, resource use, and population health
- Telehealth and digital technology are important emerging modalities

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## Nursing Care and Patient Navigation

*Victoria Harmer, Cathy Hughes, David Odada, and Vinayak Sonawane*

### Specialist nursing in breast care

Specialist nursing in breast care is an example of extended practice to meet patient needs. These senior nurses have undertaken additional studies in breast care and have, or working towards, master's or doctoral-level academic qualifications. They should be using evidence-based nursing with the ability to problem-solve, reflect, analyse, and think critically. They should have the skills to communicate the complex information given to patients and their families in breast clinics, supporting informed decision-making. The specialist nurse should holistically assess the patient and advocate for them within the multidisciplinary team (MDT).

Specialist nurses also provide strong leadership and positively impact the training and development of other staff in order to provide patient-centred, safe, and effective solutions to the ever-changing demand for quality healthcare. Poor nursing leadership has been identified as leading to a declining professionalism and tolerance of poor care in many failures in care reports.

Patient advocacy groups have ranked specialist nurses higher than other health and social care professionals with regard to understanding their needs, being transparent, and honest, designing and implementing care pathways and obtaining patient feedback (1).

Specialist nurses require support from the MDT to develop safe patient pathways embedded with quality nursing care, and to ensure any service development or role extension is adopted successfully (2).

### Nurse specialist/clinical nurse specialist

There are four central threads to the nurse specialist/clinical nurse specialist (CNS) role (3):

- Expert practice
- Patient advocacy
- Holistic assessment and referral
- Service development

In the UK, the breast care CNS (a recognized role) is generally introduced to the patient at the time of diagnosis and is responsible for providing information and support to patients and their families throughout their breast cancer treatment trajectory. European standards

recommend that patients have nurse counselling at the time of primary treatment and direct access to a breast care nurse specialist for information and support with treatment-related symptoms and toxicity during the treatment, follow-up, and rehabilitation (4).

The CNS will case manage the patient and their families while they are undergoing ever-changing treatment pathways and support complex decision-making and discussion of treatment options, often representing the one constant throughout care pathways using differing treatment modalities. The CNS has a key role in limiting and suggesting solutions to any unwanted consequences of treatment, in the identification of disease progression, as well as providing expertise over a range of environments for a number of different domains of care (Table 20.1). The CNS will be vigilant, spot red flag symptoms, and escalate, while continuously assessing the patient in order to dovetail support to unmet needs.

The impact of the CNS can be measured in the quality and experience of care, safety, productivity and efficiency, and leadership. Patients treated at hospitals with more CNSs have a better experience, receive better emotional support, and benefit from healthcare professionals working well as a team. Timely interventions can deflect expensive care episodes and promote efficacy (5, 6). The benefits of a CNS include reduced waiting times, avoidance of unnecessary and unplanned hospital admissions, reduced postoperative length of stay, reduced treatment drop-out rates, freeing up of consultant time, innovative service delivery

**Table 20.1** Clinical domains of practice associated with the clinical nurse specialist

|                                                                                        |
|----------------------------------------------------------------------------------------|
| Family history and genetics (includes prevention, screening, and prophylactic surgery) |
| Benign breast conditions                                                               |
| National Health Service Breast Screening                                               |
| Patients newly diagnosed with breast cancer                                            |
| Patients undergoing chemotherapy (and related side effects)                            |
| Patients undergoing radiotherapy (and related side effects)                            |
| Patients on endocrine therapy (and related side effects)                               |
| Breast surgery                                                                         |
| Breast reconstruction                                                                  |
| Prosthesis fitting                                                                     |
| Management of menopausal symptoms                                                      |
| Management of lymphoedema                                                              |
| Management of fungating wounds                                                         |
| Treatment-induced fertility issues                                                     |
| Metastatic disease                                                                     |
| Social issues and finance                                                              |
| Recovery, rehabilitation, and follow-up (including lifestyle changes)                  |

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and improvement, delivering services at the point of need, and educating health and social care professionals (7).

## Nurse practitioners/advanced nurse practitioners

Nurse practitioners (NP), advanced nurse practitioners (ANP), and more recently advanced clinical practitioners (ACP), focus on direct clinical assessment, diagnosis, and treatment, as well as health education and disease prevention. Although aspects of CNS and NP roles can overlap in relation to leadership, patient and staff education and service improvements, the breast nurse practitioner roles tend to be grounded in the diagnostic pathway. Advanced practice is a level of practice, rather than a type of practice. ANP are educated at master's level in clinical practice and have been assessed as competent in practice using their expert clinical knowledge and skills. They have the freedom and authority to act, making autonomous decisions in the assessment, diagnosis and treatment of patients (8). In the UK, they work within the four pillars of:

- Advanced clinical practice
- Leadership
- Facilitation of education and learning
- Evidence research and development

The extended remit of the nurse practitioner often incorporates functions traditionally allocated to physicians, such as performing breast examinations, taking a history, and ordering diagnostic tests. Evaluation of effectiveness, safety, and patient satisfaction with the NP role, although limited, has been encouraging (9).

## Consultant nurses

The consultant nurse (CN) was introduced in the UK in the 1980s and is at the pinnacle of the clinical nursing career ladder (10). There are four components to the CN role in line with the four pillars of advanced practice above:

- Expert practice
- Professional leadership and consultancy
- Education, training and development, and service improvement
- Research and evaluation

Consultant nurses possess the skills and competencies of the specialist nurse and advanced practitioner but with greater breadth, depth, and complexity. They have a clinical role that ensures clinical credibility and effective role-modelling but they also focus on the whole service, developing research, service improvement, education, and acting as an expert resource. The CN should have completed, or be studying for, a relevant doctorate. The CN should be a transformational leader who fosters widening participation and collaboration, and who contributes to national and international strategies and policies as an expert in their field.

## Hospital and community care

Healthcare and therapies traditionally delivered in a hospital or secondary care setting are increasingly being delivered in the community or primary care setting and more drugs are being administered orally. Consequently, thorough assessment of a patient's ability to self-manage with enough information and support, requires new ways of working across boundaries and remotely. For patients to effectively receive care at home or closer to home, there needs to be good communication with healthcare professionals who work in the community. Appropriate support structures need to be in place (11).

## Cancer survivorship

Many more people are living longer following cancer treatment, due to earlier detection and diagnosis, and more treatment opportunities, yet many of these cancer survivors experience long-term side effects from treatment or from the disease burden of the cancer itself. Cancer survivors have significant unmet needs, and specialist nurses are increasingly their key accessible professional and point of contact. Specialist nurses act as an expert resource to support the patient's process of returning to normal, or a new normal (normalization). They support cancer survivors in developing the skills to self-manage while ensuring they also understand any red flag symptoms and the route to promptly report them to their healthcare provider (3, 12).

## Metastatic breast cancer

In the UK, there is an increasing number of CNSs dedicated to the management of those with metastatic breast cancer. These specialist nurses provide support and information to people with life-limiting disease. These patients often need to revisit the cancer landscape and adjust their expectations (13). Seamless care across boundaries is important to achieve personal goals, and a realistic view of the future.

## Workforce

The extension of nursing roles impacts workload. In addition, treatments are becoming more numerous, sophisticated, and personalized to individual patients and their disease. It is often the specialist nurse's remit to explain, communicate, and manage patient care. The 'Independent Cancer Taskforce in England' documented the need for all cancer patients to have access to a CNS or key worker to coordinate and plan care. They note, however, that there should be a strategic review of workforce deficits and the skills mix required to deliver a modern, high-quality service (14). The number of CNSs in breast care has remained the same in England since 2007, despite an 18% increase in the number of new breast cancer cases (15). There is a need for the number of specialist nurses to be addressed, in order that quality of care is not compromised (4).

There is a global shortage of nurses, although this is most acute in low-income countries, with high-income countries recruiting internationally against this backdrop. The average nurse: population ratio in high-income countries is almost eight times greater than in low-income countries, and there is a link between the number of nurses and health outcomes (16). The ongoing trend in nurse shortages is worrying for the provision of healthcare and patient safety.

## **Patient navigation**

### **London teaching hospital experience**

#### **Overview—identifying the problem**

Historically, on diagnosis of breast cancer, patients were given the CNS telephone number in case of ongoing queries. The telephone number went directly to an answerphone, with the message that a breast CNS would phone the patient back. Patient feedback included that leaving a message on an answerphone did not give them confidence of their call being returned. Some patients with cancer were reporting feelings of bewilderment and struggling to get information, reporting issues regarding knowing who to contact and how to best manage their day-to-day lives. Issues patients were escalating via the answerphone included clinical queries, adverse effects of treatment, and issues pertaining to financial difficulties, support services, and hospital appointment queries.

#### **Navigator service—the solution**

A navigator telephone service was launched. The navigator service remains the first and single point of contact via telephone for all cancer related questions and queries. Accessible to hospital cancer patients, their family and friends, external healthcare professionals involved in their care, the navigators support patients throughout the cancer experience, providing emotional support, and finding assistance as required from other organizations. They provide a listening ear, establish what needs to happen, assess who else needs to be involved and make every effort to ensure the right outcome is met. They can alter hospital appointments, access local support centres, and signpost to those who can help. Navigators work closely with CNS teams, thus if they assess that clinical input is needed, they will book the patient into a nurse telephone clinic for that day, or the next working day. This service has greatly reduced the hours and tasks a trained nurse is required to take calls of a nature that does not require their specialist skills.

Over a one-month period, more than 3000 calls may be received by the navigators at this London Hospital, with 55% of the callers' issues being resolved by the navigator contact. Types of queries include patients chasing medication from the pharmacy, querying their upcoming appointments, requesting to book blood tests, clinical symptoms that need to be assessed by the CNS and patients requiring emotional support.

#### **Patient feedback**

Patients have continually praised the navigator service—stating the service is good, the team are patient, helpful, and supportive.

## Sub-Saharan Africa experience

### Overview

Patient navigation is crucial in sub-Saharan Africa yet hindered by financial constraints, limited resources, and cultural barriers, impeding timely access to cancer care (17). In these regions, cancer mortality and low survival rates are higher due to late-stage diagnoses, poor access to quality care, treatment affordability, fragmented health systems, and sociocultural, geographic, and financial barriers. Implemented breast cancer patient navigation programmes in some facilities have shown positive outcomes by overcoming these challenges. They enhance the cancer care journey, potentially mitigating patient difficulties, improving timely access to appropriate care, and ultimately reducing breast cancer mortality rates in low- and middle-income countries.

### Patient navigation programmes

Existing infrastructure addresses the shortage of trained personnel and the financial burdens of patient navigators through innovative strategies. One approach involves leveraging community health workers (CHWs), volunteers who connect communities with health systems. In lower-middle-income countries, CHWs serve as patient navigators, particularly focusing on breast cancer screening. They successfully conduct clinical breast examinations and act as trusted community members who guide women through post-screening care after a positive finding (18).

Another strategy is the use of a colour-coded patient navigation system for individuals undergoing primary chemotherapy to optimize resource allocation. Patients are categorized as Code Green (adherent), Code Yellow (reservations, side effects), or Code Red (non-adherent). This system efficiently directs resources to those struggling with primary chemotherapy challenges, resulting in increased adherence among initially resistant Code Red patients (19).

Additionally, the use of trained nurses as patient navigators has proven successful. These nurses provide comprehensive services, including counselling, ensuring symptom understanding, scheduling timely appointments, sending reminders, facilitating clinic tours, assisting with documentation, and offering financial counselling. This approach significantly enhances the proportion of patients returning for follow-up after receiving navigated services. Overall, these diverse patient navigation programmes effectively overcome barriers, ranging from financial constraints to logistical issues, demonstrating the potential for improved cancer care outcomes in low- and middle-income countries (20).

### Challenges faced in Africa

Sub-Saharan Africa faces an urgent need to address financial and geographical barriers, improve health service management for timely screening and comprehensive care, and provide ongoing education and supervision for frontline health workers. Research has identified challenges such as medication inaccessibility, unavailable technology, poor governance, and information system gaps, contributing to prolonged diagnostic and treatment intervals for breast cancer in the region (21).

In Kenya, breast cancer screening utilization among women is influenced by education level, marital status, and age. Older, educated, and married women are more likely to undergo

screening. Geographical obstacles and nomadic lifestyles contribute to low screening rates in some areas, while inadequate health infrastructure and financial burdens limit rural women's access to breast screening services (22). Despite two-thirds of breast cancer patients having health insurance, half are partially covered, leading to patients foregoing, delaying, or stopping treatment due to unaffordable prescribed medications (23).

In Botswana, challenges for women with breast cancer include limited awareness, fear, reliance on traditional healers, and centralized breast cancer treatment only in the capital, causing delays in seeking medical care (24).

Patient and institutional perspectives in Kenya, Ghana, and Nigeria reveal a lack of standard diagnostic procedures, prolonged turnaround times (6 months to 1 year), and patients bearing the full cost of care. Although diagnostic procedures align with developed nations in tertiary cancer centres, delays in treatment initiation persist as major barriers. Most patients pay out of their own pocket, indicating limited healthcare insurance coverage negatively impacting breast cancer management (25).

In conclusion, urgent governmental actions are required to expand healthcare resources, coverage, and awareness programmes in sub-Saharan African countries. Informed steps and prioritized investments in healthcare reforms are necessary to enhance accessibility, affordability, and outcomes in breast cancer screening, diagnosis, and treatment.

## Patient navigation in India

In India, there has been quick progress with the Cancer Navigator Programme, using untrained staff, namely Accredited Social Health Activists (ASHA) and Sakhis. Due to one company's pioneering efforts and relentless efforts, a process and teaching programme has been born.

The Ambuja Foundation based in India works with rural communities of 13 states. Community engagements, empowering people as paraprofessionals leading the development initiatives in villages remains a primary approach and also ensures sustainability of initiatives.

Rural India has its own challenges in accessing the healthcare service and referrals to appropriate health facilities for special care, eventually people drain out their savings even before reaching at appropriate centres with bad prognosis due to missing diagnosis, putting increased risk of survival and also huge financial burden. The Sakhi model has played that critical role as support system in their respective village. For these reasons, local women from the communities are selected and trained as Sakhis, building their capacity as primary healthcare service providers with skills in conducting deliveries, asphyxia management, cord care, use of ambu bag, bilta pump, high-risk identification, and recording vitals. This has changed critical indicators of neonatal and maternal mortality in villages over the period of time. Considering the trained cadre and skills, most of these Sakhis have been absorbed as ASHA under the National Rural Health Mission.

Recognizing the critical health issue of cancer, particularly breast cancer, which is prevalent in areas including India, the Ambuja Foundation made a strategic decision to introduce cancer interventions under their non-communicable diseases (NCDs) umbrella. The Sakhis in Chandrapur have helped improve health indicators, for example within diabetes, hypertension, and mental health which also played a major role during COVID-19. By healthcare

professionals training these non-medical staff on cancer interventions, there has become another layer of support added resulting in further prevention and early detection of disease. The specialized training was delivered from oncologists affiliated with Association of Breast Surgery UK (ABSUK) and the Association of Breast Surgery India (ABSI). The training focused on identifying early signs and symptoms of cancer, teaching self-breast examination techniques (including a practical training using breast prosthesis), and facilitating early diagnosis and treatment referrals. As a result, within a year, the Sakhis successfully mobilized 48 breast cancer high-risk cases for diagnostic procedures such as mammography, ultrasound, biopsy, and fine-needle aspiration cytology (FNAC), and facilitated treatment for seven cases through surgeries from 60 villages.

Furthermore, the Sakhis continue to play a crucial role in organizing and conducting regular health check-ups, and they actively participate in organizing camps focused on breast, cervical, and oral cancer awareness. Their monthly visits at households continue with a focus on awareness, resulting in women starting to come forward for check-ups and asking for help.

### Case story

Anusiya faced a challenge when, after spending ₹5000 on local treatments to remove a cancerous lump, two more appeared. Her struggle seemed endless until Sakhi Sangita urged her to attend Ambuja Foundation's health camp organized in collaboration with ABSI, ABSUK, and Tata Cancer Care in February 2023.

At the camp, the doctors advised her to get an FNAC test which revealed early-stage breast cancer. Thanks to the timely diagnosis, she underwent a successful mastectomy and 15-days treatment for just ₹1500.

Today, Anusiya lives cancer-free, with Sakhi Sangita providing regular follow-up care and medication. Her story is a testament to how early detection and support from people like Sakhis can save lives.

### Key messages

- A specialist nurse is knowledgeable in breast cancer disease, its treatment modalities, and available support.
- In the UK, there are three main types of specialist nurse in breast care: clinical nurse specialist, nurse practitioner, and consultant nurse.
- A specialist nurse will coordinate care, act as patient advocate in the multidisciplinary team, and is vital in communicating aims of treatment, potential adverse effects, and assessing the patient throughout the trajectory.
- A specialist nurse has been shown to influence better patient experience and outcomes of care and is an indicator of a quality service in Europe and the UK.
- Effective patient assessment optimizes treatment and care.
- There is significant variation in the global provision of specialist nurses with fewest in less developed countries.



- Patient navigation programmes have developed due to a global shortfall in the number of nurses and unmet needs.
- Navigation programmes have been successful in many countries, both in Europe and low- to middle-income countries such as Africa and India.
- Navigation programmes triage patient telephone calls and queries, resolving the majority, and signpost patients to areas of support or escalate to trained staff.

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## Psycho-oncological care

*Luzia Travado, Christina Signorelli, Kimlin Ashing, and Csaba László Degi*

### Introduction

Psycho-oncology is a specialty in cancer care that addresses the range of psychosocial, behavioural, spiritual, and existential dimensions that the patient and family may face throughout the cancer care continuum. A primary goal of psycho-oncology is to ensure that all cancer patients and their families receive optimal psychosocial care at all stages of the disease, including post-treatment and survivorship (1). To achieve the best clinical outcomes for breast cancer patients it is recommended that patients' psychosocial needs be regularly assessed and that psychosocial oncology services delivered by specialized professionals are available in cancer care facilities to address those needs as an integral part of quality comprehensive cancer care (2).

In this chapter, we will discuss the importance of screening for distress, evidence of the benefit of tailored psychosocial interventions, concluding with a discussion about guidelines to assist clinicians, the challenges facing low- and middle-income countries (LMICs), and an overview of progress in Europe and across the world. In this new edition, we have moved the survivorship issues and care to a dedicated chapter (see Chapter 22).

### The growing focus on psychosocial needs and assessment

To date, comprehensive cancer care has a varied history, depending on location. In English-speaking countries (Australia, Canada, Great Britain, and the USA) and in Europe in the last 30 years accreditation bodies, cancer societies, and professional organizations have responded to demand from patients and advocacy groups and have begun to embrace the standard of incorporating psychosocial care into cancer care. A particularly compelling rationale for the inclusion of psychosocial care programmes has been the number of large-scale research studies of cancer patients demonstrating the prevalence rates of morbid *distress* as affecting between 30% and 45% of patients evaluated, with estimates of 32% seen for early breast cancer patients (3). However, the distress rates increase with progression of the disease with an estimate of 60% for those with advanced breast disease (4).

In 2008 the Institute of Medicine Report on Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs recommended that irrespective of the type of cancer: whole

patient symptom management should be a requirement, there should be zero acceptance of pain, and the identification of psychosocial needs, screening, and the integration of psychosocial services should be seen as standard requirements for best practice in cancer care. In 2009, the International Psycho-Oncology Society (IPOS) ([www.ipos-society.org](http://www.ipos-society.org)) proposed a new standard for quality cancer care endorsed by the Union for International Cancer Control (UICC) and 76 other international organizations and scientific societies related to cancer treatment and care, updated in 2014, stating:

- Psychosocial care should be recognized as a universal human right
- Quality cancer care today must integrate the psychosocial domain into routine cancer care
- Distress should be measured as the 6th Vital Sign after temperature, blood pressure, pulse, respiratory rate, and pain

Later, in 2013, the UICC revised the World Cancer Declaration to include the codification of distress along with pain, stating in Target 8 that effective pain control measures, and distress management, will be available to cancer patients in all countries.

In the past, detection of distress and psychological morbidity tended to rely on ‘expert intuition’, but studies have shown the acknowledged error (generally underestimation) when relying on clinical acumen alone. As such, oncology practices have begun to systematically address the impact cancer has on the lives of individual patients through screening patients for distress.<sup>1</sup> Systematic screening for distress (referred to as the 6th Vital Sign) is becoming standard practice in comprehensive cancer care using structured and validated measures (5) to be followed by appropriate psychosocial care tailored to patients’ identified needs. Brief standardized screening questionnaires used in cancer care can help identify factors impacting physical, emotional, spiritual, and practical patient concerns related to the diagnosis and treatment of cancer. For example, the Distress Thermometers developed by the National Comprehensive Cancer Network (NCCN), and validated worldwide, in which patients rate their distress on a scale from 0 to 10, is one of the easiest tools to assist clinicians in screening for patients’ distress and in identifying their biopsychosocial needs associated with it through its problem list.

Evidence is emerging about the potential of broad-based screening for distress to improve clinical care, as well as its limitations. Given advances in psychosocial oncology, promoting screening for distress as the 6th Vital Sign for cancer patients is timely (5). This policy has been adopted in several countries and is supported by accreditation bodies such as the Quality Assurance Scheme for the Certification of Breast Units (6). Addressing patients’ distress and psychosocial needs is recommended as best practice following clinical guidelines, and recognizes the importance of including psychologists in the core multidisciplinary team (2, 6). However, the challenge lies in how healthcare providers respond to identified distress

<sup>1</sup> *Distress*, as defined by the NCCN Distress Management Guidelines panel, is a multifactorial unpleasant emotional experience of a psychological (i.e. cognitive, behavioural, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment. Distress extends along a continuum, ranging from common feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and spiritual crisis ([www.nccn.org](http://www.nccn.org)).

and psychosocial needs with appropriate resources and interventions available within their clinical setting, particularly in LMICs.

## **The need for psychosocial care for adult cancer patients in low- and middle-income countries**

Cancer is a major cause of morbidity and mortality in many LMICs and both medical and psychosocial resources are severely limited. The burden of cancer extends to health-related quality of life and survivorship outcomes such as psychological, social, cultural, and spiritual impacts. The field of psycho-oncology is currently being developed in LMICs, but the field is still in its infancy. In Africa, cancer is often diagnosed at the later stages, requiring psychosocial care, including palliative care. Psychosocial distress is a common and chronic burden for cancer survivors, leading to a profound challenge to the quality of life of survivors and their families (7). Yet a significant gap exists between the rapidly increasing cancer burden and the limited psychosocial educational interventions supporting adult cancer patients and their families in Africa, resulting in high unmet psychosocial needs (3). A priority to bridge these gaps is the training of practitioners to strengthen psychosocial aspects of care, especially palliative care. Capacity building strategies have been recommended for nurses in particular to engage in the effective delivery of psychosocial care for individuals with cancer and their family members (8).

Latin American and Caribbean countries have been underrepresented in previous cross-cultural studies of the implementation of psycho-oncology service (9). Research expanding across Latin American countries and covering a broader spectrum of cancer care is needed, particularly evidence-based psychosocial interventions and consideration of specific linguistic, cultural, and contextual factors, intervention strategies, concepts, and theoretical models that are tailored to Latino cancer survivors (10). Of the research to date, social networks and interpersonal relationships (e.g. made through church communities) are a commonly reported source of practical and emotional support, warranting interventions that strengthen survivors' interpersonal environment, and build illness-specific knowledge to adapt to their illness and manage relationships. Telehealth has been considered an effective method for psychosocial oncology care in this region (11).

LMICs in Asia are also underrepresented in the development and evaluation of psychological interventions for cancer survivors and their families. A review study conducted in India identified no societies or standard guidelines for psychosocial care in India and a lack of awareness and cancer education, compounding unmet needs due to the stigma associated with cancer and psychosocial care (12). Mathew et al. also emphasized the importance of integrating psycho-oncology services in cancer care and attempted to define the various roles that a psycho-oncologist can play across the entire trajectory in India (13). China is another large emerging economy in Asia, yet it also lacks sufficient psychological care programmes. Building the capacity of health professionals through psychological training is key to alleviating cancer patients' distress. Tang et al. compared the psychosocial care preferences of women with breast cancer in mainland China and Hong Kong and found that Chinese breast cancer patients equally prioritized disease and treatment information, and psychosocially sensitive care, emphasizing both as pillars of comprehensive care (14).

## **Efficacy of psychosocial interventions for women with breast cancer**

A range of psychosocial interventions have been proven to be effective and efficient in preventing and reducing distress, psychosocial morbidity, and the emotional and psychological burden of having cancer and/or living with cancer. Interventions are also effective in improving patients' quality of life, survival, and the ability to deal with the demands of treatment and cope with uncertainty (15). Systematic reviews and meta-analyses are generally recognized as the gold standard for summarizing existing empirical evidence about a research question. In this section, we will consider the findings of meta-analyses for the following question: *What is the evidence of the benefits of psychosocial interventions for women with breast cancer?* Existing systematic reviews and meta-analyses differ largely in terms of their scope with regard to: the populations included (mixed cancers or breast cancer specific) (15); the interventions (exercise or more general psychosocial and behavioural interventions); and outcomes assessed (ranging from broad psychosocial concerns and quality of life), to specific concerns such as pain or sexual concerns.

Jassim and colleagues conducted a recently published *Cochrane Review* on women who received psychological therapy demonstrating reductions in depression, anxiety, mood disturbance, and stress, as well as an improvement in quality of life compared with controls (16). The effect on coping and survival could not be determined because very few studies collected or reported these outcomes. Individually delivered interventions appeared more beneficial for coping and adjustment, but group-delivered interventions showed a favourable effect on quality of life (QoL). Patients with higher levels of depression and anxiety at baseline showed a greater reduction in depression and anxiety scores and this improvement was consistent throughout the follow-up (16). Overall, there was substantial variation across the studies in the range of psychological interventions used, control conditions, measures of the same outcome and timing of follow-up (16). This heterogeneity did not allow for a higher degree of certainty evidence. However, when we target specifically cognitive behaviour therapy-based stress-management interventions for cancer patients, a recent review has shown more consistent positive effects (17). By teaching stress-management skills, these interventions increase patients' confidence and self-efficacy in using relaxation, cognitive restructuring, and coping skills to deal with and reduce the impact of ongoing stressors during and after treatment. There is also current evidence for the use of physical activity and exercise programmes for reducing mostly depression but in some cases also anxiety, and mindfulness-based interventions for the reduction of both anxiety and depression (18).

It is worth noting that the impact of psychosocial interventions may be greater for a subset of women with breast cancer, as most studies of psychosocial interventions for cancer patients to date have recruited patients who may be experiencing little or no psychological distress, potentially 'watering down' the observed effects of the intervention. The impact that baseline level of psychological well-being can have on observed benefit of psychosocial interventions was demonstrated in a meta-analysis that included patients with all forms of cancer (15). When focusing on participants with increased distress, the observed effect sizes for depression and anxiety were  $>0.5$ . It stands to reason that psychosocial interventions can have a medium-sized effect on mental health outcomes when administered according to the guidelines, which generally recommend using

psycho-oncology interventions with patients experiencing heightened psychological distress, as discussed later in this chapter.

## **Assisting health practitioners to provide psychosocial care—the role of clinical guidelines**

Many clinical guidelines have been produced about best practice in the delivery of supportive care, maintained in the American Society of Clinical Oncology (ASCO) repository of guidelines, and the Guidelines International Network database (<https://guidelines.ebmportal.com/>). It is enormously challenging for busy clinicians to keep abreast the vast and rapidly emerging literature, thus clinical practice guidelines can be a helpful aide. Clinical practice guidelines are sets of non-mandatory rules, principles, or recommendations for practice that are non-biased, constantly updated based on systematic reviews and critical appraisal of evidence, multidisciplinary expert panels, and consider various stakeholder preferences. Guidelines are relatively new in psycho-oncology, first launched in 1997 by the NCCN introducing the Distress Thermometer (19). The first clinical practice guidelines specifically for the psychosocial care of women with breast cancer were launched in Australia in 2000 by the National Breast Cancer Centre, and later broadened. These innovative guidelines were designed for use by all members of the treatment team, and incorporated recommendations about communication techniques and strategies for non-psychosocial clinicians to explore and respond to anxiety and depression.

The NCCN Distress Management Guidelines for evaluating and treating various psychological problems, also promotes care by mental health professionals, as well as social workers, counsellors, and chaplains, including a flowchart to aid decision-making regarding psychological problems related to distress. This approach requires skills development across various healthcare roles (nurses, oncologists, surgeons, radiation oncologists, and other personnel), including those who may not consider it their primary responsibility. While not specific to breast cancer, the ASCO guideline on patient-clinician communication provides recommendations for interactions across all cancer phases, emphasizing core communication skills and their application, advocating for communication training including practice, experiential learning, and self-reflection. Psycho-oncology guidelines differ from others, advocating a tiered care model where all patients benefit from good communication with health professionals, not just those with high distress. As patient need and distress increase, the model recommends specialized interventions for patients with higher distress, delivered by psychologists, social workers, or psychiatrists.

Implementation of psychosocial guidelines is thus more complex than recommendation of specific behaviours (such as handwashing) for which the clinician is solely responsible. The development of guidelines alone does not change practice and there is an emerging body of research describing the complexity of translating evidence into practice. Implementation strategies need to be tailored across stakeholder groups, addressing identified barriers, for example, overcoming changes in mindset in which local opinion leaders are likely to play an important role in promoting evidence-based practice. Adherence to guidelines may require individual healthcare provider factors (e.g. stronger professional confidence, 'unlearning' habitual practices), as well as awareness of enablers and barriers related to policymakers and healthcare managers and providing feedback for all staff in the implementation process.



‘Knowledge tools’ which are short, flexible and focused on the clinical problems raised by the patient may prove valuable in assisting clinicians to implement evidence-based care.

## Progress to date—delivery of psychosocial care in Europe and across the world

The translation of evidence into clinical practice requires changes in policy and attitudes towards clinical care. In 2000, the Charter of Paris promoted awareness of cancer epidemiology gaps and the need to improve care. On 4 February of the same year, the first World Summit Against Cancer brought together more than 100 international leaders of government, patient advocacy leaders, cancer research organizations, and corporations to sign The Charter of Paris Against Cancer, committing to the global eradication of cancer and maximizing QoL of those living with or dying from cancer. The Charter’s 10 points intended to mobilize efforts and investments to empower those affected by cancer, guarantee their human rights, and improve treatment worldwide. The Charter of Paris is a landmark in the world’s response to cancer and has set the stage for further actions; 4th February was thus assigned ‘World Cancer Day’.

This activity led to further initiatives. The European Cancer Patients’ Coalition was formed in 2003 with the motto ‘Nothing about us without us!’. This Coalition began strategic lobbying with the Members of European Parliament, setting up an informal all-party forum—Members of European Parliament Against Cancer (the MAC group)—committed to promoting action on cancer as an EU priority. This initiative was supported by the Portuguese and Slovenian EU Presidencies, which led to the 2008 European Resolution on *Reducing the Burden of Cancer in Europe*, signed by the 27 Member-States, recognizing for the first time the role of psychosocial care in cancer. It also led to the 2009 launch of the *European Partnership for Action Against Cancer* (EPAAC), co-financed by the European Commission, to promote best practices in cancer prevention, control, and care (<http://www.epaac.eu/>). The EPAAC has propelled the recognition and advancement of psychosocial oncology care. For example, the introduction of the *European Guide for Quality National Cancer Control Programmes* (NCCPs), which includes a chapter on psychosocial oncology care (2) as part of the main components of effective and high-quality NCCPs. A set of indicators for psychosocial cancer care was also proposed to best monitor the services and their resources.

In 2016, a report conducted by the European Commission Initiative on Breast Cancer (ECIBC) identified an irregular landscape regarding the provision of psycho-oncological support for women treated for breast cancer in European Breast Units (20). The report proposed that the identified gaps could be overcome by making the provision of psycho-oncological care a requirement for the accreditation of Breast Units. This was accomplished by the development of a new independent, innovative, and voluntary *European Quality Assurance Scheme for Breast Cancer Services*, based on the accreditation legal framework and scientific evidence from guidelines, which includes psycho-oncology care as a requirement (21).

Despite advances, psychosocial concerns of cancer patients are often underestimated, and psycho-oncology services are not regularly offered. A global survey by the IPOS Federation of National Psycho-oncology Societies<sup>2</sup> revealed that 50% of countries with National

<sup>2</sup> This survey was conducted in the 28 countries worldwide that have a National Psycho-oncology society federated in IPOS; the other countries that do not have such a society are likely to not have psycho-oncology organized.



Psycho-oncology Societies lack integrated psychosocial care in mainstream cancer services. Africa, South America, and South-East Asia face the greatest challenges, while North America and Australia are better resourced yet still face funding and workforce shortfalls (22). A European Partnership for Action Against Cancer survey revealed that only one-third of countries allocate specific budgets for psychosocial oncology care in their National Cancer Control Plans. The study concluded that more resources, equitable care delivery, and promotion of training and certification in this area are needed across European countries, along with national cancer policies recommending the use of existing psychosocial cancer care guidelines (23).

## **Europe's Beating Cancer Plan—the case of successful joint efforts**

Recently, Europeans saw these efforts of the last 15 years being fulfilled. The European Commission launched the Beating Cancer Plan in 2021 as a comprehensive policy document to combat cancer by providing equal access to high-quality preventive, screening, diagnostic, treatment, and aftercare services across all European nations. This plan proposes the establishment of comprehensive cancer infrastructures in each European Union Member State and devises an evaluation methodology to establish fundamental principles of high-performing cancer networks and provide tools to measure their quality and effectiveness. This cancer policy plan aims to reduce mortality, increase survival rates, and enhance cancer patients' and survivors' QoL by expanding knowledge, improving care quality, and decreasing inequalities through interventions on actionable psychosocial determinants. It details ten flagship initiatives designed to tackle cancer prevention, early detection, diagnosis, treatment, and QoL for both cancer patients and survivors, such as new technologies and research; sustainable cancer prevention initiatives; early detection improvements; high standards in care provision; improving survivors' QoL; decreasing inequalities in cancer care, as well as strengthening focus on paediatric cases. Overall, the European Beating Cancer Plan acknowledges the value of psycho-oncological care and interventions, including those for breast cancer patients, as part of an integrative cancer care approach across Europe that meets the psychosocial needs of people affected by cancer.

Unfortunately, so far, differences in cancer care across countries have led to different patient outcomes, with psycho-oncological services not reaching all people in some instances. To optimize patient outcomes, distress screening and psycho-oncological services must become part of standard cancer care, from diagnosis through treatment phases into survivorship. With Europe's Beating Cancer Plan, the critical role played by psychosocial care and interventions in mitigating cancer's emotional toll on individuals affected by breast cancer is recognized. It underscores the IPOS International Standard of Quality Cancer Care that distress screening and psycho-oncological services should be part of standard cancer care from diagnosis through treatment to survivorship. Resourcing psycho-oncological care for breast cancer patients living in LMICs poses many challenges and obstacles, including disparities in accessing evidence-based and culturally appropriate psychosocial support services, limited resource allocation, lack of training opportunities, and potential barriers preventing the integration of psycho-oncology programmes into standard medical curricula (24). Also, technology integration poses unique difficulties due to limited technological resources and

training needs that must be fulfilled to deliver eHealth psycho-oncology interventions in LMICs (11). Furthermore, family caregivers in these countries face enormous strain due to an absence of adequate cancer care resources; therefore, prioritizing services that address emotional needs and stress on caregivers must be of utmost concern. That emphasizes the need to strengthen services that meet caregivers' emotional needs and integrate psycho-oncology into patient care to reduce disparities and address contributory factors that lead to health inequities.

Combatting disparities, efficiently allocating resources, and training appropriately are all vital parts of providing psycho-oncological care to breast cancer patients in LMICs (24). Recent research has also demonstrated that using patient support services is linked with reduced instances of guideline-discordant care for breast cancer survivors. In contrast, social isolation and communication issues with cancer care providers increase such cases. All these highlight the significance of addressing disparities, efficiently allocating resources, and providing training regarding psycho-oncological care for breast cancer patients in low-income countries. Finally, psychosocial interventions for women living with breast cancer should move beyond distress to wellness promotion including tackling inequalities. For instance, an integrative review focusing on psychosocial vulnerabilities after breast cancer diagnoses related to paid work revealed vulnerabilities such as changes in identity, role functioning, re-integration strategies, and coping supports, which could have detrimental impacts on QoL during recovery or survival from breast cancer (25). Psycho-oncology should be integrated into breast cancer patient care to minimize disparities by identifying contributing factors, and reach best outcomes.

The European and global landscape surveys on psycho-oncology resources report unequivocally that there is a lack of widespread availability of professional psychosocial care and what is offered varies greatly between regions and countries as well as across continents. Services are linked mostly to the country's income and health budget, and the organization of cancer care, namely, the existence of an effective National Cancer Control Plan as well as accreditation of clinical centres. We have learned that to bring about change and improvement in cancer policies, including specialized psychosocial cancer care in treatment plans, treatment guidelines, and its provision in routine cancer care, requires political will. This may be achieved through joint efforts of public demand and lobbying by psycho-oncology and advocacy organizations.

## Key messages

- Around 32% to 60% of breast cancer patients have high levels of cancer-related distress, and the impact of their disease and treatment on their lives is broad-reaching.
- High levels of distress have negative consequences for clinical outcomes, QoL, and well-being.
- Inequalities in cancer care across countries contribute to different outcomes for patients.
- It is recommended that patients' distress and psychosocial needs be regularly assessed as the sixth vital sign and that psychosocial oncology care services be delivered by specialized professionals.

- Psychosocial interventions can have an important benefit in effectively reducing distress and psychological morbidity, and in improving patients' well-being and QoL across the cancer continuum.
- Psychosocial oncology care guidelines assist clinicians in delivering care and promote standardization of clinical practice through the best available science translated into evidence-based recommendations tailored to patients' needs.
- Psychosocial oncology care is considered one of the main components of effective and high-quality cancer care and of the accreditation of breast cancer units.
- Psycho-oncological services are irregularly provided across countries and regions, and there is much work to be done to ensure quality standards and guidelines are implemented.

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## Survivorship

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### Introduction

In 2005, the Institute of Medicine (IOM) report: 'From Cancer Patient to Cancer Survivor: Lost in Transition' was released, providing a template for improving the delivery of care for cancer survivors. Despite improved cancer treatment success in recent decades, there is growing recognition that the impact of cancer extends well beyond the conclusion of treatment. In several low-resource countries, where the burden of cancer is greater, survival rates remain lower than developed countries, leading to additional challenges (1). Many nations also anticipate a rise in the number of long-term cancer survivors within their populations, warranting improvements to the delivery of, and access to, survivorship care globally (2). Adapting to life after cancer treatment, in the survivorship phase, presents distinct challenges and opportunities for patients within their cancer trajectory. Historically, little emphasis was placed on the long-term or delayed effects of cancer and its treatment, as survival rates were low and patients were not anticipated to live beyond their illness. Supportive care efforts were primarily directed towards those in the terminal stages of cancer rather than those surviving cancer or transitioning beyond it. However, over the past 20 years, there has been a significant shift in this paradigm.

### Moving beyond distress to encompass wellness

There is a growing appreciation of the enduring physical health issues that survivors experience post-treatment, and the psychosocial issues beyond the immediate physical impacts of their illness. Recently, the World Health Organization published the 'package of interventions for rehabilitation' including a module specifically focused on cancer, highlighting the diverse physical, cognitive and psychosocial needs of cancer survivors (e.g. fatigue, sleep problems, pain, anxiety, depression, cognitive and sexual functioning, oedema) and the importance of ongoing rehabilitation to address these (3). Physically, survivors may experience lymphedema, bone density loss, cardiovascular issues, menopausal symptoms, loss of libido, or weight changes. Psychosocial concerns often emerge during active treatment and can persist over time, including fatigue, disruptions in body image, changes in social dynamics, limitations in work capacity, and reduced quality of life. Furthermore, survivors remain vulnerable to challenges that may arise months or years following treatment cessation, stemming from cancer or its therapies. Among these, the prospect of recurrence or developing a second cancer poses significant psychosocial hurdles. However, long-term adjustment may also entail managing fears of recurrence, addressing depression or suicidal thoughts, navigating infertility, and adapting to altered life trajectories.

Treatment completion itself can induce significant stress for survivors. Concerns about cancer recurrence are not uncommon, coupled with managing ongoing effects of the illness. Survivors may experience heightened discomfort compared to pre-treatment and may grapple with the uncertain return to normalcy and resuming their prior routines. Anxiety often accompanies departing from the treatment environment and the supportive cancer team, heightening feelings of isolation from those who shared their journey. This separation can magnify feelings of alienation, particularly in geographical regions where cancer remains a taboo topic or where cancer survivorship is a relatively new concept that carries stigma (4). Questions arise about post-treatment care provision and expectations from family and friends, who may anticipate a potentially unrealistic swift return to pre-cancer normalcy. When combined, these multifaceted challenges contribute to the tumultuous transition to recovery and survivorship.

## Cancer Survivorship Care Quality Framework

As outlined in the Cancer Survivorship Care Quality Framework (5), post-treatment care for all cancer survivors may encompass care coordination and transition, care planning, and communication, health promotion, surveillance, and support aimed at addressing physical, psychosocial, and informational needs. This care may include regular follow-up appointments to monitor for recurrence and manage treatment-related side effects, personalized survivorship care plans outlining ongoing care and health promotion strategies, access to supportive services such as psychological support, rehabilitation, and support groups, and clear communication regarding potential long-term effects of treatment and strategies for their management (Box 22.1) (6).

Providing cancer survivors with the resources to assist them in recovering from the psychological and physical impact of cancer and its treatments is now considered a fundamental requirement for quality cancer care. Enabling survivors in getting back to their lives and carrying on their roles and tasks with as minimal impairment as possible is a societal duty, and an economical health issue given recent estimates of the burden of breast cancer reached over 17.42 million disability-adjusted life-years globally (7). The number of cancer survivors is growing more rapidly than ever, necessitating a focus on the rehabilitation and recovery process to maximize quality of life and minimize the potential burden to themselves, their family, and demands on healthcare systems.

### Box 22.1 Five components identified by the ESMO Expert Consensus on cancer survivorship

- (1) Physical effects of cancer and chronic medical conditions
- (2) Psychological effects of cancer
- (3) Social, work and financial effects of cancer
- (4) Surveillance for recurrences and second cancers
- (5) Cancer prevention and overall health and well-being promotion

Source: data from Aebi S, Davidson T, Gruber G, Cardoso F. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2011;22:vi12–vi24.

Additionally, post-treatment care should focus on empowering survivors to advocate for their health needs and engage in self-care practices to optimize their well-being and quality of life. At the 5th Breast Health Global Initiative Summit, attendees additionally identified priorities for post-treatment supportive care (Table 22.1), that can be tailored to the resources accessible in different countries (8).

**Table 22.1** Health systems: health education, community awareness, and psychosocial patient support after curative treatment

|                                      | Basic                                                                                                                                                                                                                                               | Limited                                                                                               | Enhanced                                                                                                                                                                                                                                         | Maximal                                                         |
|--------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| <b>Health professional education</b> | Breast cancer recurrence, second primary cancer<br>Long-term treatment complications<br>Women's health<br>Psychosocial (survivorship) considerations<br>Lifestyle modifications                                                                     | Psychosocial risk assessments<br>Psychosocial complications of survivorship<br>Sexual health          | Psychosocial screening methods                                                                                                                                                                                                                   |                                                                 |
| <b>Patient and family education</b>  | Breast cancer recurrence or new cancers; symptoms to report<br>Long-term treatment complications<br>Appropriate use of complimentary alternative medicine<br>Women's health issues<br>Psychosocial issues (survivorship)<br>Lifestyle modifications | Follow-up schedules<br>Adherence to endocrine therapy<br>Sexual health                                |                                                                                                                                                                                                                                                  |                                                                 |
| <b>Community awareness</b>           | Community awareness of breast cancer survivorship issues                                                                                                                                                                                            |                                                                                                       |                                                                                                                                                                                                                                                  |                                                                 |
| <b>Psychosocial (survivorship)</b>   | Patient and family education<br>Psychosocial (survivorship) considerations<br>Peer support by trained Breast cancer survivors                                                                                                                       | Psychosocial assessments including depression<br>Emotional and social support by health professionals | Screening and referral for depression/distress by mental health specialist<br>Psychosocial counselling by mental health specialists<br>Availability of pharmacotherapy<br>Social service counselling for financial, employment, and legal issues | Psychiatrist-, psychologist-, or social worker-coordinated care |

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## Survivorship care models and resources

To ease the post-treatment challenges that survivors face, educating and empowering cancer survivors is critical. Navigating the survivorship phase is complicated, necessitating resources and processes that promote communication between patients, providers, caregivers, and the wider survivorship care team (9). One strategy involves advocating for the creation and dissemination of a survivorship care plan (SCP). SCPs are commonly comprised of two components: (i) a treatment summary detailing their cancer history, diagnosis, treatment/s received, and health complications; and (ii) a follow-up care plan outlining steps for the surveillance of recurrent/new cancers, addressing ongoing side effects, preventing late adverse effects, and health promoting behaviours, along with information on responsible parties (Box 22.2) (10). Ideally, SCPs are formulated based on the systematic assessment of the individual patient's physical and psychosocial needs and discussed during a collaborative transition meeting involving the survivor and treating staff, arguably the most critical aspect for maximizing their use and potential benefit. There is some evidence that patient health assessments and symptom checklists may have the potential to improve survivorship care for cancer survivors and promote patient-centred follow-up consultations (11). Evidence suggests that SCPs (11, 12) may improve survivors' quality of life, their awareness of and engagement with survivorship care and health recommendations and enhance providers' knowledge of survivors' health issues and care (13).

Available models of breast cancer survivorship care encompass various approaches, including traditional oncology-led follow-up, primary care-led follow-up, and shared care models, each tailored to optimize long-term outcomes and address survivors' unique needs. There is some evidence comparing the effectiveness of these models on patient and health system outcomes (14). There appears to be no difference in effectiveness in managing survivors' physical and psychosocial outcomes among different survivorship models of care, although nurse-led and primary care provider-led models may generate cost savings for both cancer survivors and healthcare systems (14). It has been suggested that less intensive follow-up may lead to delays detection of cancer recurrence, yet it remains unclear how different survivorship models impact survivors' health-related quality of life, anxiety and depression, or additional patient symptom education/monitoring and the provision/receipt of survivorship

### Box 22.2 Survivorship care plan (SCP) contents per the IOM

1. Surveillance for recurrence or new cancer
2. Assessment and treatment or referral for persistent effects (e.g. pain, fatigue, sexual dysfunction, functional impairment, depression, employment issues)
3. Evaluation of risk for and prevention of late effects (e.g. second cancers, cardiac problems, osteoporosis); health promotion
4. Coordination of care (e.g. including frequency of visits, tests, and who is performing these)

*Source:* data from Hewitt M, Greenfield S, Stovall E. From cancer patient to cancer survivor: lost in transition: National Academies Press; 2005.



care plans. Models of care and survivorship practices vary greatly across countries and by income level (15). In lower resource settings, more personalized risk-based models could be better suited, requiring oncology and supportive care professionals to recognize the individual needs of each patient as well as the resources available within their local communities. Newer and innovative models of survivorship care tend to be more psychosocially grounded, yet a recent meta-review highlighted that this is more common in primarily Western or high-income countries (14).

Meeting the psychosocial needs of breast cancer survivors demands a multifaceted strategy and effective communication among oncologists, primary care physicians (PCPs), and survivors. Although PCPs do not have a formal role in providing survivorship care after cancer in many countries, studies show that an increase in PCP consultations after breast cancer treatment, highlighting the important role of the PCP. Thus, collaboration among healthcare professionals is essential to offer comprehensive support, aiding survivors in navigating their recovery journey and enhancing their overall well-being in survivorship. Research indicates that breast cancer follow-up by PCPs does not diminish patient safety, well-being, health-related quality of life, or satisfaction. Furthermore, it has been found that both PCPs and patients support a greater role for PCPs in survivorship care, provided better coordination between secondary and primary care and clear guidelines are available (16). Promoting ongoing communication between PCPs and survivor can ‘close the loop’ within the oncology care model, helping to ensure survivors’ needs are met.

As the population of cancer survivors continues to grow, healthcare systems that are already burdened with limited workforce and clinical resources will need to find newer and more sustainable approaches to provide high-quality survivorship care. Potential strategies will need to support the stratification of care to maximize strained resources, as well as be technology-based, as e-healthcare continues to grow. As the majority of women after breast cancer treatment may be able to self-manage the most common symptoms after treatment, improving patient self-management through patient education will be a valuable approach in improving the outcomes of breast cancer survivors, and digital self-management interventions have increasingly been developed (17).

Another innovative approach has been the development of patient-reported outcome measures (PROMs) in oncology to monitor patient symptoms in order to provide prompt intervention (see Chapter 7).

## **Clinical guidelines for the management of health issues in survivorship**

Several clinical guidelines are available that provide recommendations on surveillance for recurrence, management of treatment-related side effects, psychosocial support, lifestyle interventions, and long-term follow-up care for breast cancer survivors (6, 18, 19). They cover aspects such as surveillance for recurrence, management of treatment-related side effects, psychosocial support, lifestyle interventions, and long-term follow-up care. These guidelines aim to optimize the health and well-being of breast cancer survivors by offering evidence-based strategies for survivorship care tailored to individual needs. Available guidelines can offer clear protocols for assessing and addressing potential issues that may arise during survivorship, as summarized earlier. By following these guidelines, healthcare providers can ensure

consistent and evidence-based care for breast cancer survivors, enabling timely referrals to appropriate specialists or support services as needed. This systematic approach helps optimize the quality of survivorship care and promotes the overall well-being of breast cancer survivors.

Despite the availability of clinical guidelines and recommendations, the extent to which guidelines are based on evidence-based recommendations is limited, and more typically based on expert opinion or clinical practice. Adherence to these guidelines among patients and clinicians is also suboptimal (20). While oncologists report high adherence to guidelines for surveillance of recurrence, less engagement has been shown for recommendations regarding provision of survivorship care plans and assessment and management of psychosocial long-term and late effects. Guideline use among clinicians is also less common in LMICs, which is unsurprising given that most guidelines are developed in HICs and thus less relevant to lower-resourced settings. This has prompted initiatives such as the Breast Health Global Initiative (BHGI) Guidelines for Breast Cancer Control in Low- and Middle-Income Countries: Survivorship Care Recommendations, which provide a framework for survivorship care tailored to lower resource settings (8) (see Chapter 32).

## **Considerations in breast cancer survivors living long-term with incurable cancer**

In recent years, there has been an increasing awareness about a relatively new group of breast cancer survivors: those living long term with a diagnosis of metastatic breast cancer, which is currently incurable. The Advanced Breast Cancer (ABC) Global Alliance ([www.abcgloballiance.org](http://www.abcgloballiance.org)) is making progress in this regard, as a worldwide organization dedicated to extend the lives, and enhance the quality of life, of people living with advanced breast cancer, by developing actions to address the most urgent and actionable gaps in the treatment and care of patients with advanced disease, which include quality of life. Issues facing patients who are diagnosed with incurable cancers have traditionally been the domain of palliative and end-of-life care research due to their poor prognosis. However, thanks to improved treatment options, these patients may now live for years with their diagnosis, making issues of survivorship increasingly relevant to this patient population (21, 22).

Expanding the current focus of survivorship research, which has primarily focused on the post-treatment phase, to also include women undergoing prolonged treatment, is also in line with the National Cancer Institute's definition of a cancer survivor as an individual from the time of diagnosis (23). The issues facing this subpopulation of breast cancer survivors are complex, and future research is needed to fill the numerous evidence gaps that have been identified, which include the lack of epidemiological data on this population living long-term with cancer, the need to understand the impact of newer therapies on survivor needs, and to develop and test innovative models of survivorship care tailored to these patients and their caregivers (24).

## **Reflections on advocacy: important drivers of change**

Cancer survivorship care requires a holistic approach, drawing upon interdisciplinary collaboration and forging international alliances. Patient representatives and consumer groups have a growing influence on research methods, advocacy, and policy, which can be further

fostered to propel change in practice. They have the potential to influence healthcare policies at local, national, and international levels. Patients and their families' lived experience of their cancer and survivorship needs generate important ideas about what research and policy change is needed to enhance their survivorship experience and their daily quality of life.

These efforts are complemented by robust collaborations and advocacy spanning medical professionals, researchers, and patient advocacy organizations worldwide to assist those affected by cancer. Recent initiatives have significantly propelled efforts to overcome disparities in cancer survivorship care, enhance accessibility, improve care standards, and to maximize quality of life. For example, the 2030 World Health Organization (WHO) Rehabilitation 2030 stresses the need for patient-centred and data-driven evidence-based care, patient empowerment and coordinated care at local, organizational, and (inter)national levels (25). A central objective moving forward will be to unite stakeholders globally to enhance the health and well-being of people affected by cancer, ensuring every patient has the best chance at survival as well as a fulfilling life after cancer.

## Meeting the needs of cancer survivors

There is an increasing global awareness of the needs of cancer survivors, including advocacy for the acknowledgement of psychosocial cancer care as a human right (26). Despite this, cancer survivors report significant unmet needs globally. A recent global survey conducted by the International Psycho-Oncology Society (IPOS) Survivorship working group suggested that models of care vary greatly internationally, highlighting suboptimal practices and resources to adequately address the psychosocial survivorship needs of cancer survivors in particular. The survey revealed challenges delivering optimal psychosocial care in survivorship, even in high-income countries, due to significant barriers at patient-, provider- and system-levels (15). IPOS is a leader in advocacy efforts to raise awareness about the psychosocial needs of individuals affected by cancer across the globe, and to influence policies that support cancer survivors' well-being.

Non-government and patient advocacy organizations also provide vital support networks and resources for cancer survivors and their families. By connecting individuals with peer support groups and survivorship programmes, advocacy groups help survivors navigate the challenges of life after cancer and access the support they need to thrive after cancer. Particularly in settings where there is a lack of organizational support or limited providers and healthcare systems resources, non-governmental organizations can promote collaboration among systems to improve access to survivorship care. Overall, patient advocacy serves as a catalyst for positive change in cancer survivorship care by amplifying the voices of survivors, shaping policies, driving research agendas, and providing essential resources. By actively engaging in advocacy efforts, individuals and organizations can work together to improve the quality of life and outcomes for cancer survivors worldwide.

## Key messages

- The impacts of cancer continue beyond the end of treatment.
- Survivors face both physical and psychosocial challenges, which necessitate ongoing rehabilitation and supportive care.

- Quality post-treatment care includes monitoring for recurrence, managing side effects, psychological support, and promoting overall well-being.
- A holistic, interdisciplinary approach that integrates patient advocacy into research, policy, and practice improvements must be achieved.
- Clinical guidelines support the surveillance and management of breast cancer survivors, although further effort is needed to improve adherence, particularly in LMICs.

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## Genetics

*Marjanka K. Schmidt, Teresa Ramón y Cajal Asensio, Tanja Španić, and Seigo Nakamura*

### The concepts of breast cancer inheritance and germline genetics

The accumulation of somatic mutations in breast tissue leading to the development of breast cancer occurs largely by chance. However, well-established breast cancer risk factors, including hereditary genetic variants, lifestyle, and hormonal factors, place women at higher risk of developing breast cancer. About 10–30% of breast cancers are estimated to be explained by known (modifiable and non-modifiable) lifestyle and environmental factors such as body mass index and use of hormones; this is population dependent. Based on monozygotic twin studies, it has been estimated that another 20–30% of breast cancers can be explained by hereditary genetic variation (Box 23.1).

The influence of germline genetics on breast cancer risk is reflected by the strong relationship observed between family history of breast cancer and risk of breast cancer for an unaffected female relative. The incidence of breast cancer in males is low (approximately 1% of all breast cancer cases), but, based on limited data, a larger proportion of male breast cancers compared to female breast cancers is thought to be heritable. In Figure 23.1, an example of a breast cancer family pedigree is shown, including inheritance through the male line in the middle generation.

### Breast cancer genes and variants

#### High-risk breast cancer genes

The first breast cancer risk genes discovered were Breast Cancer 1 and 2. These genes, abbreviated *BRCA1* and *BRCA2* and which harbour pathogenic germline variants, were discovered in 1994 and 1995 using linkage analysis of a large group of families with cases of early-onset breast cancer. Depending on the population, about 3–5% of all breast cancer cases are related to pathogenic germline variants in the *BRCA1* or *BRCA2* genes, and these are estimated to explain around 15% of the total heritable risk of breast cancer. In several populations, founder *BRCA1* and *BRCA2* mutations with a higher prevalence have been described. The best-known are founder mutations in the Ashkenazi Jewish population (prevalence approximately 2.5% and accounting for approximately 85% of carriers). However, specific founder mutations in *BRCA1* have also been identified in other populations (accounting for

### Box 23.1 Explanation of part of hereditary breast cancers by genetic variation

Genetic inheritance is defined as the passing on of the genetic makeup from parents to child. This inherited genetic make-up of persons is also referred to as germline genetics. The proportion of variation in a particular disease that is attributable to germline genetics is called the heritability or heritable risk of a disease. For breast cancer, two heritable forms are defined, specifically familial breast cancer, which is breast cancer in a family with more (breast) cancers than statistically expected, but no specific pattern of genetic inheritance, and hereditary breast cancer, which is breast cancer with an apparent autosomal dominant inheritance. Breast cancer that is likely not due to germline genetics is called sporadic breast cancer. Gradually, this concept of a separation between heritable breast cancer and sporadic breast cancer is shifting with the realization that all breast cancers have a (small) heritable component.

Genetic variants, often called mutations or pathogenic variants if disease-related, that a child inherits within the genetic make-up from its parents are called germline variants. Most pathogenic variants are protein truncation variants, but also a proportion of missense variants are disease-related. Because such a variant was present in the egg or sperm cell, it is present in all cells throughout the body of the offspring. Gene variants that are not inherited from a parent but acquired throughout life are called somatic variants. These variants can be acquired in any type of cell and can also cause various diseases, cancer being the most common. Another type of somatic variation acquired early in embryonic development, called mosaic mutations, can also cause predisposition for a disease similar to germline variants but limited to the specific tissues that originated from the embryonic stem cell.

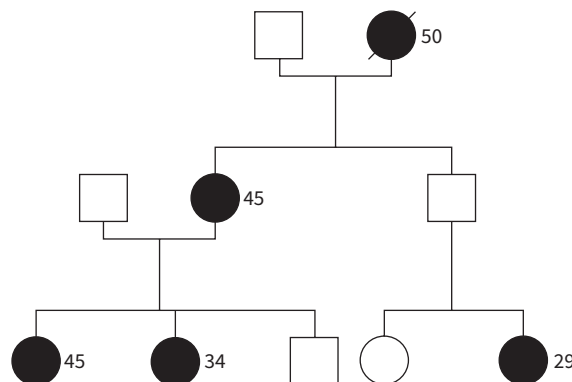


**Figure 23.1** Pedigree of a family with familial/hereditary breast cancer. ○: female without breast cancer; •: female with breast cancer; ✕: female deceased with breast cancer; □: male without breast cancer. Ages at diagnoses for the breast cancer are indicated.

approximately <20% of carriers in those populations), for example, the Dutch, Polish, and Chinese populations.

Carrying a pathogenic germline variant in the *BRCA1* or *BRCA2* gene leads to a high risk of breast cancer (1). The risk is estimated to be between 27% and 80% by age 70 years, with *BRCA2* mutation carriers on the lower end of the range and *BRCA1* mutation carriers on the higher end. Relative risks for *BRCA1* and *BRCA2* mutation carriers compared to non-carriers are similar globally, although the absolute risks differ according to differences in population baseline risks. The risk for ovarian cancer is also substantially increased in *BRCA1* (about 44%) and *BRCA2* (about 17%) mutation carriers compared to women not carrying these germline mutations. Clinicians should be aware that *BRCA* pathogenic variants, specifically *BRCA2*, also predispose to other cancers such as pancreatic and prostate. Specific regions and mutations in *BRCA1* and *BRCA2* may determine a differential relative breast cancer risk compared to ovarian cancer risk. Moreover, the large interindividual variability in the risks of breast and ovarian cancer for *BRCA1* and *BRCA2* mutation carriers is also determined by other genetic (e.g. polygenic risk score) and lifestyle factors (2).

Knowledge of gene mutation carriership may also be relevant in the adjuvant treatment setting. It has been suggested that mutations in *BRCA1* or *BRCA2* make tumours more sensitive to adjuvant chemotherapy. Poly(ADP-ribose) polymerase (PARP) inhibitors have shown treatment benefit and been approved for the treatment of ovarian cancer, and advanced breast, pancreatic, and prostate disease in *BRCA1* and *BRCA2* mutation carriers. Because of the expanding role of germline genetics in treatment decisions for patients, including a clinical geneticist in the multidisciplinary breast team is of great importance and will become even more relevant in the future with the evolving developments in this field.

## Breast cancer risk variants in other genes

Large panel sequencing studies (mostly in European and Asian populations) have established other breast cancer risk genes including the high-risk gene *PALB2* and moderate-risk genes (relative risk approximately two), including *ATM*, *BARD1*, *CHEK2*, *PALB2*, *RAD51C*, and *RAD51D* (3, 4). Other, very rare, risk genes implicated in multiple cancer syndromes have also been identified, such as *TP53*, *STK11*, *CDH1*, and *PTEN*, but the exact risk estimates are less precise. Increasing efforts of exome and whole genome sequencing have shown that there are potentially more breast cancer genes to be discovered (5).

## Variants of unknown significance

Pathogenic germline variants in high-risk genes are mostly protein-truncating variants, resulting in aberration or even loss of function of the transcribed protein. Although it is generally accepted that different pathogenic variants in the same gene may lead to different increases in risk, risks are currently estimated for all such pathogenic mutations together per gene. This is largely because specific individual variants are rare, making it very difficult to derive variant-specific prospective risk estimates. In addition, for a large number of variants that do not appear to cause protein truncation, the effect on protein function is unknown or unsure, making it difficult to predict the consequences on cancer risk. Such variants are



called ‘variants of unknown significance’ (VUS). For example, in the *BRCA1* and *BRCA2* genes, many VUS have been reported; up to 20% of the genetic tests will report VUS. While the majority of studies show that when VUS are classified, only a small percentage (<10%) of VUS are upgraded to being potentially pathogenic, these remain reported as VUS, because the misinterpretation of VUS can lead to clinical harm for women and their families (6). An increasing number of tools and algorithms and *in-vitro* tests are being developed to classify VUS in breast cancer genes.

## Common risk variants and polygenic scores

Hundreds of low-risk breast cancer susceptibility variants, discovered through genome-wide association studies by multinational consortia, have provided new insight into the role that common variation in the genome sequence contributes to our understanding of missing heritability for breast cancer (7). A polygenic risk score (PRS) is a weighted score of multiple variants with small effects (Figure 23.2). Although the risk conferred by each contributing variant is too small to predict clinically relevant risk, their combined effect on a PRS provides potentially actionable and personalized risk information.

The best predictive PRS for breast cancer in general and breast cancer subtypes to date includes 313 SNPs (PRS313) found in genome-wide association studies (GWAS), including mainly postmenopausal women with oestrogen-positive breast cancer and those of European descent (6). Its performance was evaluated on test datasets and further validated in external prospective data sets to assess generalizability in both clinical genetics and population settings. Its predictive value in other populations, such as Asian, African, and Latin, is reasonable but less compared to European populations (8, 9, 10). Furthermore, PRS313 follows a comparable distribution in male cases, especially for ER-positive disease. The relative lack of GWAS data from women of non-European ancestral origin, younger women, or specific breast cancer subtypes is a critical gap which needs to be addressed. The Confluence

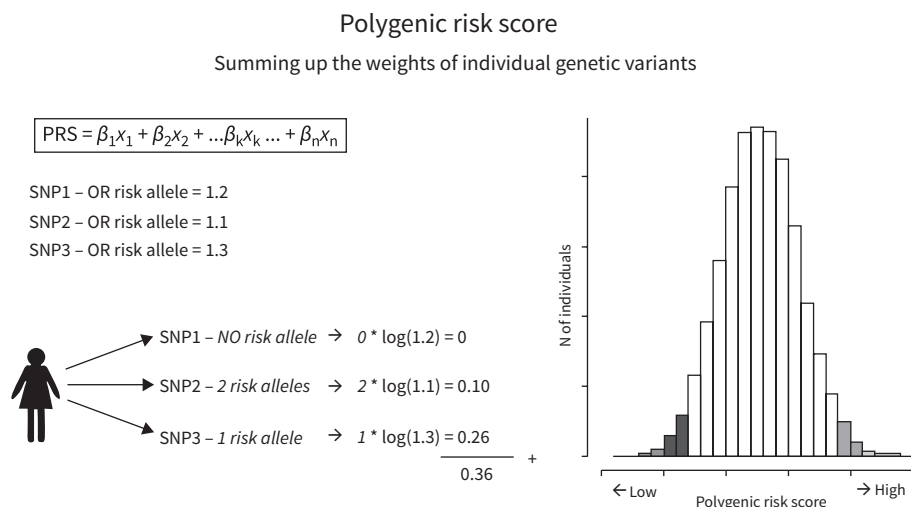


**Figure 23.2** Polygenic risk score.

project is currently building a large research resource of at least 300,000 breast cancer cases and 300,000 controls to conduct a multi-ancestry GWAS. The large increase in sample size and diversity of populations will enable us to unravel the genetic architecture in female and male populations of different ancestry backgrounds.

A successfully constructed PRS is a continuous measure that is normally distributed around a mean relative risk of 1. Therefore, most individuals in a population will fall within a range corresponding to a moderately increased to moderately decreased risk of breast cancer, and a small number of individuals will fall at the extremes of the distribution. Women in the top 1% of the PRS313 distribution have a predicted risk that is 4-fold larger than the risk of those in the middle quintiles (40–60th percentiles), leading to clinically relevant absolute breast cancer lifetime risks.

## Comprehensive breast cancer risk prediction

It is a long-standing observation that cancer risks associated with rare pathogenic variants in high and moderate-risk breast cancer genes appear to vary in different families and several studies have now confirmed that common variants, in the form of a PRS modify the penetrance of high-impact genes. These effects have been studied in greater detail in carriers of pathogenic variants in *BRCA1* and *BRCA2*, where the relative degree to which the PRS modified breast cancer risk was found to be somewhat less than in the general population. Furthermore, the magnitude of the association of PRS with breast cancer decreased with increasing age and was slightly lower when measured in individuals with variants expected to result in complete loss of protein expression (11).

New personalized screening approaches based on comprehensive risk prediction models, including breast density and PRS, have emerged as very promising strategies to improve individualized breast cancer risk assessment and population risk stratification in contrast to ‘age-based’ screening programmes. Prior to the integration of the PRS into comprehensive prediction models, several studies first demonstrated the lack of interaction between the PRS and all other classical risk factors except family history and, subsequently, the improved accuracy of risk stratification resulting from the addition of PRS compared to models restricted by age or family history (12). The clinical validity of the BOADICEA v.6 model, based on the joint effects of the full multifactorial model including PRS and rare pathogenic variants in *BRCA1*, *BRCA2*, *PALB2*, *CHEK2*, *ATM*, *RAD51C*, *RAD51D*, and *BARD1* susceptibility genes has been demonstrated in a large independent prospective cohort of women of European descent. The model is well calibrated when all risk factors or subsets of factors are included and discrimination is maximal when all risk factors are considered (AUC of 0.70) (13). The model also validated in a prospective cohort of *BRCA1* and *BRCA1* mutation carriers (14). Other available breast cancer risk models are for example the Tyrer–Cuzick and Gail models. Of note, none of those models have been validated or shown to be valid for the prediction of contralateral breast cancer (Box 23.2).

Data from large international research initiatives supporting the implementation of screening programmes based on PRS-personalized risk assessments and implementation of PRS are underway. Two international randomized, controlled trials, the Women Informed to Screen Depending on Measures of risk (WISDOM) and My Personalized Breast Screening (MyPEPBS) studies, compare the efficacy of personalized screening (using clinical risk

### Box 23.2 Second cancer risks in breast cancer survivors

Germline genetic variants also predict the risk for a contralateral breast cancer (cancer in the opposite breast from where the first breast cancer developed). Mostly the high and moderate breast cancer genes, as well as *PRS313*, have been shown to be associated with an increased risk of contralateral breast cancer, though generally relative risk estimates are a bit lower compared to those for the first breast cancer (15). There is not yet a clinically widely used model for contralateral breast cancer, though those have been developed, e.g. PREDICT-CBC.

scores and polymorphisms) versus standard screening for advanced breast cancer detection in women aged 40 to 74 years. In addition, the Predicting-Risk-Of-Cancer-At-Screening (PROCAS) study evaluates the management of ‘new groups’ of women in the population identified at the extremes of the PRS. This trial examines changes in the screening interval, the feasibility of tailoring the mammographic interval based on individualized risk and offers high-risk women preventive strategies.

While further evidence of the clinical utility of implementing PRS in clinical genetics is being gathered, several studies, including a Dutch study (2), support the implementation of comprehensive risk prediction, as the addition of PRS changed the screening recommendation in up to one-third of individuals from panel-negative families and carriers of pathogenic *ATM* and *CHEK2* variants.

Future challenges also include being able to provide better dynamic models, which show changing risks with increasing age and changing lifestyle risk factors and, then, keeping these models up to date. For many populations, it is likely that the two factors most likely to affect the performance of the model are the increasing population age-specific incidence of breast cancer and the decreasing sizes of families.

Population-based panel genetic testing for cancer susceptibility, independent of family history, has currently only been done for *BRCA1* and *BRCA2* germline mutations in defined population subgroups with a high incidence of founder mutations. Extending population-based genetic testing to non-founder populations creates considerable financial and infrastructural challenges, but is already being considered (16). As more information for more accurate breast cancer risk prediction becomes available and testing methods become cheaper, it might be of interest to use broader genetic information for breast cancer risk prediction in the general population.

## Counselling and testing at clinical genetic centres

A woman who is at increased risk of breast cancer, determined by an (extensive) family history of cancer or young age at breast cancer diagnosis, should be referred for genetic counselling. Referral can be done by any treating physician. Although referral guidelines for genetic counselling differ among countries throughout the world, they are all based on family history and age with minor differences in the details (17). Other indications are strongly associated

with being a *BRCA1* and *BRCA2* mutation carrier and are also used for referral for genetic counselling. These include being a member of a population with a high incidence of *BRCA1* founder mutations such as Ashkenazi Jewish, having bilateral breast cancer or both breast and ovarian cancer, having a triple-negative breast cancer (oestrogen receptor and progesterone receptor and HER2 negative), and having male breast cancer. In several countries all male breast cancer patients are candidates for referral to the Clinical Genetic Centre.

At clinical genetic centres, specialized physicians (clinical geneticists) and genetic counsellors estimate the *a-priori* probability of a woman carrying a breast cancer-causing or -associated mutation, and they provide counselling on whether genetic testing is appropriate. In most countries, testing is criteria-based, i.e. a threshold for genetic testing of  $\geq 10\%$  *a-priori* probability of carrying a *BRCA1* or *BRCA2* mutation. Several breast cancer risk prediction models, such as the BOADICEA or BCRAPRO, can also assess the *a-priori* probability of being carrier of a *BRCA1* or *BRCA2* mutation.

Increasingly panel tests including multiple genes are being used in clinical genetics. A challenge there is the commercial availability of gene panels including genes for which the association with breast or other cancer risk may not be well defined. It is best practice that clinical genetic centres are appropriately supported by a certified laboratory with either the automated pipelines or the appropriately trained laboratory clinical genetic specialists to assure the appropriate selection of genes to be tested and the right classification of the detected germline variants. For the classification of variants (see 'Variants of unknown significance'), resources are available as well as decision-support software programmes (18). The result should be communicated in an unequivocal letter to the counsellor, who should discuss the outcome with the counsellee. Counselees should discuss the outcome of the testing with their family, but, for example, in the Netherlands, the counsellors are increasingly proactive in approaching family members with the consent of the counsellee with the test result. Notably, genetic counselling and testing services are currently underdeveloped in low- and middle-income countries, including in many parts of South America, Africa, and Asia (19).

## When to test?

The timing of genetic counselling and testing of healthy women is of course dependent on the manifestation of a family history of breast cancer and a woman's age. Hereditary breast cancer rarely manifests before age 20–30 years, so counselling will not change screening and follow-up recommendations before then. Some countries have introduced preimplantation genetic testing for *BRCA1* and *BRCA2* to give mutation carriers the opportunity to conceive children without passing on a *BRCA1* or *BRCA2* mutation. However, there is still limited consensus with respect to preimplantation or prenatal genetic testing for (breast) cancer susceptibility mutations.

For *BRCA1* or *BRCA2* mutation carriers who have developed breast or ovarian cancer, having the genetic testing results could still help determine treatment choices including choice of surgery or chemotherapy for breast cancer or the choice of chemotherapy or targeted therapy for ovarian cancer. Since it is possible to generate DNA test results quickly after diagnosis, this has led to the concept of 'rapid genetic testing', or 'treatment-focused genetic testing'. Rapid genetic testing provides a window of opportunity for the counselling and genetic test results to guide the choice of surgery and systemic treatment. Moreover,

given that there is currently insufficient capacity for genetic counselling services to meet future demands of genetic testing in the current infrastructure, it has become critical to review the mode of delivery of genetic counselling and genetic testing from conventional clinical genetics services to surgical and oncological departments. Therefor another alley for providing genetic testing mainstreaming, in which a test is being requested by another treating physician who is not a genetics specialist. Only when a genetic test is 'positive' will the patient be referred for counselling by a genetic specialist. Although mainstreaming can lead to increasing access to genetic testing and other advantages of this approach have been identified, there are also several challenges. Among others, the education of non-geneticists to ensure appropriate information and support is provided when offering a genetic test, plus a solid infrastructure to ensure all patients with a 'positive' test or complex case are referred (20). Mainstreaming initiatives, especially also for ovarian cancer patients, are expanding in several countries including for example Australia, the Netherlands, Malaysia, and UK.

## Advice based on the testing result

The results of a genetic test, positive or negative, are used to inform the assessment of breast cancer risk of the referred person and her family, preferably using up-to-date breast cancer risk prediction models. Based on this assessment of risk, further counselling will be provided. Advice will be provided regarding preventive measures to decrease the breast cancer risk, such as intensified surveillance (screening) or prophylactic risk-reducing surgery of the breasts (and/or ovaries and tubes to reduce the risk of ovarian cancer). The counsellor also discusses and recommends that all family members of a high-risk family, who might also be at increased breast cancer risk, are informed. In the future, with more personalized risk estimations on their way, each family member may receive their own risk estimates including other personal genetic and lifestyle factors. The advice given to women is based on the estimated risk, the woman's age, and taking the woman's preferences into account. The process of counselling, but also the guidelines on how to deal with different estimated risks, differ among countries (see for example the National Institute of Health and Care Excellence guidelines in the UK, <https://www.nice.org.uk/>; the Dutch guidelines, <https://richtlijnendatabase.nl/>; or EMSO guidelines (21)).

Women with a very high estimated lifetime risk for breast cancer, such as *BRCA1* and *BRCA2* (or *PALB2*) mutation carriers, can, instead of intensified surveillance, also choose prophylactic risk-reducing bilateral breast mastectomy as an option to manage their breast cancer risk. After a risk-reducing mastectomy the risk for breast cancer falls to less than 1% (22). Uptake of prophylactic mastectomy is generally high among high-risk women carrying a *BRCA1* or *BRCA2* mutation, but with large differences between countries. These differences may in part be explained by attitudes towards risk-reducing surgery of physicians and women in different countries. When considering prophylactic risk-reducing surgery many factors should be considered such as the estimated breast cancer risk, options for surveillance and thereby early detection, the advantages but also disadvantages of the surgery and possible breast reconstruction, and psychosocial aspects (such as negative body image and problems with sexual functioning). Specifically, for *BRCA1* and *BRCA2* mutation carriers, salpingo-oophorectomy to reduce ovarian cancer risk should be discussed as part of the risk management strategy.

Notably, there is currently no evidence on the impact of increased screening or prophylactic risk-reducing surgery on carriers of genes other than *BRCA1* and *BRCA2*, due to lack of data. While risk reduction for carriers of *BRCA1* and *BRCA2* pathogenic variants is well established, there is only limited evidence that risk-reducing mastectomy reduces in (short-term) mortality in *BRCA1* and *BRCA2* mutation carriers. In this context, advice regarding prophylactic risk-reducing surgeries is increasingly complicated. For example, without a family history of breast cancer, the lifetime risk of breast cancer for *CHEK2* c.1100delC mutation carriers is estimated to be around 20%, whereas this is higher in the context of a family with a history of breast cancer in which other genetic components add up to the risk of around 35–55%. Specific age-dependent risk estimates are important (as for example implemented in the BOADICEA model and CanRisk tool), because those are needed to tailor advice regarding screening and preventive measures.

## Risk communication

Appropriate communication of breast cancer risks to women and their relatives will ensure informed decision-making about possible intensified follow-up and/or prophylactic surgeries. How to communicate and make risks interpretable for women is a challenge and consequently an evolving field of research (23). A proportion of patients tend to forget or incorrectly recall medical information. The support of written information, including pictograms to visualize risks, will lead to better recall than spoken information alone. However, it is not so much the recall of actual risk that is related to the impact on the experienced distress and risk-reducing behaviour, but more the interpretation of these risks, i.e. the perceived risk. These risk perceptions are heavily influenced by personal experience with breast cancer as well as the experiences of first- and second-degree relatives who succumbed to the disease. Thus, the perceived risk may be the motivator in risk-reducing surgery, more than the actual risk estimates themselves. Therefore, counsellors should be aware of the individual interpretation of the cancer risk, rather more than the correct recall of the actual risk.

## The role of patient organizations; empowering patient decision-making

Patient organizations play a key role in promoting awareness of familial and hereditary breast and ovarian cancer. Their mission extends beyond patients themselves, reaching out to their families, healthcare providers, and the wider public. Traditionally, these organizations have provided unwavering support to patients and caregivers. However, their impact is far-reaching, as they adapt and innovate to meet evolving needs. By fostering awareness and collaboration, patient organizations empower individuals to make informed decisions about their health.

Patient organizations employ a multifaceted approach to disseminate information about familial and hereditary breast and ovarian cancer. Their outreach spans various platforms, including printed materials, digital channels (websites, social media, video's), leaflets, and educational lectures. In close collaboration with healthcare professionals and scientists, they ensure that this information is presented in a clear and accessible language, bridging

the gap between medical expertise and patient understanding. Through group meetings and interactive sessions, these organizations empower individuals with knowledge, enabling informed decision-making. An example of a powerful patient organization is Europa Donna (Box 23.3)

Being a *BRCA1* or *BRCA2* mutation carrier, or carrier of a mutation in another gene, has multiple aspects that need to be investigated and explained to each woman. It has many effects on a relationship, and sometimes it can influence the desire for motherhood (for the fear of passing on the mutation to children). Being a *BRCA1* or *BRCA2* mutation carrier very often means that you need to live with the ‘Syndrome of the Sword of Damocles’, living with the constant fear of getting breast or ovarian cancer, who knows if or when. After Angelina Jolie came out for being a *BRCA1* mutation carrier, many authors, journalists, and physicians gave their ‘personal opinion’ about her decisions which influence the choice of women and

### Box 23.3 Europa Donna, the European breast cancer coalition

Europa Donna, an independent non-profit organization, unites affiliated groups from across Europe. The organization was established in 1994 and has since been working towards its mission of promoting breast cancer awareness, mobilizing women across Europe, and advocating for advancements in breast cancer education, screening, treatment, and research funding. Currently, the Coalition has 47 country members, united in their commitment to combat breast cancer and enhance the well-being of women across Europe.

Overall, Europa Donna plays a crucial role in uniting various stakeholders across Europe to work towards the common goal of reducing the impact of breast cancer. By fostering collaboration, raising awareness, and advocating for policy changes, the organization contributes to the improvement of breast cancer outcomes and the overall well-being of those affected by the disease.

#### Some key aspects

**Awareness and education:** Europa Donna focuses on raising awareness about breast cancer, emphasizing the importance of early detection through regular screenings, and educating both the public and healthcare professionals about the disease.

**Advocacy:** The organization advocates for policy changes and improvements in breast cancer care at the European level. This includes pushing for better access to screening programmes, quality treatment options, and increased funding for breast cancer research.

**Networks:** Europa Donna serves as a platform for affiliated groups from different European countries to collaborate, share information, and support each other in their efforts to address breast cancer issues specific to their regions.

**Research:** The organization actively supports and promotes initiatives aimed at increasing funding for breast cancer research. This includes advocating for investments in innovative treatments, early detection methods, and improved understanding of the disease.

**Patient empowerment:** Europa Donna works towards empowering breast cancer patients by providing them with information, resources, and a platform to voice their concerns. The organization believes in the importance of involving patients in decisions related to their care.

Source: data from Europa Donna website: <https://www.europadonna.org/>



the general opinion and the common sense on this delicate topic. A gene mutation carrier needs to be strictly followed and accompanied by a team of experts such as breast surgeons, psychologists, and geneticists, before doing the test, and after the results are obtained.

The possibility of undergoing prophylactic surgery to reduce the risk of breast and ovarian cancer significantly during one's lifetime needs to be well explained and discussed with women and their family (for example, the husband). It is an irreversible type of surgery, and bilateral mastectomy is not a 'cosmetic surgery': it changes the breast forever and it impacts the perception of the body. Women need to know that they will lose body sensation in the breast and the nipple, and that the breast remains cold and hard to the touch, especially in case of breast implants. If a woman and her partner are not well informed, this could create negative outcomes in the quality of life. And what about bilateral oophorectomy? It reduces the risk of ovarian cancer significantly, but, especially for younger women, it means entering early menopause with all the well-known side-effects: vaginal dryness, loss of libido, hot flashes, and rejection of maternity. So, reducing breast and ovarian cancer risk with prophylactic surgery has many objective side-effects that need to be well explained to allow a conscious choice by women.

## Looking into the future

The costs of whole exome/genome sequencing are falling, and discussions are ongoing about all aspects of genetic testing including screening of newborns (24), who then might benefit from personalized prevention and treatment during their lifetimes. One of the larger criticisms is that information relevant later in life would be revealed early. Storage of data and release of parcels of information during life would be preferable, but this generates the need for storage and protection of large amounts of sensitive data and appropriate infrastructures. Important limitations also include our current ability to integrate comprehensive genetic information into clinical care. For example, not all data generated can or should be used; filtering will need to make sure that only results will be generated for genes/variants for which risk interpretations are stable and clinical applicability is clear. Even more so, the knowledge base continues to grow with the discovery of new genes/variants and updated risk information, showing the need for a pipeline which is regularly updated. Moreover, the number of incidental findings, which generates discussions about the 'right not to know' and the amount of information becoming available, substantially surpasses our current experience. The limitations discussed regarding genetic testing in high-risk families apply far more to population-based genetic testing. Risks will be smaller, risk differences will be subtler, and decisions that need to be made based on that information become even more complicated. Several other points should be considered; the cost-effectiveness, the need for well-trained professionals and infrastructures for counselling and communication of the results, and the burden for healthy persons to receive and comprehend all of this information.

Even though there are still many considerations and challenges related to population-based genetic testing, direct-to-consumer genetic testing is already available. Traditionally, genetic tests have only been available through healthcare providers. However, in the last decades, direct-to-consumer genetic testing has also been made available through commercial companies. These genetic tests are marketed directly to consumers and allow any person to have part or their full genome sequenced without consultation with, and supervision by, a



healthcare professional. All the limitations discussed regarding genetic testing are also applicable to this situation, and a consumer is vulnerable to being misled by the results of unproven or invalid tests. They may receive incomplete, incorrect, and unclear information about their health. Genetic testing provides only one piece of information about a person's health, but many other factors affect a person's risk. These factors are discussed during a consultation with a healthcare professional, but are potentially not addressed with direct-to-consumer testing.

Because of the potential hazards related to direct-to-consumer genetic testing, the US Food and Drug Administration (FDA) restricts commercial companies from offering direct-to-consumer genetic tests that function as diagnostic/health tests, until they have been analytically or clinically validated. In contrast to the situation in the USA, the regulatory framework in Europe is fragmented due to a lack of European Union or national legislation, and substantial differences exist among individual countries (25). Efforts are being made for harmonization of the regulation in Europe and in 2022 a new version of the European Commission's In Vitro Diagnostics directive came into force. Companies still can provide persons with their genetic information by including simple authorization by any physician (but market the test to consumers), or may provide customers with the raw genotyping data (without clinical interpretation). Interpretation of the raw data can be requested through third-party companies, but this has been shown to be highly sensitive for false positives and misinterpretation of variants in genes with potential clinical impact. Due to these potential hazards, there is an ongoing debate about the balance between medical paternalism, protecting people from the hazards of direct-to-consumer genetic testing, and individuals' right to obtain information about themselves.

## Key messages

- Women with a family history of breast cancer should be referred for clinical genetic testing
- A genetic test should include the eight known breast cancer susceptibility genes
- Genetic tests detect actionable pathogenic variants, but also variants of unknown significance in a substantial proportion of women
- Polygenic risk scores are entering the clinical domain and have clinical benefit in a clinical genetic setting
- Ideal risk stratification is based on family history and genetic test results, as well as information on breast density and lifestyle factors
- Knowledge of *BRCA1* and *BRCA2* pathogenic variants is also relevant for breast cancer treatment
- Patient organizations (e.g. Europa Donna) and national support groups provide accessible information to women about genetic testing

## Acknowledgement

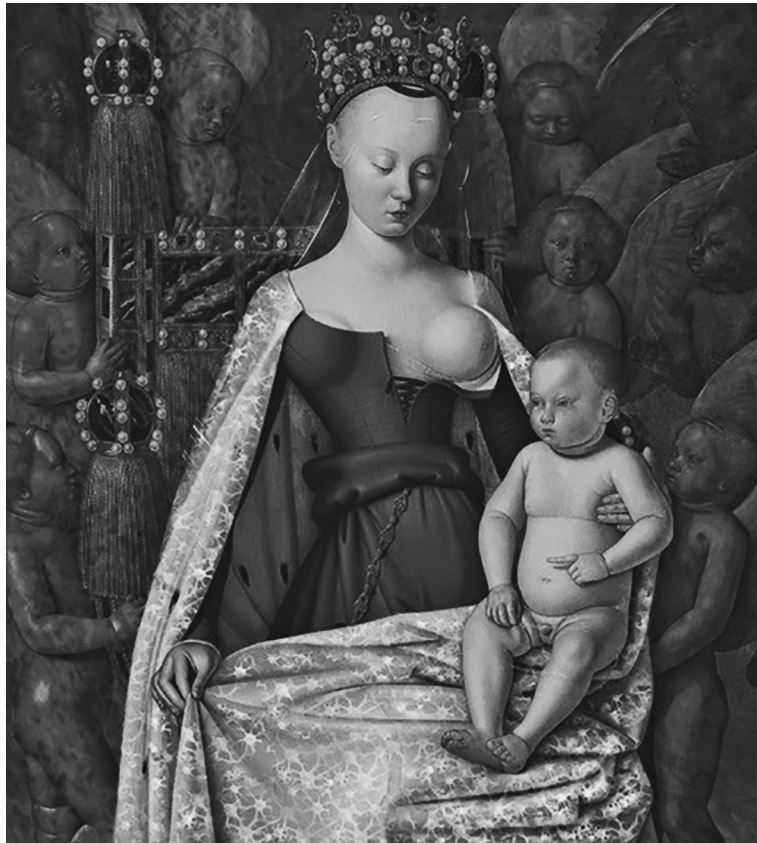
We gratefully thank those who contributed to the previous edition of this chapter, especially Alexandra J. van den Broek, Mark E. Robson, and Soo Hwang Teo.

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## PART 6

# HEALTH INFORMATION TECHNOLOGY



‘The Antwerp Madonna of Jean Fouquet: when old masters meet new technology’. Visual poetry by Pascale Pollier.

Original image Jean Fouquet, *Madonna Surrounded by Seraphim and Cherubim*, KMSKA, <https://kmska.be/en/masterpiece/madonna-surrounded-seraphim-and-cherubim>.

Adapted under Creative Commons PDM 1.0. Public Domain Mark 1.0 Universal Deed, <https://creativecommons.org/publicdomain/mark/1.0/deed.en>.

AI Midjourney Discord used in creation of the lace pattern, Histology slide overlayed on background of angels, lace robe created and edited in Adobe Photoshop.

© Created by Pascale Pollier MAA, Registered Medical Illustrator, Artem Medicalis



## Information technology

*Fernando Suarez, Gabriëlle Speijer, and Tolga Ozmen*

### Introduction

Advances in diagnostics and treatment, in addition to a rapidly growing ageing population, are putting an unprecedented strain on care services across the globe. There is a radical need to transform and modernize the way that care is delivered to meet the needs of our society now and in the future. The triple aims of care (better health, better care, lower cost) still prevail—however, we need to think about how we can deliver care more intelligently and importantly at pace to meet these increasing demands.

### The potential of connected health

Advances in information and communication technology (ICT) offer a means of providing solutions to the significant challenges that we face and crucially acting as a mechanism to enable and sustain much-needed system transformations. Technologies are constantly developing, advancing, and becoming smarter. Devices such as smartphones and sensor technologies are growing in availability and decreasing in price. Increasingly large and diverse data systems are integrated, from DNA sequencing to electronic health records and to the linkage of large medical or non-medical databases built for other, often administrative, purposes (1, 2).

The field of connected health has emerged in response to this significant demand and pervasiveness of ICT within all aspects of our society. Connected Health is defined by Richardson (3) as ‘patient-centred care resulting from process-driven healthcare delivery undertaken by healthcare professionals, patients and/or carers who are supported by the use of technology (software and/or hardware)’. It is a virtual ecosystem of care that extends beyond the confines of physical healthcare establishments—using deepening technology integration, information exchange, data analytics, and advances in genomics to intelligently support citizens and patients to stay well within their communities for as long as possible, and—crucially—quickly access services in times of need.

While the vision of connected health has significant potential to transform and revolutionize the ways that healthcare is delivered now and, in the future, we need to be cognisant of preventing information overload and, importantly, identifying what information we need and in what format to optimize and enable the delivery of this model of care.

For example, in the field of breast cancer in 2022, there were more than 30K papers published on this subject alone, and close to 1000 of those papers were on breast cancer clinical

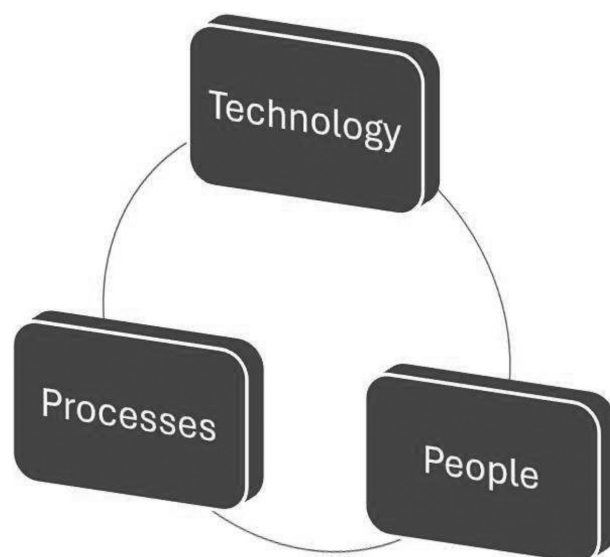


**Figure 24.1** The potential of connected health.

trials. Furthermore, the number of publications on genomics and breast cancer grew from one thousand between 2001 and 2010 to more than six thousand in the period between 2011 and 2022, and while this explosion in research has led to advancements in our understanding of cancer and by extension to better treatments, it has also created the problem of cognitive overload for clinicians.

In the field of genomics, the advancements and clinical adoption of DNA sequencing technologies have had an impact on the cost of sequencing. The cost of a complete human exome has fallen below the \$1000 mark and now at close to \$200 with little signs of stopping this trend in the near future (Figure 24.1). As the field of cancer moves from genomics to ‘panomics’, the data is only going to grow and making sense and visualizing the data will be the challenge in the coming years. The positive impact that this will have on patient treatment and care will be unprecedented. Today, there are more than 500 drugs with pharmacogenomics information on their label, and about half of those are for oncology (4). Moreover 73% of drugs currently in development have the potential to become personalized medicine (5). Access to genomic data enables clinicians to provide personalized care, with over 500 drugs now having pharmacogenomic labels.

## Emerging technologies and trends

All these advancements in the field of oncology are being enhanced by significant developments in the field of information and communications technology and data analytics. A patient will potentially generate close to 1.2 Petabytes of information in their lifetime. The data will be made up mostly of non-traditional sources both structured like wearable devices and home monitoring systems and non-structured educational records, employment records, and social media. Thirty per cent will be made up of genomic and other molecular tests and the last 10% from their Electronic Medical Record (Figure 24.2) (6, 7). This data, at present, is

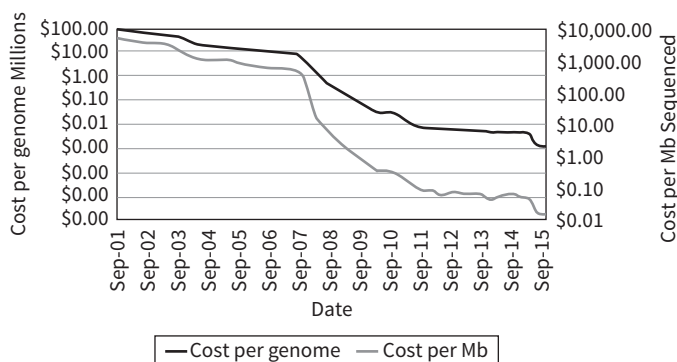


**Figure 24.2** Change in cost of DNA sequencing.

Source: data from <https://www.genome.gov/sequencingcostsdata/> and Lyman GH et al. Impact of a 21-Gene RT-PCR Assay on Treatment Decisions in Early-Stage Breast Cancer. An Economic Analysis. *Cancer* 2007 Mar 15;109(6):1011–18.

often disorganized, redundant, and in many cases not available to the clinician or the patient. The human mind alone cannot process such large amounts of data and importantly deem what is and what is not useful. The optimal utility of such data will rely on the use of cognitive technologies and artificial intelligence. Such systems can deal not only with the volume of data but also with the velocity, variety and veracity required to provide the clinician in general and the oncologist in particular a complete view of the ‘quantified self’ (8).

It is currently impossible for a single doctor to keep up to date with all these developments in a traditional way and only with the assistance of information and communications technology will patients and clinicians benefit from this revolution. The promise of truly personalized medicine can only be reached by our ability to bring those three spheres together, patient records, new research, and genomics. Generation of insights using AI and machine learning (‘Learning rules from data’ (8)) will be the driving force of healthcare now and in the future (Figure 24.3).

## Artificial intelligence

Recent advancements in artificial intelligence (AI), the development of computer systems able to perform tasks normally requiring human intelligence, have further revolutionized the healthcare landscape. In particular, deep learning algorithms, a type of AI that uses neural networks modelled after the human brain, are now capable of analysing complex medical images, predicting disease progression, and even assisting in personalized treatment planning. For example, Google’s DeepMind Health project has developed an AI system capable of diagnosing eye diseases as accurately as top human experts (9). In oncology, AI models have been trained to predict the response of specific tumours to various treatments, enabling a level of personalized care that was previously unattainable. Furthermore, AI’s role in precision medicine has expanded rapidly, with systems now capable of analysing genetic information alongside environmental and lifestyle data to determine an individual’s risk of developing certain diseases (10). These AI systems can provide clinicians with actionable insights in real time, augmenting their decision-making capabilities and ultimately leading to

## Personal Data is Exploding

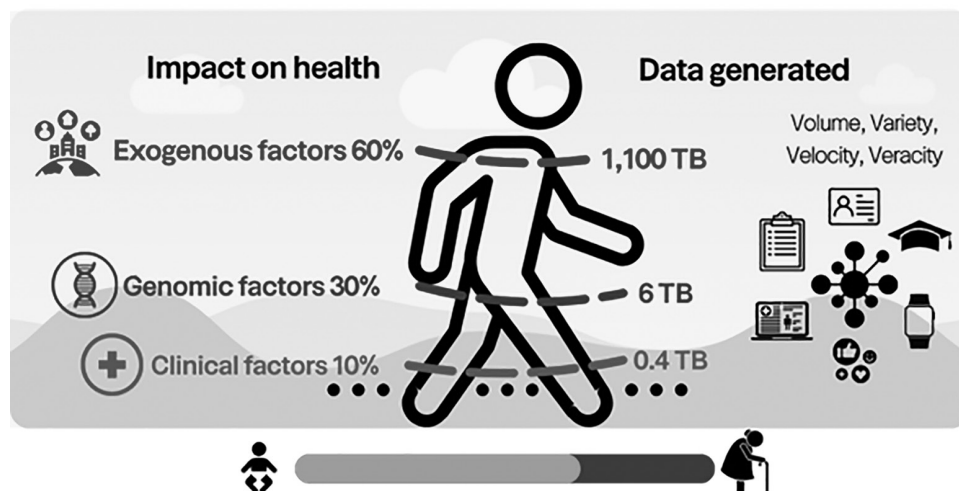


**Figure 24.3** The quantified self.

Source: data from Ahmed, Mohamed Nooman, Andeep S. Toor, Kelsey O'Neil and Dawson Friedland. 'Cognitive Computing and the Future of Health Care: The Cognitive Power of IBM Watson Has the Potential to Transform Global Personalized Medicine'. *IEEE Pulse* 8 (2017): 4-9

improved patient outcomes. AI systems assist clinicians by analysing complex data for insights, predicting disease progression, and supporting treatment decisions (see Chapter 13) (Figure 24.4).

Alongside all these revolutionary advancements, it's important to remain vigilant about cybersecurity concerns. The same data used to empower better treatment options and drive

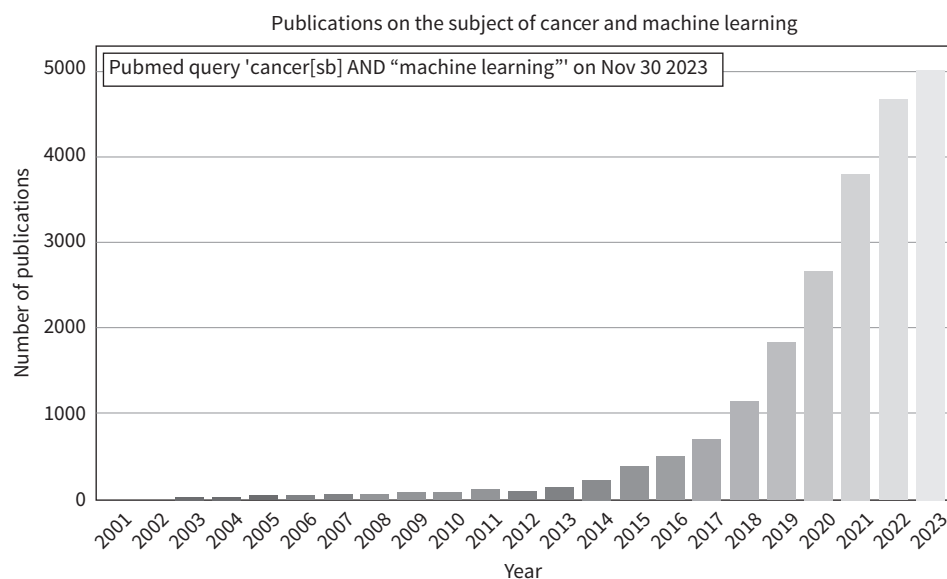


**Figure 24.4** Trends in machine learning and cancer research.



personalized care can be misused if proper safeguards aren't in place. This presents risks to patient privacy, with potential downstream impacts on insurance, employment, and financial well-being. Public trust in the entire system depends on our ability to protect healthcare data—making the responsibility of data security a shared duty between patients, providers, and policymakers. Maintaining secure technology infrastructures, preventing breaches, and educating healthcare workers remain crucial, especially as more sophisticated technologies like AI are introduced.

## Conclusions

Furthermore, even the most sophisticated AI technologies present potential challenges. Generative AI (GenAI) and large language models (LLMs) hold the potential to transform healthcare access in third-world countries, including specialized areas like breast cancer care. These technologies can analyse vast medical data sets, assist with remote diagnosis, and generate patient-specific treatment recommendations (11, 12). This could address personnel shortages and provide vital clinical decision support in areas where oncologists are scarce. However, it's crucial to address bias in training data to ensure these AI systems don't inherit disparities present in historical medical records, leading to inaccurate diagnoses or treatment inequities. Ethical considerations around privacy, informed consent, and how AI could augment—but not replace—human doctors remain central when deploying GenAI for healthcare in underserved regions (13, 14).

The discussion of AI highlights the power of data access and analysis. Digital pathology represents another technological breakthrough with transformative potential, but with its development centred in the Western world, there's a risk of increasing global inequities. Fortunately, advances in edge and mobile computing, combined with global cloud platforms, could enable African nations to leapfrog older technology infrastructures and burdensome regulations. This paves the way for a more decentralized digital healthcare world, driven by patient consent and supported by data models that understand medical information as a community-level resource (15). Embracing emerging technologies like genomics and AI can empower clinicians with the knowledge and tools needed to provide optimal personalized care, ultimately improving patient outcomes. This is happening now. In April 2024 the AI-MARRVEL Knowledge-Driven AI System for Diagnosing Mendelian Disorders showed the huge potential for AI supporting genomics knowledge discovery and improving the accuracy of genetic diagnosis (16).

The convergence of these technological advances positions healthcare at a transformative moment where truly personalized medicine is becoming reality. Recent breakthroughs in breast cancer care exemplify this transformation on a global scale. The largest real-world study to date, involving over 463,000 women across Germany's national screening programme, demonstrated that AI-supported mammography increased breast cancer detection rates by nearly 18% while maintaining stable recall rates (17). Meanwhile, the FDA's historic approval of Clairity Breast—the first AI platform to predict five-year breast cancer risk using only routine mammograms—represents a fundamental shift from simply detecting existing cancer to predicting future risk (18). These advances are further supported by studies from Korea and Sweden, showing that AI can improve cancer detection by 13–29% while significantly reducing radiologist workload (19, 20). The emergence of medical AI systems

specifically designed for healthcare applications promises to integrate diverse data sources—from imaging and genomics to clinical records—enabling unprecedented precision in diagnosis and treatment. As these technologies mature globally, they offer the potential to democratize expert-level cancer care, addressing the critical disparities between developed and developing nations while fundamentally changing how we approach early detection and prevention worldwide.

## Key messages

- **Harnessing ICT for healthcare transformation:** ICT is essential for modernizing healthcare delivery to meet global demands.
- **The power of connected health:** Connected health leverages advancements in technology that enable integration, information exchange, and data analytics to support patient care beyond traditional healthcare settings.
- **AI's role in personalized medicine:** Artificial intelligence can enable personalized treatment by analysing vast amounts of health data, potentially leading to improved patient outcomes.
- **Ensuring data security and ethical standards:** Protecting healthcare data and upholding ethical standards are crucial to maintain patient trust and privacy, necessitating robust cybersecurity measures and ethical guidelines.
- **Embrace the future of decentralized digital healthcare** by leveraging genomics and AI to deliver personalized care, driven by patient consent and secure data management, to improve patient outcomes, and empower individuals with control over their medical information.

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## Tele-oncology

*Gert Van den Eynden, Frederik Deman, Hans Junkermann, and Gabriëlle Speijer*

### Introduction

Digital diagnosis and treatment for breast cancer can be automated and digitized with various diagnostic imaging and genetic tests. These diagnostic tools are essential for medical teams to choose the optimal treatment path and adjust it if needed. Tele-oncology can improve cancer care, facilitating remote consultations with specialists, thus mitigating healthcare disparities for remote patients.

In low- and middle-income countries (LMICs), where resources and healthcare professionals are scarce, digital accessibility to experts in developed nations can bridge critical gaps. These experts, supported by state-of-the-art technology, can offer their services remotely, negating the need for a physical presence. Consultations can adapt to a variety of modes (either virtual or in-person), timings (synchronized or not), locations (be it a hospital, home, or elsewhere), and can be initiated by either healthcare professionals or patients themselves.

However, it is imperative that locally trained professionals are on hand to provide physical support to patients. Maintaining a physical presence is vital for fostering a trust-based relationship, which is crucial for a comprehensive understanding of the patient's health condition. Additionally, it is essential to gather feedback on breast cancer outcomes from less-developed countries due to the variations in local populations, as these differences may lead to varying risk levels for these groups on a global scale.

Tele-oncology has the potential to enhance research in areas where breast cancer care is underdeveloped. Since it is driven by local needs and priorities, tele-oncology is well-positioned to help reduce the global disparities in breast cancer care. This means tele-oncology data need to be available by design for secondary use in breast cancer research.

LMICs have the advantage of adopting new technology within innovative network organizations that are patient-oriented, with trusted professionals, and centred around specific cases. The previously published analysis on challenges related to tele-oncology in sub-Saharan Africa seems a misconception as digital pathology solutions will invest in distributed computing models whereby computing takes place in proximity to edge computing empowered microscopes and scanners meaning the data is processed locally at the 'edge' of the network, rather than on a centralized server in the cloud (1, 2).

LMICs implement these technologies at the regional or national health system level, thus enjoying benefits comparable to leading digital governments, such as Estonia. As a result digital security and ubiquitous equal access to health services is provided with a better value over cost ratio than that of developed countries.

## Tele-surgery

Worldwide, more than 80% of people with cancer will require surgery during their disease course, but less than 25% have access to safe, affordable, and timely surgery (3). Among the barriers to increasing surgical capacity are the time and costs required to train novices. Oncologic surgical care in many LMICs, when available at all, is often provided by non-physician medical officers, general physicians, and surgeons without formal oncologic training or certification. Subspecialty training in oncology in the western hemisphere is expensive, and many trainees from LMICs do not return home after becoming qualified (see Chapter 9).

One of the most promising tele-surgery innovations is robot-assisted surgery (RAS). As a field in rapid development, RAS offers the potential to improve the quality and outcomes of surgical interventions. Support from evidence-based surgery (EBS) is crucial for tele-surgery to effectively reduce the time and costs of cancer diagnosis and treatment, while improving the quality of life and satisfaction of patients. The transformational impact of tele-surgery is made possible through the robot connected to the international network, enabling top surgeons, even in the LMICs, to assist the local medical teams. Like artificial intelligence (AI), it supports local health services with global knowledge and expertise. Maroeska Rovers is a proponent of equitable, collaborative partnerships between high-income countries (HICs) and LMICs and stresses the inclusion of patient and societal values in RAS assessments (4). By embedding EBS principles within RAS, there is hope for a shift towards more impactful, value-based cancer care delivery.

## Teleradiology

Teleradiology enables the transmission of breast images as mammograms, ultrasounds, and MRIs to a location distant from the image acquisition. It thus enables interpretation and reporting by experts where no expertise is locally available.

Screening mammography is the situation most amenable to teleradiology in breast imaging. Independent double reading by two experts is supported by specialized software. With divergent results a teleconference and/or arbitration is easily performed before the women are invited for the assessment of detected lesions.

Recent results from magnetic resonance imaging breast cancer screening programmes for high-risk women support the idea that double reading is just as advantageous in this situation (5). With the lower number of cases, it is even more difficult for the local radiologist to acquire the necessary experience for a high-quality evaluation of the images.

In symptomatic breast disease, the advantage of teleradiology is less obvious. The clinical examination typically leads to symptom-guided ultrasound examination, which is complemented by mammography except in well-defined situations. The ultrasound examination is performed with a handheld ultrasound probe. The documented images are dependent on the operator's technique and not as easily suited for an independent second opinion. Mammograms must be interpreted in the context of the clinical and the ultrasound examination. The decision on further assessment by needle biopsy should be rendered immediately

after the examination, and it is demanding to include the result of a second opinion by teleradiology into this decision-making.

In situations where access to diagnosis and treatment, however, is restricted by the absence of trained physicians, mammography machines, and/or unaffordable cost of travel to a sufficiently equipped clinic like in remote areas in some HIC and many LMIC an approach using ultrasound devices operated by trained medical assistant personnel and immediately interpreted by internet-connected specialists could greatly improve breast healthcare (5, 6)

For mammography each reading station (local or distant) should meet the requirements regarding expensive high-resolution monitors not necessary for general teleradiology. The software should be able to display and exchange annotations. The distant reader should be involved in the quality management of the technical aspects of mammography acquisition (especially positioning of the breast).

It may be anticipated that teleradiology will be increasingly used in breast imaging with the aspects of knowledge-sharing, auditing, quality management, and education. This will potentially lead to a higher and more evenly distributed quality of breast imaging, especially in LMICs but also in HICs.

## Digital pathology, telepathology, and AI

Further improvements in (high-throughput) whole slide image scanning technology, IT-infrastructure (storage capacity and network speed) and available image management software have significantly accelerated the implementation of digital pathology (DP) in clinical practice over the last couple of years. More and more pathologists are switching from their microscopes to computer screens for their daily work, especially in resource-rich settings. In fact, in these settings, a significant number of resources are now already being invested in the next step, which is the implementation of AI and computer-assisted pathology.

The expectations from clinicians, patients, and healthcare providers towards high-quality pathology have never been higher and are expected to grow even further. Modern pathologists are the ‘guardian of the tissue’ in an era of rapidly increasing knowledge on tumour biology, of an extensive technical arsenal, of more exhaustive tumour subtyping and of more complex and personalized therapeutic options. These increasing demands contrast to the expected decrease in pathologists over the next decade. DP can help overcome some of the most pressing challenges in smaller institutions and low(er)-resource settings. The two most important advantages are knowledge-sharing within (long-distance) networks of (expert) pathologists and the introduction of AI.

The implementation of telepathology platforms, assisted by networks of expert pathologists, can offer support to laboratories and/or hospitals with limited pathology resources, regardless of whether the cause is due to small institutional size, limited pathology manpower, lack of availability of pathology subspecialist knowledge, remote location, or a combination of factors. Telepathology support in such situations can serve multiple needs. For instance, easy access to a colleague’s expertise for a second opinion in challenging cases, and/or assistance during difficult intraoperative examinations, can prevent bottlenecks in treatment. On the other hand, primary reading of cases in situations of pathology manpower shortages enables hospital/laboratory management to ensure short turnaround times and continuity of care. Telepathology can also facilitate certain aspects of the laboratories’ quality management

system, such as continuous auditing of cases, third line/external quality control, and continuous education of pathologists.

Digital pathology is the basis for the implementation of AI. AI within pathology can be divided into five practical implementations: pathology reporting support, region of interest detection, quantitative AI, predictive tools, and quality control tools. Each type of tool has its own purpose and can have additional value to the pathologist. Current breast pathology applications are the quantification of biomarkers (f.e. ER, PR, HER2, Ki-67) apart from other decision support tools that help with the finding and classification of lesions on a biopsy by marking region of interest in a heatmap. The tools can classify lesions into malignant versus premalignant versus benign lesions, help with subtyping of the malignant lesions while other tools are helping pathologists finding metastasis in lymph nodes. There are also AI tools that are marking morphological biomarkers in a whole slide image (WSI) such as tumour Infiltrating lymphocytes (TILs) or mitotic figures. The expectation is that the amount of computational pathology tools will further increase the following years with also tools coming into the market that can predict prognosis or compliance to specific therapies, better than the human eye can do.

The implementation of AI tools can have a significant impact on the field of pathology and lead in the future to computer-assisted pathology. However, many challenges remain, especially in low(er)-resource settings. First, at this moment they come with a relatively high cost on top of the high investment cost for digitizing the pathology lab. Furthermore, DP and AI must be adapted to and embedded in the local situation, with specific ethical, medico-legal, and technical challenges. One aspect that should not be neglected is the fact that the performance of AI tools depends entirely on the training data used to develop them. This is especially true for tools with prognostic and/or predictive outcomes. Most AI tools are developed on western data sets from resource-rich settings. Their performance should therefore be validated in specific settings before using them in clinical decision-making (7, 8).

## Tele-oncology for breast cancer case-teams

A User Experience driven development, focusing on relational care, is a response to this. This approach ensures that the platform is built to facilitate trust and collaboration between the patient and their care team, thereby enabling them to securely integrate their respective networks for better outcomes. The case of the patient is central for the collaborative team. It's by design connected to the space for research and innovation, where the patient and the doctor jointly make the data accessible. This is even more important as increasingly more clinical AI research needs to be translated into clinical workflows (10).

This is demonstrated in the Minimal Viable Platform (MVP) FluKs (9), which is designed around the doctor-patient relationship and principles of Shared Decision-Making (11). The underlying data and specifications of this MVP have been made available via a permanent repository (9).

## Conclusion

In conclusion, DP and AI are implemented faster and faster in routine pathology and have the potential to fundamentally change the field. Currently, this evolution is mainly centred



on resource-rich settings, although the potential of the technology to contribute to modern quality pathology also in lower-resource settings is high. Therefore, it will be the responsibility of all stakeholders to ensure that this implementation does not further widen the gap between high- and low-resource settings.

However, the digital breast cancer diagnosis and treatment health system in the emerging markets can be dramatically different because breast cancer care process in the developing countries will be accelerated because the digital technology is available at the individual patient and healthcare professional level. It's found everywhere and at the same time because it's fully integrated on the internet. So available for everyone globally. Its' only limited by the speed of the adoption of the people that embrace this.

Best practices must be identified for each local setting in LMICs. Best practices, identified through user-driven co-creation, will enable patients and health professionals to create their own digital platform and to build their own care pathways. Thereby optimizing for digital interfaces and ensuring they are patient centric. This approach also allows for the fluid integration of insights from research and innovation directly into clinical practice, thereby closing the gap between discovery and application.

LMICs will get much higher return because the value/cost ration is much higher, because for cost they don't need to change legacy IT application, they don't need to integrate healthcare enterprise silos. The return will get much bigger than in western countries as tele-oncology will be adopted much faster. They will generate health value as they organize along the patient care pathway instead of integrating the healthcare service provider organizations. The healthcare delivery is in those countries virtual by design, as it is not on one location.

## Key messages

- Although tele-oncology experiences in developing countries are promising, human resource and technological barriers must be addressed to realize its full impact on cancer care.
- Breast cancer care in developing countries will advance rapidly due to widely available digital technology, limited only by the pace of adoption among users.
- Telementoring and teleconsultation can be highly effective in enhancing surgical skills among surgical trainees in low-resource settings.
- Teleradiology has the potential to improve many aspects of the care for breast health in HIC, as well as especially in LMIC.
- The role of the local pathologist as the guardian of the patient's tissue remains essential.
- Tailored best practices in LMICs, developed through user-driven co-creation, enhance digital healthcare centered on the doctor-patient couple by directly integrating research and innovation into clinical practice.
- LMICs will achieve a significantly higher return due to a much more favourable value/cost ratio, primarily because they bypass the costly need to update legacy IT applications and integrate entrenched healthcare enterprise silos prevalent in developed nations. This allows these economies to seize the opportunity to 'leapfrog' toward more robust, resilient health systems fitting their contexts.



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**PART 7**

**BREAST CANCER RESEARCH**



## The changing clinical research pathway

*Eva Sophie Lunde Pedersen, Karan Jatwani, Daniëlle Verschoor, Alain Tardit, and Eva Segelov*

### Introduction

The past decade has yielded paradigm shifts in breast cancer research. Improved prevention, screening, diagnosis, and therapeutic strategies have contributed to a decrease in breast cancer deaths in the USA by 39% between 1991 and 2015 (1). However, an estimated 70% of breast cancer mortality occurs in low- and middle-income countries (LMIC), disproportionate to incidence, resulting in the significant challenge of ensuring that both small and large breakthroughs can be translated into the global setting.

Major changes in breast cancer research since this book's first edition include:

- Sizable shift towards a personalized therapy approach based on molecular tumour characterization, although much remains to be done to truly 'personalize' treatment.
- Rapid explosion of new therapeutic options, particularly immunotherapy, targeted drugs, and antibody-drug conjugates (ADC).
- Novel trial designs, driven by concerns about length and cost of research and the decades between discovery and incorporation into clinical care, incorporating Bayesian methodology (to reduce the number of patients needed in early phases and facilitate more rapid results) and quality of life (QoL) indicators, such as patient-reported outcome measures (PROMS).
- Integration of global oncology, gender medicine, and equity and diversity in research participation and practice.
- Use of big data, real-world data, and synthetic data.
- A focus on repurposing drugs and reducing treatments, to lessen toxicity, including financial and travel/time toxicity for patients, and costs and health facility utilization for providers.
- Widespread acceptance of the vital role of patient and public involvement (PPI) in research, including the requirement for this in funding applications.
- Persistence of primary and secondary prevention and screening strategies as important research questions, including risk stratification and investigations of lifestyle interventions such as specific diets, weight control, and exercise.
- Growing appreciation of the importance of health service and implementation research, including health economics, communication and shared decision-making, quality assessment, and survivorship.

- Use of artificial intelligence (AI) throughout the diagnostic and treatment pathway, to improve accuracy and speed.

This chapter summarizes major advances in key areas of breast cancer research to update and expand themes addressed in the first edition of this book.

## From preclinical to late-stage clinical research

### Preclinical advances

As understanding of disease biology has improved, significant research initiatives are being implemented to correlate genomic, phenotypic, and environmental factors impacting breast cancer risk, diagnosis, and treatment. Groundbreaking advances in laboratory technologies, including ‘-omics’, molecular imaging, and molecular epidemiology, have fuelled discoveries that have translated through to clinical benefit. Experimentation using 3D models that mimic human pathophysiology is now more realistic, due to advances in biomaterials and tissue engineering.

### Screening and diagnosis

Advances in technologies include:

- Improved ultrasound (US) techniques, such as contrast-enhanced spectral mammography, which adds information on neovasculature in breast lesions and is independent of breast density; optoacoustic US, which detects tumour-driven angiogenesis using light pulses; and US transmission tomography, which offers 3D images resembling magnetic resonance imaging (MRI). Automated breast US, which captures an image of the entire breast, eliminates the need for X-ray technicians and allows remote reading.
- MRI with diffusion-weighted imaging can improve the distinction between benign and malignant lesions.
- Positron emission tomography imaging may have a role in screening, although radiation exposure and costs limit its utility.
- AI models based on deep learning algorithms from large datasets can be used to triage the likelihood of malignancy, with diagnostic accuracies approaching that of radiologists.

### New techniques, technologies, and medical devices

Innovative functional imaging and sensing systems have the potential to improve the approximately 18% reoperation rate of primary surgery for localized disease. Miniaturized specimen-computerized tomography and MRI imaging, and the use of intraoperative devices using rapid evaporative ionization mass-spectrometry and other physical properties are entering clinical trials. To improve reconstruction outcomes, novel surgical techniques

including the use of dermal matrix and other tissue engineering products and AI-based pre-operative planning for microsurgical reconstruction are being tested.

## Research in LMICs

There is a significant disparity in the number and type of trials between high-income countries (HICs) and LMICs. From 2014 to 2017, <10% of global trials were conducted in LMICs, despite data demonstrating cost-effectiveness and a larger magnitude of clinical benefit (2). In 2018, LMICs were significantly less likely to have Phase I/II studies in breast cancer, and many of those were limited to the metastatic setting. Most countries in Africa had no breast cancer trials registered between 2010–2017 (3). Of radiotherapy trials registered between 2014–2017, of which breast cancer constituted 14%, none were recruited from low-income countries (4). Reasons for disparities include low economic investment in cancer research, lack of reliable population-based cancer registries and accurate clinical data sources, and underinvestment in capacity building as a result of research between HIC and LMIC.

## Survivorship and health services research

As survival rates improve, research into the physical, social, and psychological health of people cured and/or living with breast cancer has become paramount. Long term physical effects are associated with poor QoL and reduce adjuvant therapy adherence. Persistent fatigue, described in up to 30% of breast cancer survivors at 10 years after diagnosis, is the subject of much research regarding cause and mitigation. Fertility preservation is another crucial area, with trials and real-world data (RWD) showing temporary interruption of endocrine therapy is safe to allow pregnancy, although longer term data is awaited. Alterations in body composition, including weight gain, predisposition to diabetes and impact of early menopause, are being studied. Cardio-oncology has become a subspecialty discipline covering both short and long treatment toxicity from radiation and pharmaceuticals, including anthracyclines, anti-Her2 agents, CDK 4/6 inhibitors, and more recently, immune checkpoint inhibitors, which may accelerate coronary artery disease. Mental illness undetected after cancer diagnosis is known to increase all-cause mortality and many studies are focused on optimizing survivor wellbeing, including addressing fear of recurrence.

Health service research in breast cancer has yielded advances, including demonstration that formal survivorship care planning improves patient experience, reduces costs, and adds efficiency. In Korea, breast screening programmes aligned with cultural expectations led to improved uptake (5). The financial and time toxicity of a breast cancer diagnosis is being increasingly studied, particularly in LMICs, where up to 79% of breast cancer patients are affected, compared to 35% recorded in HICs. Research has identified three major contributors: unexpected medical and nonmedical expenses, lost revenue from missing work, and changes in budgeting to prioritize medical bills, such as early retirement withdrawal (6).

Other foci of research in LMICs are understanding the individual, social, cultural and health system barriers that influence breast cancer screening and care delivery, including fear of death, permanent deformity, and social stigmatization. Use of innovative strategies including mobile screening for geographically hard-to-reach areas, training of

general healthcare workers in simplified breast US and adoption of telemedicine are all being evaluated.

## **Evolving therapeutic approaches**

### **Surgery**

Optimization of surgical techniques to enhance QoL includes the expansion of Oncoplastic surgery, a method of correcting lumpectomy defects at the time of resection. This has gained acceptance as a standard front-line procedure, with good safety outcomes and lower re-excision rates than traditional lumpectomy. It has been shown to be safe and efficacious in LMICs, although use is limited by economic factors, less experience among surgeons, and lower patient awareness.

### **Radiation therapy**

Major reduction in treatment time has been achieved through randomized clinical trials (RCTs) of hypofractionated and ultrahypofractionated therapy. The duration of whole breast radiation has decreased from 5 to 7 weeks using 25–33 + fractions, to five days comprising five fractions (7). This has been possible through rigorous testing of new techniques, such as inverse planned intensity-modulated radiation therapy and stereotactic body radiation therapy, along with respiratory gating to reduce radiation exposure of normal tissues. The use of intraoperative breast radiation has also grown, providing convenience for the patient, but at the cost of an expensive setup and the need for the close coordination of experts, which can be challenging for a hospital system.

### **Systemic therapy**

Between 2010 and 2020, the US Food and Drug Administration (FDA) granted 30 new approvals for breast cancer indications (8). Understanding optimal combinations of therapy and factors that enhance response and limit toxicity remains a strong focus for translational research. Precision oncology has facilitated the development of drugs for biomarker-identified cancers, particularly Her2 + and Luminal A cancers. Evolving after many years where hormone therapy and chemotherapy were mainstays of treatment, the era of Her2 targeting has seen the adoption of ADC and small molecules into routine care (9). More recently, immunotherapy has become a backbone of treatment, particularly for the notoriously unresponsive triple-negative cancers. The critical role of the human microbiome in modulating response to immunotherapy is a potentially targetable new field within the domain of host-response interactions. Along the trending theme of minimizing treatment, molecular testing to predict benefit of adjuvant therapy for early breast cancer has become commonplace in HICs after key RCTs, but with remaining critical questions (10).



Other key advances include:

- **Stem cell models:** First reported in 2003, breast cancer stem cells have been studied extensively. Single-cell transcriptomics and genetic lineage tracing allow extensive phenotyping to test pathogenetic and therapeutic pathways.
- **Chimeric antigen receptor T (CAR-T) cell therapy:** Modification of the patient's own T cells to recognize certain cancer antigens has been more challenging in solid compared to haematological tumours. Nevertheless, trials in breast cancer are underway for many antigens, including ROR1, MUC1, and NKG2D.
- **PROTACS:** PROteolysis TArgeting Chimera therapeutics allow the ubiquitin proteasome system to target a particular receptor. In breast cancer, vepdegestrant (ARV-471), targeting the oestrogen receptor, has been assessed in early-phase clinical trials.
- **Cancer vaccines:** Desoxyribo nucleic acid (DNA) vaccine development against antigen targets like Her2 and Globo H (a carbohydrate antigen on breast cancer cells) have accelerated based on technologies used for COVID-19 vaccines.

## Observational big data

The use of observational big data, such as real-world data (RDW), is rapidly increasing. Many questions will benefit from a hybrid methodology, combining the strengths of RCT and RWD studies (11). RWD is essential to validate and properly quantify the impact of RCTs, as it has been shown that gains achieved in RCTs are effectively smaller in the real-world setting (the efficacy-effectiveness gap) (12). Reciprocally, RWD can identify important areas for clinical trials, outline gaps in practice patterns, contextualize PROMs, facilitate health economic analyses, describe outcomes in patients under-represented or completely excluded from trials, provide insights into rare breast cancer subtypes, and provide data regarding treatment sequences and safety.

The huge explosion in RWD research has been enabled by massive improvements in information technology, including platforms for data sharing, widespread introduction of electronic medical records in health systems and the capacity to process complex bioinformatics. There has been a global effort to improve RWD collection and use it to inform regulatory decisions. Universal healthcare systems, such as those in Australia and Canada, can link multiple types of data, although privacy concerns and bureaucratic processes make this type of research slow and expensive. The United Kingdom has the Systemic Anti-Cancer Therapy database, an electronic prescribing system used by National Health Service Trusts since 2014. In Europe, consortia such as the Integrative Cancer Research Through Innovative Biomedical Infrastructures (INTEGRATE), developed by the Breast International Group, facilitate access to data from 29 European cancer centres, to assist the development of breast cancer predictive methodologies.

Synthetic data generation has been proposed as an effective mechanism of sharing data from RCT and large cohort and other studies (13). Combining data from multiple sources is an emerging pathway for re-evaluating the original research question in a much larger data set, to address safety, efficacy, bias, and robustness/reproducibility of results. In addition, new hypotheses can be examined through statistical and machine learning AI.

In cancer, it is notable that most of the current RWD reflects HICs, dominated by participants of Western ancestry. Both RWD and RCT data sets need to overcome this bias through efforts for inclusive participation. Another major barrier is the legal framework for sharing data, underpinned by privacy concerns, including potential selling of data to for-profit organizations such as pharmaceutical companies. Standards for data quality and regular quality management procedures are also key.

## Choosing the best (new) statistical methods in breast cancer research

### Research involving data sets

There are many considerations when selecting a statistical model. Rarely there is only one 'right' method; sometimes a well-established simple model is sufficient, while newer complex models may be needed to correctly represent the patterns in a complex data set. The best model is one that explains patterns in the data and is interpretable. The statistical model must be fit for purpose and able to:

1. Answer the actual research question (e.g. associations, causal inference, or prediction)
2. Fit the study design (e.g. cross-sectional, longitudinal, or evidence synthesis)
3. Be suitable for the data set (type of variables, size of data set, quality of data)

There is a complex relationship between research characteristics and statistical models (Figure 26.1). For research questions on associations, non-parametric tests, or simple regression analyses can suffice. *Example: Whether the prevalence of breast cancer is higher in urban compared to rural areas.* For causal inference questions, the statistical model depends strongly on study design and available data. *Example: Does smoking cause breast cancer?* To answer causal inference questions using cohort data, statistical models need to allow adjustment for confounding, which in turn requires a larger sample size. With the emergence of large and very large data sets such as genetic data, newer methods such as Mendelian Randomization, a method to adjust for residual confounding which is not easily captured in epidemiological studies, have been used.

For research questions focused on prediction, regression models can often be applied. *Example: whether 10-year survival can be predicted by age at diagnosis.* However, these models usually require researchers to make decisions on type and number of predictors, modelling of non-linear effects and possible interaction terms (14). To avoid this, supervised or unsupervised machine learning models such as neural networks, classification trees, or cluster analysis can explore associations or predictions.

An important, relatively recent trend is to include health services and economic aspects within trials. In addition, most RCTs now give significant weight to PROMs and patient-reported experience measures (PREMS). These ideally have both quantitative and qualitative aspects, requiring broad statistical expertise for both the design and analysis phases of clinical studies.

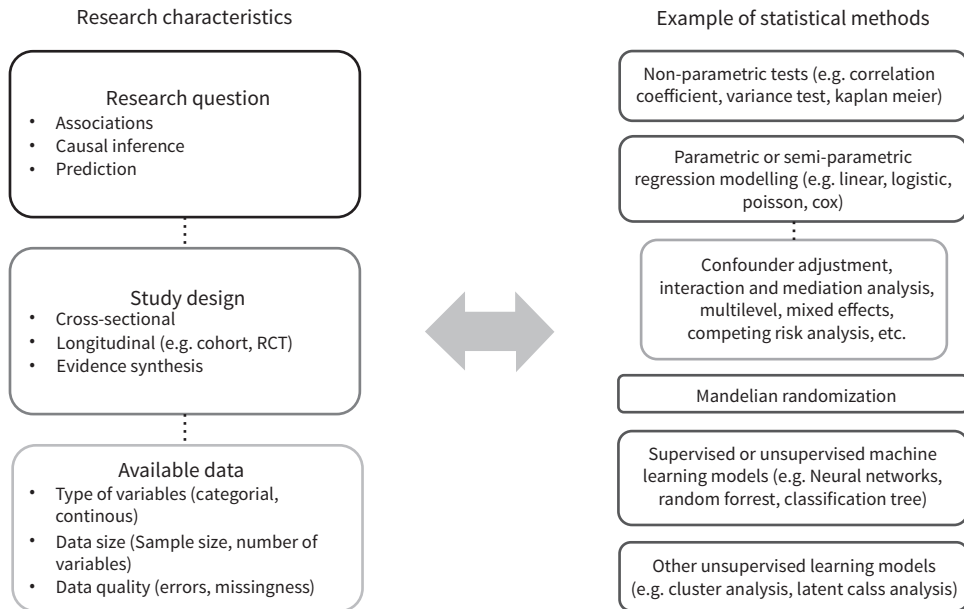


**Figure 26.1** Interplay between research characteristics and choice of statistical method.

There is a modern emphasis on reducing unnecessary exclusion criteria and ensuring collection of PROMs, as well as incorporating health economic analyses. To ensure trials are more representative of real-world populations, the FDA has recently mandated steps to increase participation of underrepresented racial and ethnic populations.

## New clinical trial methodologies

Novel and particularly adaptive trial designs, such as master protocols, N-of-1 trials, basket, and umbrella trials, have significantly evolved in response to the challenges of assessing targeted drugs and multiple drugs within one class, as well as the use of complex multimodal imaging and combinations of biomarkers. Bayesian designs have significant strengths, although as cancer therapy evolves, there will likely need to be further optimization of trial methodologies. The number of these trials is rapidly increasing (15). For breast cancer, the I-SPY 2 trial (clinicaltrials.gov NCT01042379) was a landmark study, using an adaptive design which allowed investigators to add newly available options and patients to change treatments within the one study.

Although the RCT remains the gold standard for determining causal inference, ethical considerations, expense, under-recruitment, and the need for clinical equipoise continue to pose challenges. One alternative to randomization is use of virtual controls, where advanced prognostic models are used to predict the risk of the outcome without an intervention. This allows all recruited participants to then access the new intervention. Another alternative is registry-based RCTs, where registry participants serve as the control group. This saves time and cost recruiting a control group.

## Lessons from the pandemic

The COVID-19 pandemic had a devastating impact on all aspects of healthcare, with breast cancer care no exception (16). The halt in screening led to more advanced stage at diagnosis,

and surgical delays translated to reduced overall survival. The US National Clinical Trials Network (NCTN) reported a reduction of 42% and 44%, respectively, in accrual to the 61 breast cancer screening and intervention studies open in 2020. A corresponding 40% decrease in specimen receipt and 60% decrease in distribution was reported from NCTN Biobanks. The FDA, the European Commission, the Italian Medicines Agency and many other bodies issued special guidance for the conduct of clinical trials during the COVID-19 emergency, providing recommendations to assist industry, investigators, and institutional review boards to ensure the safety of human subjects.

The pandemic provided opportunities for practical innovation, and as a positive unintended consequence, actually accelerated many long-discussed innovations in clinical trial design. Foremost among these was the adaptation of decentralized (also called hybrid) trials, which take a patient-centric approach by decreasing or eliminating the time, financial, and logistical burden of travelling to a trial centre to receive study testing or treatment, with little to no impact on data quality (17). These trials utilize telemedicine, mobile or local health providers and/or mobile technologies to allow remote participation. Safety concerns about travelling to clinical trial sites, temporary closure of sites, and the need to reduce exposure to COVID-19, especially for neutropenic and other medically vulnerable patients were key factors that drove the rapid adoption of decentralized clinical trial models. Persisting social factors, such as increasing work from home and more flexible work patterns have permanently impacted trial participation, both positively and negatively; for example, increased availability of carers for transport.

The pandemic disproportionately affected people with breast cancer, who face health disparities (18). Theoretically, decentralized trials should reduce inequities and improve access for diverse populations, although data is needed to confirm there are no unintended consequences, such as excluding people without technological devices or know-how, which may bias against older people or those of lower economic status.

## Patient and public involvement (PPI)

PPI is defined as research that is carried out ‘with’ or ‘by’ members of the public and not simply ‘to’, ‘about’ or ‘for’ them (19). PPI is founded on reciprocity to the ultimate funders of clinical research, i.e. the taxpaying public. Breast cancer research is an exemplar for adopting PPI activities, which can be implemented at any phase of a research project, including the identification of the research question, study design development, management, and study process, data analysis, communication and implementation, and evaluation (Figure 26.2).

In the setting of breast cancer research, PPI contributors should include people with a current or previous diagnosis, caregivers, and advocates from formal patient organizations. Additionally, inclusion of other stakeholders, such as people with premalignant breast disease, males with breast cancer, and people with a false positive screening result, may also provide valuable insights. PPI is a key strategy in addressing the pressing issue of underrepresented subpopulations in breast cancer trials (20). Data on trial enrolment from the USA showed underrepresentation of older adults in breast cancer trials between 2015 and 2019. Among breast cancer patients aged 65 years and older, only 1% were enrolled into clinical trials, while among patients aged less than 65 years, almost 4% were enrolled into clinical

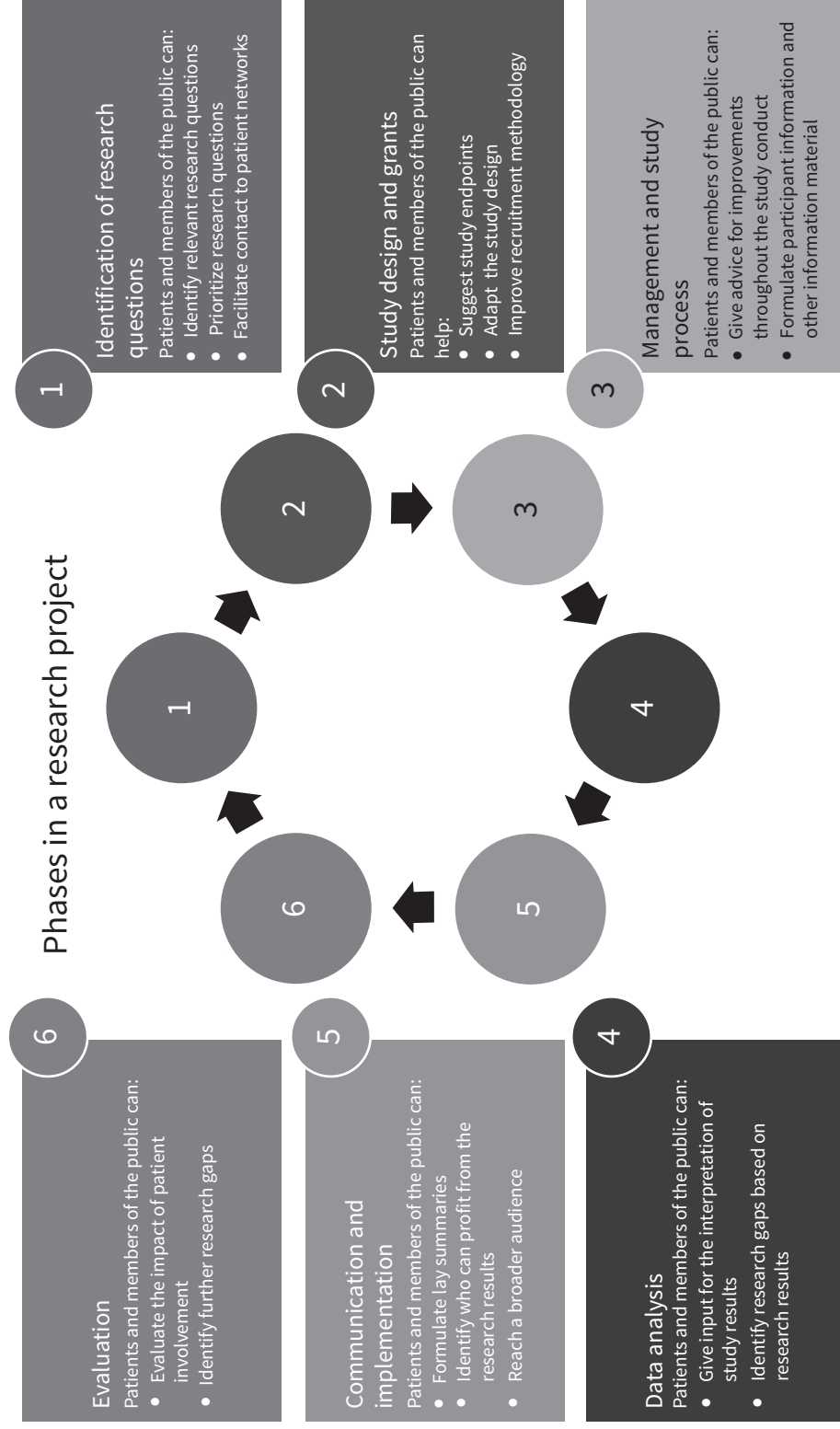


**Figure 26.2** Implementation of PPI at different study phases.

Adapted with permission from the Swiss Clinical Trial Organisation (SCTO). Organisation SCTO: Patient and public involvement, factsheet: Swiss Clinical Trial Organisation; 2024. Available from: <https://www.scto.ch/en/patient-and-public-involvement.html>

trials (21). Further, while approximately 1% of breast cancer cases occur in males, men comprise only 0.4% of patients enrolled in breast cancer trials between 2000 and 2017 (22).

As PPI has become standard in cancer research due to perceived benefit on study design (feasibility, recruitment, compliance) and above all, ensuring that study goals are relevant for patients (23), research on PPI to document benefit and measure specific impact in breast cancer is emerging. One trial of 674 adults with breast cancer showed that shared decision making aids developed in collaboration with patient-representatives improved patient engagement in the trial process (24). More broadly, a meta-analysis of studies, including breast cancer patients, showed that PPI interventions increased the odds of a patient enrolling in a clinical trial by about 16% (23).

## Key messages

- Improved prevention, screening, diagnosis, and therapeutic strategies tested through rigorous research protocols have contributed to a decrease in breast cancer deaths.
- Advances in pre-clinical research include sophisticated and integrated laboratory technologies and bioinformatics for assessing ‘-omics’, molecular imaging, and molecular epidemiology.
- Improvements in surgical techniques, radiation, and systemic therapies have led to decreased toxicity, and improved QoL among breast cancer patients.
- Real-world data is essential for validating and quantifying the impact of RCT findings.
- As breast cancer survival rates further improve, an emphasis on clinical research on physical, social, and psychological health among survivors is vital.
- Addressing global disparities in breast cancer research is a high priority and requires investments in clinical research, improving research networks, and supporting population-based cancer registries.
- The COVID-19 pandemic led to delays in clinical trials but paved the way for practical innovations such as decentralized trials, with decreased burdens (travel, financial, time) for study participants and their families and carers.
- Evolving clinical trial designs and statistical methods for analysing data have expanded opportunities for new and more complex research questions and should reduce the lengthy time for innovations to reach a standard of care.
- The value of PPI is increasingly recognized and adopted in all aspects of breast cancer research.

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## Barriers for research

A perspective from LMIC

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### Introduction

Research in the field of breast cancer has led the way with a huge impact on patient outcomes. Global collaboration in breast cancer research has made significant strides and progress over the past few decades, with advances in technology, increased understanding of cancer biology and international partnerships. However, these collaborations are limited to high-income countries (HIC) and the extent and efficacy of global cooperation remain uneven, particularly from the perspective of researchers in low- and middle-income countries (LMIC). The African continent accounts for 15% of the world's population, but accounts for only 2% of world research. These disparities underscore the need to identify and address gaps and barriers to foster a more inclusive and effective global research network (1). The Pan African Clinical Trial Registry (PACTR; <https://pactr.samrc.ac.za>), available as an open-access platform, reported in 2025 only 53 breast cancer-specific trials in 88 recruitment sites in Africa, with 34 trials in Egypt, 15 in Kenya, 12 in Ethiopia, 11 in South Africa, and 8 in Nigeria, respectively.

According to the International Agency for Research and the WHO report, the incidence of cancer cases is growing in LMIC as the proportion of the ageing population increases and traditional risk factors such as smoking, unhealthy diet, physical inactivity, and harmful use of alcohol result in a disproportionate share of morbidity and mortality in LMIC. Breast cancer is currently responsible for the highest number of cancer deaths in LMIC. Data on age-standardized cancer prevalence estimate that one in 10 new cancer cases is diagnosed in a patient aged 20–39 years in the developing world (2). Inadequate diagnostic and treatment options (3) and a limited progress in understanding the African genome are important factors in the increasing mortality.

### Current state of global collaboration in breast cancer research

Over the past several decades, there has been an increase in global cooperative activity in the areas of science and knowledge, with a focus on global grand challenges (large, complex problems that require collective action on a global scale). Indeed, the scale and complexity of these



### Box 27.1 Illustration: The African Breast Cancer—Disparities in Outcomes (ABC-DO) Study

The ABC-DO study exemplifies successful international cooperation in breast cancer research (11). This multi-country study, funded by international agencies, investigates disparities in breast cancer outcomes across different African countries. It involves researchers from both HIC and LMIC working together to collect and analyse data, with a focus on understanding how socio-economic, cultural, and healthcare factors impact breast cancer prognosis.

Key outcomes of the ABC-DO study include:

Large variations in breast cancer survival in sub-Saharan African countries were found, indicating that improvement is possible.

- Identification of barriers to early diagnosis and treatment.
- Development of context-specific intervention strategies.
- Training of local researchers and healthcare workers in advanced research methodologies.

*Source:* data from McCormack V, McKenzie F, Foerster M, et al. Breast cancer survival and survival gap apportionment in sub-Saharan Africa (ABC-DO): a prospective cohort study. *Lancet Glob Health* 2020;8(9):e1203–12.

global challenges necessitate cooperation across national borders by researchers from different countries. The current landscape of global collaboration in breast cancer research is characterized by robust networks primarily driven by HIC. Initiatives like the Breast Cancer Research Foundation (BCRF), International Breast Cancer Study Group (IBCSG), and multinational clinical trials have set benchmarks for cooperative research. These collaborations facilitate knowledge exchange, standardized treatment protocols, and enable large-scale epidemiological studies. Despite these advances, researchers in LMIC often face systemic challenges that hinder their participation (4). Limited funding, inadequate infrastructure, and a scarcity of trained personnel are significant obstacles. Furthermore, the research agendas in LMIC may not align with those of HIC, leading to gaps in addressing region-specific breast cancer problems. There are therefore concerns about how to ensure that LMIC derive tangible benefits from international collaborative research projects and how to guarantee ethical behaviour by all stakeholders and transparency of processes (5) (see Box 27.1). The conduct of clinical trials is ‘high on the list’ of enterprises which can leapfrog Africa into the recommendations of ranking bodies like Bloomberg. ‘Adopt New Technologies and develop capacity to nurture innovation as the only strategy to move Africa up the development ladder.’ To bridge these gaps and enhance global cooperation, the following key concepts must be embraced.

## Equitable resource allocation

There is a need for equitable distribution of funding and resources to ensure LMIC researchers have access to modern laboratories, advanced technologies, and training programmes. Funding bodies and international organizations should prioritize investments in LMIC research infrastructure (6). AORTIC (African Organization for Research and Training

in Cancer) was formed in 1983 by African cancer care workers (<https://aortic-africa.org>). Their mission is to transform cancer control in Africa through collaboration in education, research and delivery of equitable and timely interventions to minimise the impact of cancer.

## **Capacity building and training**

The key step in engaging the researchers from LMIC requires training programmes aimed at enhancing the skills of researchers and healthcare providers. Capacity building initiatives should focus on advanced research methodologies, data analysis, and clinical trial management (7).

## **Context-specific research agendas**

Collaborative research should prioritize the unique epidemiological and cultural contexts of LMIC. Studies must address local risk factors, genetic predispositions, and environmental influences on breast cancer (8).

## **Ethical and inclusive partnerships**

Partnerships between HIC and LMIC institutions should be based on mutual respect, ethical standards, and inclusivity. Researchers from LMIC should be involved in all stages of the research process, from planning to publication (9). Data integrity of clinical trials conducted in Africa remains a concern of the Pharmaceutical companies which needs addressing by laying the foundations for research governance in LMIC.

## **Data sharing and open access**

Creating platforms for data sharing and ensuring open access to research findings can enhance collaboration and accelerate scientific discovery. Data repositories and collaborative databases can facilitate cross-border research efforts (10).

## **Opportunities and facilitators to promote global cooperation**

Promoting global cooperation in breast cancer research requires a concerted effort from multiple stakeholders (12):

## **Increased funding and grants**

International funding agencies and philanthropic organizations should increase grants dedicated to breast cancer research in LMIC. Funding should support infrastructure development, training programmes, and collaborative projects.

## Policy advocacy and support

Governments and policy-makers in LMIC should prioritize cancer research and create conducive environments for international collaboration. Policies that incentivize partnerships with foreign institutions can drive progress.

## Technological advancements

Leveraging technology to bridge the gap between HIC and LMIC researchers is crucial. Telemedicine, virtual conferences, and online training modules can facilitate knowledge transfer and collaborative work (see Chapter 25) (13).

## Creating collaborative networks

Establishing global networks and consortia that include LMIC researchers can enhance collaboration. Platforms like the Global Breast Cancer Research Initiative (GBCRI) can coordinate efforts and ensure that LMIC voices are heard.

## Public-private partnerships

Engaging the private sector in funding and resource allocation can provide additional support for breast cancer research. Pharmaceutical companies, tech firms, and healthcare providers can play pivotal roles in driving innovation and research. In 2017 under the purview of African Access initiative (AAI), The African Consortium for Cancer Clinical Trials (AC3T) was launched by BIO Ventures for Global Health (BVGH) to build an oncology clinical trial capacity in African countries while improving patient outcomes (14) <https://bvgh.org>.

## Recommendations for enhancing global cooperation

One key recommendation to enhance global cooperation for breast cancer research to reduce health inequalities and inequity in breast cancer, particularly between HIC and LMIC, is to establish a specific and tailored breast cancer research platform for LMIC. Furthermore, increased and sustained resources or funds must be provided to ensure that breast cancer research is sustainable and supported for bi-directional collaborations that include long-term relationships rather than ephemeral collaborative links (15). Moreover, capacity building initiatives for health researchers can be enhanced to attract early and mid-career researchers to engage with opportunities in global health research and to become principal investigators (16). Opportunities for collaborations in breast cancer research should also be facilitated. The creation of adequate regulatory, administrative, and management frameworks is needed to ensure quality and ensure protection to research institutions that may collaborate with various countries. The role of supranational organizations like the WHO, IARC and the UN

in promoting regional capacity building to enable ‘contribution’ to global knowledge and ensure social benefits is of utmost importance (17). Lastly, an international collaboration with well-defined roles should ensure that LMIC researchers are treated as equal partners in such collaborations (18).

## Key messages

- LMIC have different cancer statistics, research priorities, capacity, and health systems than HIC. Drugs administered on the African continent must be optimized for African patients.
- Research findings of HIC are not necessarily relevant in LMIC and there is urgent need of more regionally oriented relevant research.
- Global cooperation in breast cancer research holds immense potential to address disparities and improve outcomes worldwide. Success will require collaboration between governments, funding agencies, researchers, and the community.
- Focusing on equitable resource allocation, capacity building, context-specific research, ethical partnerships, and data sharing will lead the global community to a more inclusive and effective research landscape.
- By addressing the barriers and leveraging opportunities, the global research community can make substantial strides towards equitable and impactful breast cancer research.
- LMIC present excellent opportunities to address important questions with a potential for global impact.
- Pharmaceutical companies must invest in clinical trials on African soil. This is a tangible way to address racial inequity in global drug development.

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## Challenges and threats

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### **Do clinical trial designs meet the needs of patients with breast cancer?**

Despite the advances in breast cancer research, a gap remains between clinical trial design and patients' needs. New anticancer agents have reached clinical practice faster than in the past, but some redundancies remain in their development. For instance, assuring equity and diversity in access to clinical trials remains a major challenge worldwide. Efforts should be made to design inclusive registration trials or generate evidence on unmet-need clinical settings such as subpopulations of ethnic/racial minorities, younger or older patients, male breast cancer patients, or patients with brain metastases (1). Moreover, improvements in progression-free survival or disease-free survival (DFS or invasive DFS) are rarely translated into overall survival and/or quality of life gains. In the metastatic setting, despite the efforts of validating response rate (2) and/or progression-free survival (3) as overall survival surrogate endpoints, post-progression treatment crossover should be considered for assessing the impact on overall survival. Therefore, it is critical to stimulate pragmatic trials aiming to investigate optimal treatment sequencing strategies, focusing not only on survival endpoints but also on quality of life (e.g. patient-reported outcomes) and cost-effectiveness (4). In the early setting, many adjuvant trials are underpowered for overall survival, and those that consider this in their design frequently struggle with long-term follow-up and patient retention. Although pathologic complete response is an acceptable surrogate endpoint for regulatory conditional approval in early breast cancer (5), registrational neoadjuvant trial design should seek co-primary outcomes that incorporate a survival endpoint for proper confirmatory evidence. The commonly used endpoints might not be the most appropriate for all disease types (e.g. proliferative biomarkers are better surrogate endpoints than complete pathological response in luminal disease) (6) or treatment class (e.g. onset, depth, and duration of response are different for immunotherapy). The use of promising novel surrogate endpoints, such as circulating tumour DNA (7) or early metabolic response by PET-CT scans (8), should be stimulated, but the study design frequently misses their integration with a patient-centred approach (e.g. post-neoadjuvant treatment strategy modelled based on circulating tumour DNA clearance).

Patients should play an active part in the clinical trial design, and patient-centred clinical research is needed for optimizing patients' compliance in the trial conduction and improve clinical impact of the results. They have the right to benefit from more innovative approaches of drug development, but also the right to optimized patient care pathway and proper

supportive care investigation to improve or maintain quality of life during and after treatment. Collecting additional biopsies can help researchers predicting tumour response, but this invasive procedure should result on a tangible benefit to the patients. Improved understanding of informed consent is also needed for patients' involvement. Optimizing informed consent remains the responsibility of the treating physician, but this task should be facilitated by communication training by qualified professionals and shorter or less complex forms (9).

We also need closer collaboration between the large pharmaceutical industry, small biotech companies, investors, collaborative research groups, clinical trialists, and patient representatives. High-performing sites are essential for the efficient conduction of clinical trials, particularly for early phase trials in collaboration with biotech companies. Improved cross-border access for early phase trials and de-bureaucratization and de-centralization for large registrational clinical trials should not be neglected (1). True standards for research centres must be developed to assure independent, transparent, and effective research units, streamlining the acceptance of its value by trial sponsors, contract research organizations, patients, regulators, and researchers. An emphasis on a culture of competence and high performance is most relevant for robust accreditation (10).

Importantly, in low- and lower-middle-income countries, the challenges of clinical trial design are even more pronounced. Resource limitations, such as inadequate healthcare infrastructure and limited access to advanced diagnostic tools, pose significant challenges. Additionally, diverse patient demographics, genetic backgrounds, and disease presentations in these regions are not always considered in global trial designs. It is essential to develop more inclusive and adaptable trial protocols that account for local realities and ensure broader representation in breast cancer research. Efforts to enhance local capacity through training and infrastructure development, as well as fostering international collaborations, are critical for closing the gap between clinical trial design and patient needs in these regions (11).

## Challenges of clinical research and precision medicine

In the era of precision medicine, there is an urgent need for optimized drug development methodology. More biomarkers are being studied as treatment target for patients' selection, prognostic/predictive value, or as surrogate endpoints. Their use in clinical trials is currently being challenged by the European regulations on *in vitro* diagnostic medical devices (IVDR), and there is a need for guidance on efficient biomarker development (12). It is critical to achieve proper analytical and clinical validation of biomarkers in preclinical and early phase trials, respectively, before its use in late phase trials and their translation to clinical practice. Therefore, new trials must integrate translational research with clear potential for clinical practice, and sponsors might consider questioning case-by-case the utility of trial methodological burdens (13), reconducting resources to translational research objectives. Although precision medicine is highly promoted among clinicians and patients, a limited number of actionable/targetable mutations have been described in breast cancer. Despite the identification of a targetable mutation in 46–73% of patients tested with next-generation sequencing (NGS), only about 9–13% receives molecularly guided treatment or is enrolled in genomically matched clinical trials (14). However, the ESCAT tier upgrade of ESR1 mutations to level IA in oestrogen receptor-positive/HER2-negative advanced breast cancer (15), and the recently

demonstrated 93% sensitivity for detection of germline alterations of genes related to homologous recombination deficiency in tumour NGS (16), have led ESMO to recently recommend the use of NGS in clinical practice for advanced breast cancer (17). The increasing use of NGS across tumour types and the low prevalence of each actionable/targetable molecular alteration, even in common cancers as breast cancer, will urge rethinking molecularly guided treatment trials towards a novel tumor-agnostic drug development framework to facilitate timely evidence generation for these rare subpopulations, avoiding delayed access to tumour-agnostic indications (18).

The implementation of precision medicine is hindered by significant barriers in low- and lower-middle-income countries, including limited access to advanced technologies such as NGS, insufficient funding, and lack of infrastructure to support comprehensive genomic research. Legal frameworks can constrain the exportation of samples to central laboratories located outside the participating countries, further complicating the logistics and increasing the turnaround time for results. Mitigation requires a multifaceted approach with increasing investment in healthcare infrastructure, enhancing training for local healthcare professionals, and fostering international collaborations to provide the necessary resources and expertise. Moreover, developing cost-effective and scalable solutions for biomarker testing and molecular diagnostics is crucial to ensure that the benefits of precision medicine can be expanded to all breast cancer patients, regardless of geographic location or economic status (19).

## **Bridging the gap between innovation and clinical practice**

Reforming the health system from an ‘innovation-centred’ to a truly ‘patient-centred’ and value-based health system requires optimal collaboration between all stakeholders in drug development, clinical trial design, and regulatory/health technology assessments. For instance, regulators’ involvement in early scientific advice has been shown to be associated with a higher likelihood of medicines approval (20). In subpopulations for whom clinical trials are not feasible or unethical, efforts should be made for optimal use of real-world data and accurately report the results of real-world evidence studies (21). The use of real-world evidence for regulatory evaluation of clinical efficacy is increasing (22) and may be used to complement the main evidence from clinical trials. However, regulatory approval by the competent authorities does not guarantee patients’ access to innovative treatments. Each country determines national accessibility and affordability based on its own criteria for pricing and reimbursement. There is a need for a standardized value-based reimbursement model for tackling regional discrepancies in anticancer medicines accessibility (23), that ultimately informs efficient trial design.

On the other hand, trialists and sponsors should optimize trial design for minimizing overtreatment and financial toxicity. Advances during the last decades of adjuvant trials have improved clinical outcomes, increasing the risk of new regimens leading to overtreatment with minimal benefit. Large, well-funded, pivotal adjuvant trials of trendy and expensive medicines are usually designed on a risk-independent escalation approach, adding experimental drugs into standard regimens. However, unselected use of adjuvant therapeutics (e.g. do we need adjuvant pembrolizumab for patients with triple negative breast cancer achieving pathologic complete response?) or potentially too long adjuvant regimens (e.g. do we need



three years adjuvant ribociclib for hormone receptor-positive/HER2-negative breast cancer patients?) may harm the system. Most trials fail to answer practical questions, such as risk-adapted experimental modulation of post-neoadjuvant treatments based on early endpoints (24). Moreover, competitive trials by different companies are performed in similar settings, but comparative studies between drugs of competing companies are rare (e.g. CDK4/6 inhibitors or immune checkpoint inhibitors). These are less fashionable scientific questions, unlikely to be addressed by pharma-sponsored trials. Therefore, funding should be prioritized for academic research focused on these aspects with potential cost-return for society. Scientific journals should promote the results of these academic initiatives, ideally in open access, with special attention to results from negative trials, which are often neglected.

## Challenges and threats to breast cancer research

The performance of pivotal trials for regulatory and reimbursement purposes remains important, but we also need trials with more personalized translational research that makes use of well-designed biomarkers and a biological rationale, focused on a patient-centred approach. To be successful, we need a new and pragmatic model for clinical research networks between stakeholders to bridge the gap between innovation and clinical practice, reaching all breast cancer patients, regardless of geographic location, gender, ethnicity, or economic status. This improvement in trial design should encompass endpoints that more accurately reflect patient needs (25). Together, all stakeholders must ensure accountability and make the best use of resources (Figure 28.1).

Highly selected eligibility criteria are an important bias in clinical trials, and the population addressed in clinical research cannot be seen as a window to the real-world. Equity and diversity in clinical trial accessibility should be fostered and the use of real-world data may provide important complementary evidence for comparative effectiveness assessment in underrepresented subpopulations or as external comparator arm of single-arm phase II trials, whenever randomization is impractical or unethical.

## Key messages

- There is a need to tackle disparities in clinical trial access, regardless geographic location, gender, ethnicity, or economic status, particularly for underrepresented subpopulations.
- Facilitating cross-border access for trials conducted in specialized centres and promoting de-bureaucratization and de-centralization for large registrational clinical trials.
- Properly funded academic research should address the impact of clinical and financial toxicity of new medicines, investigating optimal risk-adapted therapeutic strategies, such as treatment de-escalation or sequencing.
- Investigators should develop more clinical research to study patient care pathways, supportive care, and quality of life improvement.
- Clear and patient-centred endpoints must be defined and understandable for all stakeholders, and these must take patient needs into account, including patient-reported outcomes.

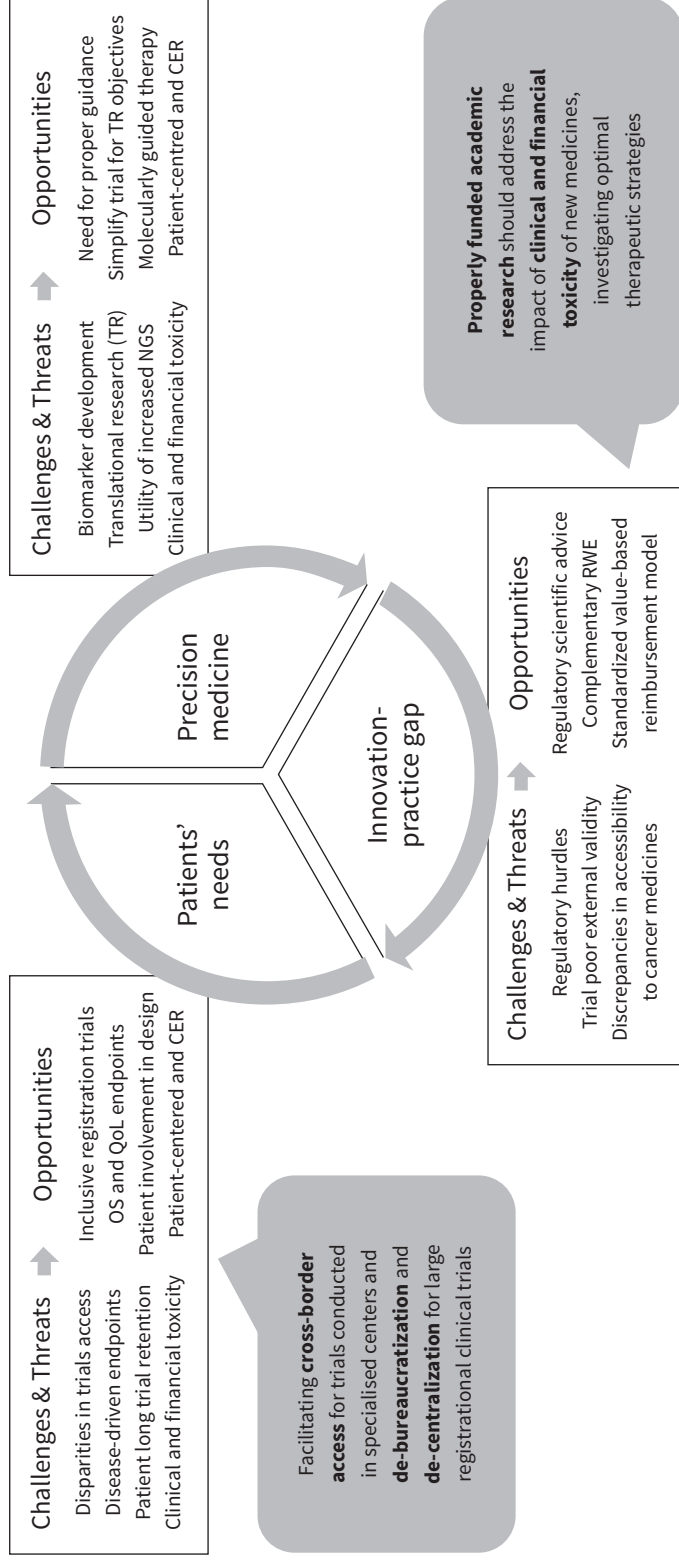


**Figure 28.1** Challenges and threats in breast cancer research and respective opportunities.

CER: cost-effectiveness research, NGS: next-generation sequencing, OS: overall survival, QoL: quality of life, RWE: real-world evidence, TR: translational research

- Interaction between the multiple stakeholders should streamline proper clinical trial design and evidence generation for optimal regulatory and health technology assessment.
- Patients are the risk-takers in the clinical trials and must be represented in the design of the trials. Informed consent has to be understandable for the patients.

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**PART 8**

**ECONOMICS OF BREAST CANCER CARE**



## Costs and value

*Manuela Joore, Xavier Pouwels, Alexandru Eniu, Merel Kimman, and Bram Ramaekers*

### Introduction

The total cost of cancer amounted to €199 billion in Europe (the 27 European Union member states plus Iceland, Norway, Switzerland, and the United Kingdom) in 2018 (1). Health expenditure on cancer care made up half of these costs (€103 billion), of which approximately one-third (€32 billion) is for cancer drugs. The healthcare expenditure differed considerably between countries: from €160 per capita in Romania to €578 per capita in Switzerland. Indirect costs of productivity loss due to premature morbidity (20 billion) and mortality (49 billion) were also considerable. Breast cancer accounted for the highest healthcare expenses of the total cancer-related costs in the European Union (2). Medication costs accounted for approximately 50% of the healthcare costs relating to breast cancer treatment (approximately 3 out of the €7 billion), which represents 20% of the total economic burden of breast cancer in the EU. Similarly, productivity losses due to mortality and informal care are both associated with high costs (both exceeding €3 billion). The total economic burden of breast cancer was estimated to be €15 billion, representing on average €13 per capita in the EU in 2008. Globally, breast cancer accounted for 701 (647–752) thousand deaths in 2019 (3). Improvements in screening, and in systemic treatment of early stage and metastatic stage have improved patient survival considerably over the past decades. In the United States, the age-adjusted breast cancer mortality rate was 48/100,000 women in 1975 and 27/100,000 women in 2019 (4).

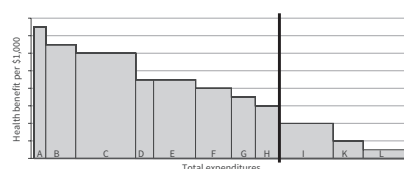
However, the increasing healthcare expenses for screening and treatment may not be sustainable. Several initiatives aim at containing these increasing expenses by preventing overdiagnosis and overtreatment (e.g. Choosing Wisely) (5). Precision medicine (PM) may also be promising for containing healthcare expenses by improving breast cancer treatment efficiency. However, a systematic review of the literature stated that PM interventions were found to have modest health benefits compared with non-PM (6). Further development and implementation of PM may determine whether it contributes to a more efficient use of limited healthcare resources.

Decision-makers resort to health economics to inform reimbursement decisions on new breast cancer interventions. A fundamental objective of health economics is to determine the optimal use of the limited funds that are available (7). The underlying principle is that a decision-maker will allocate the funds available in a way that health is maximized. This means that priorities are set: some interventions are reimbursed, while others are not or only partially (Box 29.1). To make these priority-setting decisions, decision-makers can rely on the results of cost-of-illness studies and budget-impact analysis (to assess affordability),

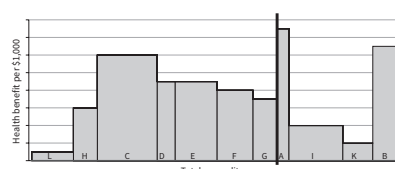
## Box 29.1 Priority-setting using cost-effectiveness to maximize health

To use cost-effectiveness analyses for reimbursement decision-making, it is necessary to specify a willingness to pay threshold, i.e. the amount society should be willing to pay per additional unit of effect, often specified as QALY. Setting this willingness to pay threshold incorrectly (e.g. too high or too low) will lead to opportunity costs and health benefits forgone. This is illustrated below using hypothetical health systems (I-IV), wherein each bar represents an intervention with a certain height (representing the health benefit per \$1,000), and a certain width (representing the total costs of this intervention). The vertical line in the figures represents the budget limit. All interventions left to this line are reimbursed in the hypothetical health system, while the others are excluded given the constrained budget. In health system I, the interventions are prioritized based on cost-effectiveness, as a result, interventions A to H are reimbursed while interventions I to L are not. In health system II, interventions are prioritized based on other criteria than cost-effectiveness, as a result interventions A and B, which generated a relatively large amount of health benefit per \$1,000, are displaced by intervention L which generated a relatively low amount of health benefit per \$1,000. As a result, with the same budget, health system II produces less health (i.e. health benefits forgone) compared with health system I due to prioritization based on other criteria than cost-effectiveness.

I: prioritized based on cost-effectiveness

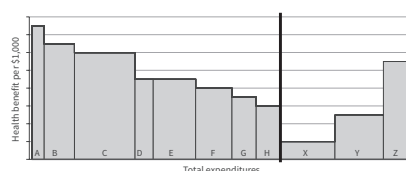


II: prioritized based on other criteria than cost-effectiveness

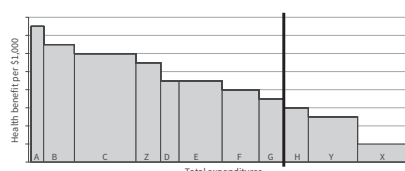


Health system III is confronted with the question of whether to adopt interventions X to Z. From a cost-effectiveness perspective, it should be questioned whether these new interventions produce more health benefit per \$1,000 than the interventions that are already adopted (interventions A-H). Given that the health benefit per \$1,000 for intervention Z is above this 'threshold', this intervention should be adopted as shown in health system IV. Here it also becomes clear that this threshold is inherently dependent on the healthcare budget, for instance, if the healthcare budget increases then the 'threshold' should be altered to also include interventions producing less health benefit per \$1,000 (e.g. readopting intervention H again in health system IV).

III: adopting new interventions (X to Z) in health system A



IV: intervention H is displaced by intervention Z



Source: data from Culyer et al. 'Cost-effectiveness thresholds in health care: a bookshelf guide to their meaning and use'. Health Economics, Policy and Law. Volume 11, Issue 4. pp. 415–32. Copyright © 2016, CUP. DOI: <https://doi.org/10.1017/S1744133116000049>



as well as economic evaluations (to assess efficiency) of new interventions. The following sections contain an explanation of these techniques, as well as examples of applications to breast cancer care. In addition, the use of these techniques in healthcare policy decision-making is described.

## Assessing the costs of breast cancer care

Cost-of-illness (COI) studies estimate the costs associated with a specific condition. A COI study starts with determining the target population, which is a subset of the population with the disease (for instance, patients with HER2-positive breast cancer). The population with the disease is a subset of the general population, which is particularly relevant to consider when a preventive intervention (such as breast cancer screening) is considered, since prevention will impact the incidence of the condition. Once the target population is defined, resource use by patients in this population is estimated. Depending on the perspective, this might include only healthcare resources, or be broadened to include costs in other sectors (productivity, for instance) and patient and family costs (such as out-of-pocket expenses, travel costs, and informal care costs). A distinction can be made between a prevalence-based and an incidence-based approach. In the prevalence-based approach, the resource use of all patients affected in a certain period is considered. In the incidence-based approach, the resource use over the remaining lifetime of incident patients in a specific period is considered.

A budget-impact analysis (BIA) can be used to inform budget planning or evaluation. In a BIA, the expected expenditures associated with the adoption of a new/other healthcare intervention are assessed (8). This means that the COI considering current care is compared to the COI after adoption of the new intervention. In most instances, a cost calculator approach will be suitable to estimate COI and budget impact. However, in cases where characteristics such as the population size, the patient mix, or treatment patterns cannot be credibly captured by using the cost calculator approach, a cohort or patient-level condition-specific model may be used. The advantage of a modelling approach is that it allows for appropriate handling of patients entering and leaving the eligible population over time (Figure 29.1).

A cost-of-illness study based on real-world data from 597 patients in 2010-2014 from the Netherlands showed that the average lifetime hospital costs of patients with advanced breast cancer were €52 709 (standard error €405) (9). Costs differed considerably between patient subgroups, ranging from €29 803 for patients with a triple-negative subtype to €92 272 for patients with hormone receptor-positive and human epidermal growth factor receptor 2-positive cancer. Apart from the cancer subtype, several other factors, including age and survival time, were independently associated with patient lifetime costs. Overall, a large share of costs was attributed to systemic therapies (56%), predominantly to a few expensive agents, such as trastuzumab (15%), everolimus (10%), and bevacizumab (9%), as well as to inpatient hospital days (20%).

BIAs are used by budget holders. Who holds the healthcare budget differs between jurisdictions, and may include administrators of national healthcare programmes or private insurance plans, employees of healthcare delivery organizations, and employers who pay for healthcare of their employees. It is important to tailor the perspective of the BIA to the budget holder. The Professional Society for Health Economics and Outcomes Research (ISPOR)

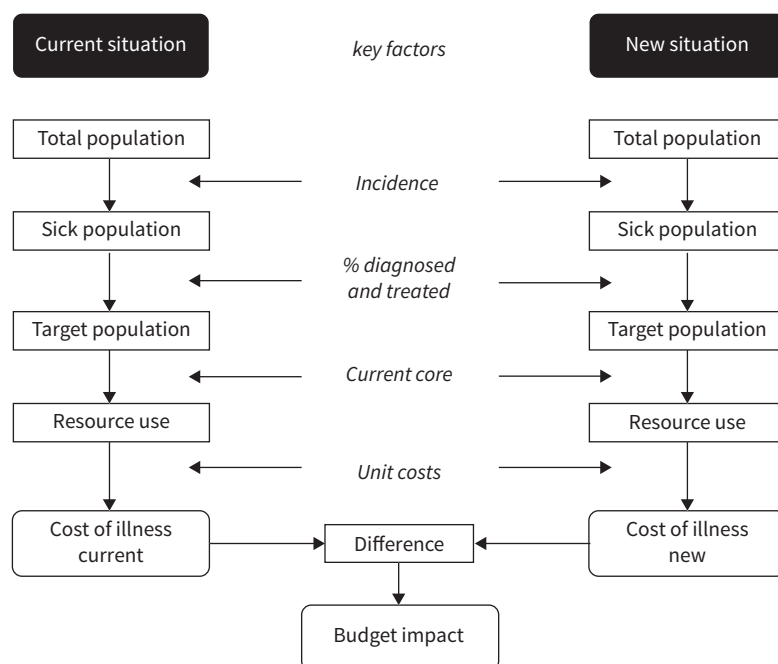


**Figure 29.1** Cost of illness and budget impact analysis.

Adapted with permission from Sullivan et al. 'Budget Impact Analysis-Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II task force'. *Value in Health*, Volume 17, Issue 1, pp. 5–14. Copyright © 2014 Elsevier Inc. DOI: <https://doi.org/10.1016/j.jval.2013.08.2291>

published principles of good practice for BIA (8). In this publication, an analytical framework containing all important aspects in the design of a BIA is described in detail.

## Assessing value for money of breast cancer care: economic evaluation

Economic evaluations compare the costs and effects of at least two interventions. The difference in costs is divided by the difference in effects between the new and old interventions to obtain an incremental cost-effectiveness ratio (ICER) (Figure 29.2).

Economic evaluations of breast cancer care are mostly cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). These two types of economic evaluation differ in the way effects are measured and valued. In a CEA, the effects are expressed in natural units, such as the number of life years gained or the proportion of patients with serious toxicity avoided. An outcome worth mentioning is the ESMO Magnitude of Clinical Benefit Score. This is a score to assess the magnitude of the relative clinical benefit from cancer therapies on survival and quality of life (or surrogate endpoints for these outcomes) (10). In a CUA, the effects are expressed in quality-adjusted life years (QALYs). QALYs are a combined measure of survival and health-related quality of life, with one QALY representing one year in perfect health. The health-related quality of life valuation used to calculate QALYs is often referred to as utility, and is mostly obtained using instruments such as the EuroQol 5 dimensions 5 Level

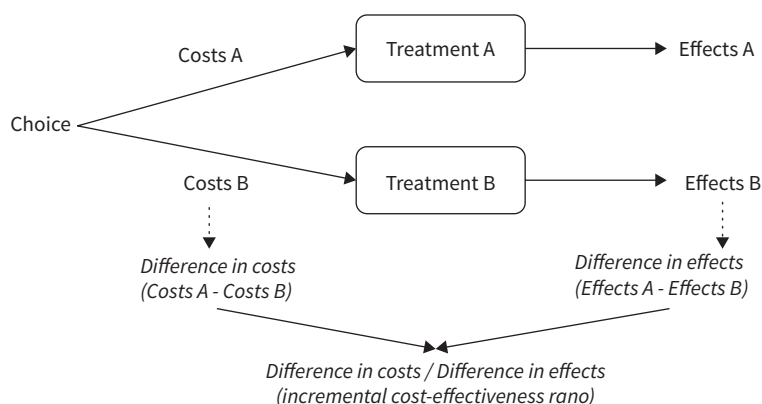


**Figure 29.2** Cost-effectiveness and cost-utility\* analysis.

\* In cost-utility analysis the effects are expressed in quality adjusted life years.

(EQ-5D-5L) (11) or the 36-Item Short Form Survey (SF-36) (12). These instruments (so-called multi-attribute utility instruments) combine a descriptive part containing questions regarding health that is completed by patients and results in a score which can be converted in a utility value using a tariff. This utility represents the value of a health state, from the perspective of the general public. Alternatively, patient's preferences for health and healthcare can be used as outcome in economic evaluations. The advantage of CEA is that it has a very clear link to the outcomes in clinical trials. The advantage of CUA is that the results of CUAs can be easily compared across all populations and for all types of interventions because the measure of effect (the QALY) is generic.

Several good practice guidelines and handbooks exist on methods for economic evaluations in healthcare and for measuring and valuing health effects in economic evaluations (7, 13, 14). There are two approaches to conducting an economic evaluation: trial-based and model-based. Trial-based economic evaluations are conducted alongside clinical trials, in which resource use is collected, besides clinical outcomes and multi-attribute utility instruments if a CUA is planned. These economic evaluations serve primarily the purpose of information gathering. Model-based economic evaluations consist of a model (a series of mathematical and statistical relationships) that describes disease progression and clinical events based on all available knowledge. Model-based economic evaluations are evidence synthesis tools to estimate the performance of an intervention in the real-world context for which a decision must be made. This context often is or cannot be observed in a trial. For instance, the trial follow-up may be too short to capture all consequences, the patient population is not representative of the real-world situation, and often not all relevant comparator interventions are observed in a single trial.

It is considered good practice to assess uncertainty surrounding the (incremental) costs, effects, and cost-effectiveness ratio. Because costs are often skewed, bootstrapping is recommended to construct confidence intervals when performing a trial-based economic evaluation. The costs and effects are calculated from each bootstrap sample, and these bootstrap estimates are then used to build up an empirical distribution of costs and effects. The number of bootstrap samples required depends on the sample data, but typically should be at least 5,000 (15). The bootstrap results are often plotted on an incremental cost-effectiveness plane;

a figure with the incremental costs on the y-axis and the incremental effects on the x-axis. A similar approach to assess uncertainty in model-based economic evaluation is called a probabilistic analysis.

To show the probability an ICER is acceptable to decision-makers, the value of the unit of effect (in CUA the QALY) has to be known. This value is established in some jurisdictions. An intervention is considered cost-effective if the ICER is below this value. The National Institute of Health and Care Excellence in the United Kingdom for instance uses a threshold of £ 30,000 for most types of intervention (16). In situations where the threshold is uncertain, a cost-effectiveness acceptability curve can be drawn, based on the results of the bootstrapping, by calculating the proportion of bootstrap replicates below the threshold for a range of thresholds.

## Priority-setting and managed entry agreements in healthcare

Given that health maximization with available resources is often one major objective of health systems, it is increasingly recognized that the mere effectiveness of a new intervention is not a persuasive case for inclusion in public insurance plans (Box 29.1). To illustrate this, Dakin et al. (17) estimated that cost-effectiveness alone correctly predicted 82% of the reimbursement decisions in the UK. Nevertheless, other factors are often considered next to cost-effectiveness when making these decisions. In the UK and the Netherlands, the willingness to pay is higher depending on the severity of the condition considered (18, 19).

Based on the cost-effectiveness evidence and other relevant criteria, decision-makers might decide whether to reimburse a (new) intervention. However, these decisions are often made under considerable uncertainty, making the trade-off between these different criteria difficult. In response to this uncertainty and growing financial risks (due to the increasing costs of medical technology), decision-makers increasingly opt for managed entry agreements (MEAs; also termed risk-sharing agreements) instead of a simple yes/no recommendation (20). MEAs are arrangements, typically between payers and manufacturers of an intervention and might involve (i) effective price changes/discounts (either dependent or independent on outcome), and (ii) the collection of evidence while the technology is temporarily adopted within a health system. In case MEA schemes are well designed and used appropriately, these arrangements can help decision-makers to optimize recommendations regarding the adoption of interventions in a predictable, transparent and rational manner (21, 22).

## Key messages

- Social healthcare expenditures, of which a considerable part is due to breast cancer care, are rising to levels that may not be sustainable in the future.
- To assist stakeholders in making decisions to secure the quality of breast cancer care while budgets are under pressure, several health economic analysis are available.
- A value-based price threshold can guide the allocation of limited resources to achieve high-quality care.

- The regulation should ensure that cancer diagnostic and treatment innovations enter the market because of not only their potential benefit but also their demonstrated comparative cost-effectiveness.
- Reimbursement decisions should not be based only on the results of traditional randomized controlled trials, but they should also include real-world data from population-based cancer registries and other sources.
- In an increasing number of jurisdictions, a threshold for an additional unit of health gain, expressed in a quality-adjusted life year, is used to determine whether a therapy provides value for money.
- Value should be defined around the breast cancer patient, in a well-functioning health-care system. The creation of value could even determine the rewards available to care providers.
- Economic evaluations of new and existing therapies can be used to inform budget allocations in a way that maximizes health outcomes and broaden the values to the patient.

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## Essential breast cancer medicines

*Didier Verhoeven and Helena Earl*

### Introduction

The estimated global economic cost of cancers from 2020 to 2050 is \$25.2 trillion in international dollars (at constant 2017 prices), equivalent to an annual tax of 0.55% on global gross domestic product. The three cancers with the highest economic costs are respiratory cancer (15.4%), colorectal cancer (10.9%), and breast cancer (7.7%). Globally, it has been estimated that breast cancer had an economic cost of 1.964 trillion international dollars in 2017 (1).

Healthcare spending per capita by source of funding varies considerably among high-income countries (HIC), middle-income countries (MIC), and low-income countries (LIC). Understanding the cost (in LMIC) is limited but critical to guide effective delivery strategies. Nevertheless, there has been substantial growth in the number of breast cancer economic evaluations in LMICs in the past decade. The per capita healthcare spending in 2019 was reported by the World Bank database ([www.dataworldbank.org](http://www.dataworldbank.org)) to be 34 in LIC, 96 in LMIC, and 5635 US Dollars in HIC. In Malaysia, healthcare financing is largely subsidized by public funding of about 51% of total healthcare spending. An important issue particularly for patients is out-of-pocket expense, namely medical care, which is not reimbursed by insurance or government payments. In 2020 this out-of-pocket spending soared to 43% of total health spending in the nation. Nigeria's health spending per capita remains even lower but with an out-of-pocket expenditure on healthcare estimated at three-quarters of the nation's healthcare expenditure in 2018. A large percentage of the Nigerian population is unable to afford—and has limited access to—cancer treatment services. In LMIC, and even in some HIC a breast cancer diagnosis can be a financial catastrophe leading to important problems for the patient and family. Medical bill problems include unexpected insurance denials, co-pays, deductibles, and out-of-pocket expenses. The rate of financial toxicity for patients with breast cancer was 78% in low-and middle-income countries and 35% in high income countries. Access to cancer drugs is a complex problem, with cost being a major barrier to optimal treatment (2–4).

Molecularisation of cancer in terms of understanding it through molecular-level factors such as genes and hormone receptors rather than environmental or behavioural factors, has led not just to its pharmaceuticalization but also to medicines gaining a dominant position in the social psyche of breast cancer care (3). The commercial model that delivers low-value, high-priced cancer medicines also incentivises poor drug development. Potential strategies

to address drug access include not only universal health coverage for essential cancer medicines but also fair drug pricing, optimizing regulatory demands and improving global supply. While the US, western Europe and Japan consume approximately 90 % of all new medications, the rest of the world population accounts for the remaining 10 %.

## Price of cancer medicines

Healthcare expenditures, of which a considerable part is due to breast cancer care, are rising to levels that may not be sustainable in the future. Treatment costs of cancer are equally high both within and outside the healthcare system. Although aspects such as direct and indirect costs, outpatient and inpatient clinic treatment costs are essential, the rising cost of cancer drugs is an important aspect in Europe (5) (Figure 30.1). The total cost of cancer differs greatly between countries, with a growing cancer drug expenditure in most countries (6). Economic evaluations of new and existing therapies can be used to inform budget allocations in a way that maximizes health outcomes and broadens the value to the patient. It is increasingly recognized that personalized care can offer more value for patients and at the same time provide value for money (see Chapter 32.) It is timely that current clinical practice guidelines are revisited toward a more personalized approach, acknowledging the patient's voice, and the burden of cost on society. An example is the recognition of the health assessments to identify appropriateness of therapy and the calculation of the survival gain of different treatments. The possibility of de-escalation of 12-month to 6-month adjuvant trastuzumab can be considered as an example of decision-making in a resource-limited setting (7), which is hampered by the difficulty in changing international guidelines. A 12-month regimen of trastuzumab had an additional annual cost of US\$6 million in Peru (8), which is too expensive considering the limited budget. The same could probably be achieved by omitting adjuvant immunotherapy after obtaining a pathological complete response in triple-negative breast cancer patients, following neo-adjuvant chemo and immunotherapy.

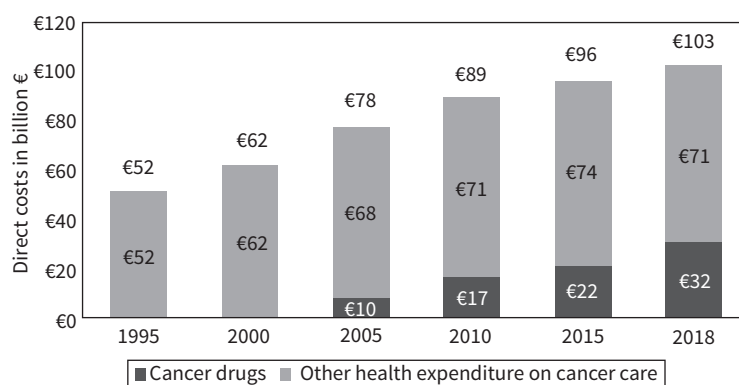


**Figure 30.1** Direct costs of cancer in Europe (in billion).

Reproduced with permission from Hofmarcher T, et al. The cost of cancer in Europe 2018, *Eur J Cancer*, Volume 129, 2020, Pages 41–9. This figure is not covered by the Creative Commons licence terms of this publication. For permission to reuse please contact the rights holder.



In LMIC in Southeast Asia, approximately three of four new patients with breast cancer experience a financial catastrophe or die within one year after diagnosis (see Chapter 31). An advanced stage at diagnosis and lower socioeconomic status are significant determinants of this poor outcome. There is an urgent need for more resources to aid early detection and policies providing adequate financial protection from the treatment costs of cancer. In an increasing number of jurisdictions, a threshold for an additional unit of health gain, expressed in a quality-adjusted life year, is used to determine whether a therapy provides value for money. In Figure 30.2, the threshold shows how the effectiveness and costs of new interventions can be evaluated (9). Improving access to medicines by reducing the cost of cancer medications should involve trade agreements and flexibility of the Trade-Related Intellectual Property Rights (TRIPS). Changes in International patent law could mitigate cancer inequity in LMIC. The Doha Declaration affirmed the rights of states to implement policies to enable access to medicines to address the national health crisis and to compulsorily licence a patent to produce generic drugs. The Doha Declaration on the TRIPS agreement and public health was adopted by the World Trade Organization (WTO) Ministerial Conference of 2001 in Doha (10). It reaffirmed the flexibility of TRIPS of member states in circumventing patent rights for better access to essential medicines. In 2017, after further extensions, enough members ratified the amendment to reach the two-thirds threshold, bringing the TRIPS amendment into effect (11). Innovations such as precision medicine with biomarkers and target identification may further reduce unnecessary treatments, but they are associated with considerable initial costs and increasingly uncertain patient outcomes due to a lack of clinical evidence. The costs hamper access: drugs do not cure anyone if patients cannot afford them. Pascale Lamy, European Commissioner for Trade at the time of the declaration, stated the agreement solved only about 10% of the problem of access to medicines by developing countries (12). The only viable road is to agree upon a broad value framework, encompassing both patient and social values. Such a framework is essential to guide transparent, fair, and evidence-based decision-making on a macrolevel. Setting a value-based price threshold can guide the allocation of our limited resources to achieve high-quality care. It can also be used to manage risks because of the uncertainty due to a lack of clinical evidence, by engaging in managed entry agreements with pharmaceutical companies. This framework can also be used to support shared

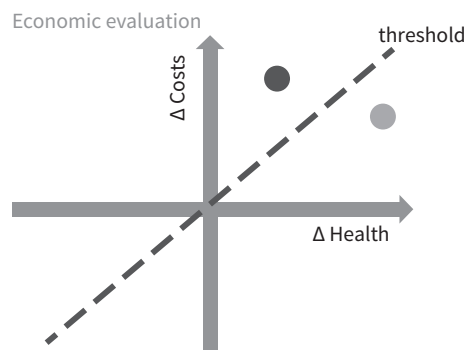


**Figure 30.2** Cost in relation to health. The left and right dots show the economic evaluation of new interventions in relation to the acceptability (willingness to pay) threshold.

Adapted with permission from Maudgil DD. Cost effectiveness and the role of the National Institute of Health and Care Excellence (NICE) in interventional radiology. *Clin Radiol* 2021;76(3):185–92.

decision-making. It integrates patient-reported outcomes, clinical evidence, and broader social considerations. It can be used to optimize personalized treatment strategies, considering the local resources.

The relation between cost and efficacy of a treatment with a drug was nicely put in a graph by Saltz presented at American Society of Clinical Oncology (ASCO) in 2017. Analysis between 2015 and 2020 indicates no association between medicine prices and the magnitude of benefits on endpoints, such as progression-free survival or overall survival, suggesting that cancer medicines are priced on what the market can stand, not the clinical benefits they provide. Similarly, no correlation was found between the cost and clinical benefit of national price-negotiated drugs for breast cancer in China (13).

Current pricing is not rational but reflects only the market. On the other hand sometimes medicines may demonstrate benefits not understood at time of approval. But mostly at that time the pharmaceutical industry has moved onto new, more expensive developments. A key economic property of expensive medicines is that they typically become lower-cost generics within two or three decades of their initial marketing. Cancer medicines have generated returns far in excess of officially reported research and development costs. Prices are rising when even basic market rules suggest they shouldn't. The last step is always more expensive even when competitors appear. Doctors are trained not to consider cost of treatment when making the choice of therapeutics for individual patients. Addressing these facts in a transparent way is fundamental to lead to fairer access to new treatments for all patients. Values of new medications have to be discussed with reference to patients, science and society (14)

## Biopharmaceutical companies and cancer medicines

Biopharmaceutical companies which develop and manufacture cancer drugs, are fundamentally about making profits for their shareholders and employees and re-investing the remaining in further research and development. Within the pharmaceutical sector, the US legislative ecosystem allows companies infinite pricing power. A power with global implications in which the cancer R & D system is overincentivized and leads to licensing of expensive new drugs with marginal benefits. Over 23 years, the mean cost in USD of developing a new cancer medicine to pharmaceutical companies has been around \$4.4 billion (15). The true costs of R&D covers a very wide range of activities, and they have never had any relationship to downstream pricing. In these calculations no account is taken of public underpinning of R&D funding which is intimately woven into the private sector. Bringing any cancer medicine to market generates substantial returns to the companies, irrespective of the return on investment. Even bringing a cancer medicine along the pipeline, ensures substantial capital flow in terms of inward R&D investment. Overall return on investment (ROI) for cancer medicines with sufficient maturity, i.e. launched between 1997–2015 is between 435 to 551%. Trastuzumab, launched in the mid-2000s, generated a ROI of 3421%. This reflects the fact that the oncology business is still driven by blockbusters. Contrary to prevailing narrative, the majority of pharmaceutical industry profits are not ploughed back into R&D but instead used for open market stock buy-backs. From 2000 to 2018, 35 large pharmaceutical companies reported cumulative revenue of \$11.5 trillion with a gross profit of \$8.6 trillion (16). These figures are staggeringly high and oncology is one of the major contributors to these figures. To be fair to pharmaceutical companies there is, in many countries also significant

‘rent-seeking’ behaviour, which is present throughout the pathways between the manufacturer and the patient. In other words, multiple actors, including hospitals and doctors take their ‘cut’ along the supply chain. If we care about unaffordable prices then it’s not enough to simply tackle industry, we must tackle the entire ‘profit chain’. In countries like the USA, direct payments to medical oncologists who set national guidelines are now the norm but even the UK has significant transparency problems. Articles in highly ranking top journals about new cancer drugs are written with medical writers paid by pharma. The fact is that there are multi-million dollar funding flows into hospitals and universities with little scrutiny as to whether the research reported reflects an important question with a well-designed study. Indeed, career advancement may be mostly due to how much money researchers bring in, not whether the research in question is of any value.

We have referred to aspects of the introduction of new cancer drugs which need urgently addressing. However, we must not forget the essential contribution of the pharmaceutical industry in developing these highly effective and life-saving medications. A very limited number of cancer pharmaceuticals have been developed in academic institutions, and if it were not for an industry dedicated to developing new medicines we would have very few available to treat patients with cancer. However some balance needs to be restored between all the stakeholders within thriving, sustainable, and innovative economies.

## Solutions

### WHO Essential Medicines List (EML)

The WHO’s Essential Medicine List Cancer Committee has absorbed pricing and affordability as key aspects of their deliberations. The list of essential medicines (EML) maintained by the World Health Organization (WHO) plays a central role in global health policy. The list is updated every two years by the expert committee. The working group regularly meets to review the applications for updating. The ‘drugs to be available’ included in the EML are defined as follows: ‘they satisfy the healthcare needs of the population’ and ‘they must be available at all times and at a price the community and the individual can afford’. The general principles are efficacy/benefit, with consideration of disease state and indication (17).

Cancer medicines are the largest therapeutic category proposed to the EML (28%). The 24th updated list of WHO essential antineoplastic agents for breast cancer was published in 2025. (<http://www.who.int/medicines/publications/essentialmedicines/en/>). Although half of the participating experts are from LMIC, there is poor consensus on whether the list is for HIC, LMIC, or both. There remains an urgent need for full access in LMICs, which does not exist at present.

Essential medicines for breast cancer patients include:

- **Supportive:** ondansetron, metoclopramide, dexamethasone, filgrastim, pegfilgrastim, zoledronic acid
- **Cytostatics:**
  - Neo/Adjuvant: carboplatin, docetaxel, 5-fluorouracil, methotrexate, paclitaxel, doxorubicin, cyclophosphamide

- Metastatic: capecitabine, cyclophosphamide, doxorubicin, paclitaxel, vinorelbine
- **Endocrine treatment:** aromatase inhibitors, tamoxifen (adjuvant and metastatic), leuprorelin (adjuvant + therapeutic alternatives as goserelin or triptorelin)
- **Targeted therapies:** monoclonal antibodies: trastuzumab (adjuvant and metastatic), including quality-assured biosimilars

To maintain a relevant essential medicine list, a clear updating process was agreed upon by the WHO.

- Step 1: Refer to the most recent WHO list of essential medicines
- Step 2: Collaborate and coordinate with relevant partners in-country for the NEML review
- Step 3: meeting relevant stakeholders, forming a review committee, creating a timeframe and requirements for additions/deletions/changes
- Step 4: collate research and evidence for submission
- Step 5: compile the evidence based on requirements and timelines
- Step 6: plan to disseminate the revised NEML in collaboration with the Ministry of Health (MoH) and relevant stakeholders
- Step 7: ongoing monitoring and evaluation to ensure the implementation of the revised NEML and increase access to essential medicines.

The use of clinical benefit scales of the ASCO (18) and the European Society of Medical Oncology (ESMO) are considered valuable tools but have not gained enough acceptance (19). National strategies and policies should ideally be inspired by the best available models to reduce the financial burden of a breast cancer diagnosis.

Accelerated approvals by FDA or EMEA could be priced lower, to be adjusted after confirmatory evidence (20). Withdrawing approvals should be more active when benefits are not confirmed by clinical trials or by real-world data.

Medicines that provide the highest benefit should be approved faster than those that provide only marginal benefits. This would be crucial in countries with few healthcare resources, but also in view of the uncontrolled rise in cost in HIC (21).

## WHO priority medical devices

Along with the EML, the WHO has also defined an essential list of medical devices. For breast cancer patients, implantable medical devices and modalities to give intravenous administration are important ([https://www.who.int/health-topics/medical-devices#tab=tab\\_1](https://www.who.int/health-topics/medical-devices#tab=tab_1)).

## Key messages

- There should be no rush to accept early access schemes despite new studies suggesting advantages.

- Policy discussions should maintain the important wider perspectives of patient care, including quality of life and socioeconomic impacts.
- The economic and commercial determinants of cancer medicines need to be checked since they are creating an unsustainable situation in terms of equitable cancer care.
- More sophisticated pricing and reimbursement systems need to be introduced.
- Contracts between the pharmaceutical industry and the private sector must include federal and philanthropic research funders.
- Funding needs to be re-allocated to the public sector with integration of socioeconomic studies into clinical trials.
- The EML list can help all countries, including HICs, to set priorities for reimbursement of new drugs.

## Acknowledgement

Richard Sullivan and Christopher Booth for their stimulating vision.

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## Southeast Asia perspective

*Merel Kimman, Yek-Ching Kong, Stephen Jan, Sanne Peters, Manuela Joore, Mark Woodward, Cheng-Har Yip, and Nirmala Bhoo-Pathy*

### Introduction

The economic burden of cancer treatments to health systems across the world will grow since the population is ageing and the availability of medical technologies and treatments is expanding. The economic burden falls not only on health systems, but also on patients, families, and societies as a whole. Most patients and families incur costs as a result of a cancer diagnosis. These can include direct medical costs, such as those associated with seeing general practitioners, medical specialists and allied health professionals and receiving treatment (e.g. surgery, radiotherapy, chemotherapy), and those associated with buying medications to help alleviate the symptoms of cancer and the side effects of treatment. The majority of patients also have out-of-pocket expenses in relation to travelling to hospital appointments. Furthermore, a rising number of young adults will be diagnosed with cancer, particularly in the age group 25 to 49 years old, when work ability and employment play an important role in their lives. They may be unable to continue working due to the burden of their symptoms, treatment, or side effects, and this leads to decreases in household income as well as costs to society in terms of lost productivity.

Health insurance generally reduces the out-of-pocket costs of treatment. The extent of financial protection, however, is highly health system-specific and varies in services covered and the level to which expenses are reimbursed. When financial protection is limited and social safety nets, such as targeted assistance programmes or disability benefits, are not present, treatment costs and loss of income may result in financial ruin for those with a cancer diagnosis and their families. The financial burden of a cancer diagnosis is felt most strongly in socioeconomically disadvantaged groups, and particularly those in low- and middle-income countries where out-of-pocket payments are the principal means of financing healthcare.

Financial burden is commonly defined in terms of the incidence of *financial catastrophe*, where out-of-pocket expenditure for healthcare exceeds a defined threshold proportion of annual income. Another important indicator of financial burden is *economic hardship*, which can be defined as a household's inability to pay living or medical expenses or the use of financial coping strategies in order to pay a living expense (1). Next to objective indicators, interviews with patients can provide crucial insights into financial burden.

In this chapter, the economic impact of a breast cancer diagnosis is illustrated using data from three studies: 1) data on financial catastrophe and economic impact from the ASEAN CoSTs In Oncology (ACTION) study; 2) focus group discussions on financial needs, and 3) focus group discussions on work experiences after cancer. Together these studies help to facilitate the development of policies aimed to provide adequate financial protection subsequent to a breast cancer diagnosis.

## The economic impact of breast cancer in low- and middle-income countries

### Financial catastrophe and death—findings from The ACTION study

#### Complete study—all cancers

The ACTION study was a unique observational study of the household burden of cancer conducted in eight low- and middle-income countries in Southeast Asia (Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Thailand, and Vietnam) (2). Patients diagnosed with a first-time cancer were consecutively recruited (within 12 weeks from the initial date of diagnosis) from 47 sites, including public and private hospitals and cancer centres, and followed through their first year following diagnosis. The main outcomes of interest of the ACTION study comprised the incidence of financial catastrophe, economic hardship, and all-cause mortality at one year following cancer diagnosis. Financial catastrophe was defined as out-of-pocket costs at 12 months equal to or exceeding 30% of annual household income. Costs included medical costs (inpatient/outpatient care, purchase of drugs, medical supplies and equipment, traditional medicine) and non-medical costs due to illness (transportation, accommodation, etc.), which were directly incurred by patients at the point of delivery and not reimbursed by insurance. Between March 2012 and September 2013, 9,513 patients were recruited into the study. Figure 31.1 shows the associations between various risk factors and both financial catastrophe and death (1). Low social status was clearly the major determinant of both.

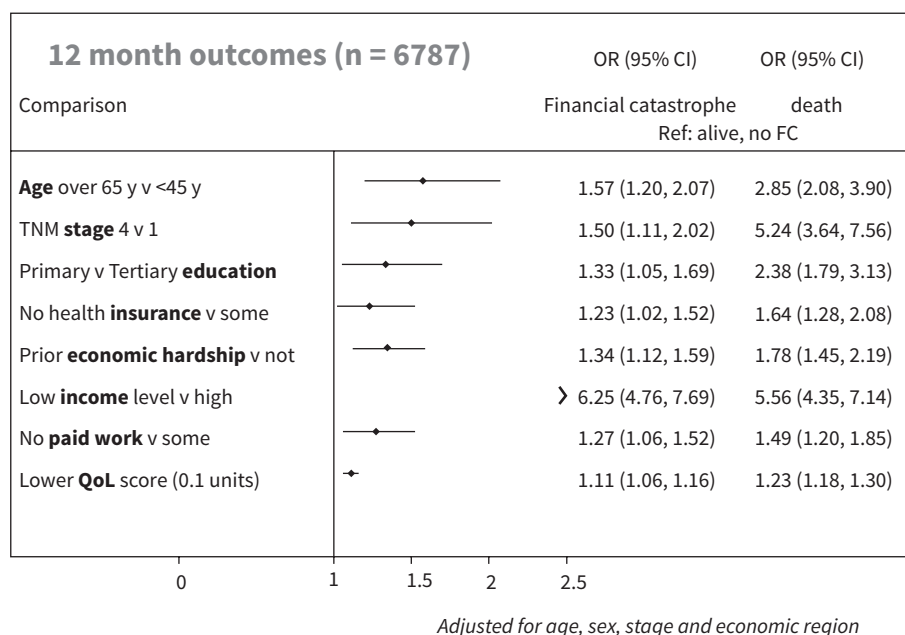


**Figure 31.1** Odds ratios (and 95% confidence intervals) for financial catastrophe and death, relative to no financial catastrophe (reference) in cancer (of any type) patients with complete outcome data (n = 6,787) from the ACTION study, adjusted for age, sex, cancer stage, and geographic region.



### Breast cancer sub-sample

Of the 9,513 patients recruited into ACTION, 2,435 were female patients with a breast cancer diagnosis. The mean age of these breast cancer patients was 50 years, with the majority diagnosed with stage II or III cancer (61%). 75% were married, only 26% went to school after 12 years, 52% had a low or medium household income, and half had health insurance.

One year after diagnosis, data on financial catastrophe and death were available for 1,667 (69%) of the breast cancer sub-sample; of these, almost two-thirds (61%,  $n = 1,027$ ) experienced financial catastrophe, 13% ( $n = 217$ ) died, and just 26% ( $n = 432$ ) had a favourable outcome one year after diagnosis, i.e. alive and no financial catastrophe (Figure 31.2a). Around 10% of the financial catastrophe cases were driven by excessive non-medical expenditures (Figure 31.2b). Factors such as high age (aged >54 years), being unmarried, having below-average income, not having health insurance, and not having paid work were associated with a higher odds of experiencing financial catastrophe.

In addition, the study found that a year after diagnosis, of patients who were financially solvent at baseline, economic hardship was reported by a quarter of families. Around 56% of these families, for example, could not pay for their cancer medicines, medical tests, or consultations, 20% were unable to pay their rent or mortgage, and 12% could not pay their utility bills (not mutually exclusive) (Figure 31.2c). To cope with economic hardship, 64% of affected families used their savings that were set aside for other use, 28% resorted to taking personal loans, and 14% had sold their assets or property (not mutually exclusive) (Figure 31.2d).

## Financial needs—findings from focus group discussions

In 2017-2018, patients with breast cancer residing in Malaysia who were diagnosed at least one year before were invited to participate in focus group discussions on the financial impact of cancer and coping strategies employed, as well as the ensuing unmet financial needs (3). Study participants were recruited from five private and public hospitals. In Malaysia, the public healthcare system, funded by general taxation, provides highly subsidized care to all Malaysian citizens irrespective of their insurance status. Individuals can also opt to purchase private health insurance voluntarily, or are offered it through their employers. The private system, which comprises mainly for-profit healthcare centres, is thus financed through either private health insurance or out-of-pocket expenses. In total, 64 women with breast cancer participated, with a median age of 49 years. The majority were married (80%) and came from low-income households (52%). About 70% owned private health insurance.

The study found that despite having private health insurance, many of the insured participants were underinsured, i.e. they still had out-of-pocket costs for treatment. Also, women found essential items, such as breast prosthesis, mastectomy bras, corsets, and wigs, costly (see Table 31.1 for quotes from participants). Many participants also described spending a substantial amount of money on traditional and complementary therapies, due to the need to leave no stone unturned. Importantly, the need to pay for their cancer care first and wait to be reimbursed later often led to financial difficulties and distress due to cash flow issues, and some participants expressed having forgone certain treatment recommendations due to financial hardship.

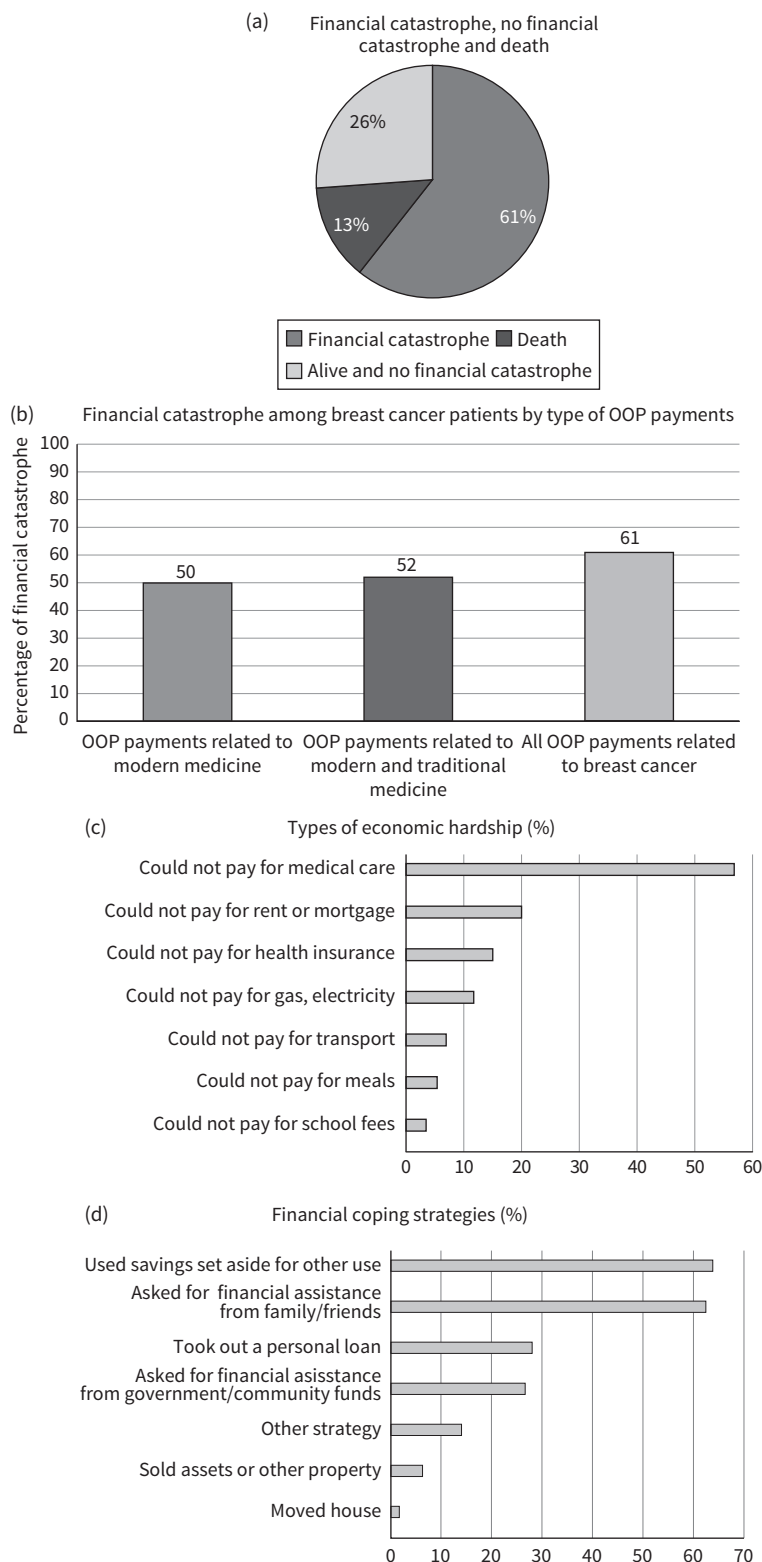


**Figure 31.2** Financial catastrophe, economic hardship, and death at 12 months after diagnosis among breast cancer patients. OOP, out-of-pocket.

(a) Study outcomes 12 months after diagnosis among breast cancer patients ( $N = 1,667$ ). (b) Financial catastrophe at 12 months after diagnosis, by type of out-of-pocket payments ( $N = 1,667$ ). (c) Types of economic hardship ( $n = 393$ ). (d) Types of coping strategies used ( $n = 393$ ).

The financial needs for non-health costs differed between socioeconomic status groups. Participants from lower socioeconomic status described facing difficulties affording very basic necessities, such as food, following their cancer diagnosis. Transportation costs (including parking fees) to the hospital for treatment and follow-up visits were also reported as a major burden. Participants from higher-income households brought up the need to spend on perceived ‘better’ food, such as organic food and dietary supplements. Furthermore, expenditures on childcare or household help increased their household expenses.

To cope with treatment costs and a decreased household income due to prolonged unpaid work absences, many participants described tapping into personal savings or borrowing money from relatives or friends. The lack of transparency and efficiency in (the application of) financial assistance programmes, if available, was also highlighted. The findings of this study point toward the urgent need for the development of financial navigation programmes that provide support to deal with financial issues and employment-related challenges. Even in a setting with universal health coverage, existing social safety nets are inadequate to support needy cancer survivors.

## Work-related challenges—findings from focus group discussions

In 2018–2019, as part of a larger qualitative study that explored the needs of cancer survivors living in Malaysia, men and women diagnosed with breast, colorectal, cervical, or prostate cancer over one year ago were invited to participate in focus group discussions on challenges related to working following a cancer diagnosis (4). Study participants were recruited from five public and private hospitals. For this chapter, data from 17 women with breast cancer were extracted and analysed. The average age of the breast cancer patients was 48 years (range 37–60 years) and almost all had paid work (88%).

The study identified three main themes with respect to challenges and needs associated with working after cancer: loss of income, dealing with side effects, and discrimination and stigma. Quotes from participants can be found in Table 31.1. Loss of income was a major

**Table 31.1** Selection of quotes from breast cancer patients participating to the focus group discussions

| Theme                  | Quote                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Underinsurance         | ‘They advised me to take hormone therapy for one year which costs about MYR150K (USD36K) [whole course]. The moment I heard the cost I said I don’t want to undergo hormone therapy. My insurance will not cover the cost due the limit of my coverage plan ... I am struggling financially and I do not think I can afford it ... I feel that financial crisis is worse than my health issues.’<br>47 years old, Indian, low-income, employment medical insurance coverage |
| Reimbursement policies | ‘That is a burden because you have to prepare the cash ... so you have to always come out with the cash and claim later. And the claim may not come instantly. So you have to have cash in hand. That is the difficulty.’<br>41 years old, Chinese, middle-income, personal medical insurance coverage                                                                                                                                                                      |

(continued)

Table 31.1 Continued

| Theme                           | Quote                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Coverage                        | <p>'It [mastectomy bra and prosthesis] comes to MYR1000+ (USD 241) which I am quite mindful. If the prosthesis is cheaper, then I will pay for it. But since it is over MYR1000, I am willing to forego it because of costs.'</p> <p>56 years old, Chinese, middle-income, no medical insurance coverage</p>                                                                                                                                                                                                                                                           |
| Transportation                  | <p>'It is a burden. Because you must come for radiotherapy every day. Everyday parking is MYR3 (USD0.75). I came 23 times ... That is not including the costs for petrol.'</p> <p>47 years old, Indian, low-income, no medical insurance coverage</p>                                                                                                                                                                                                                                                                                                                  |
| Household help/<br>childcare    | <p>'I had to hire two maids to come once a week ... I also had to hire someone to cook for me ... I needed to rest.'</p> <p>44 years old, Malay, high-income, personal and employment medical insurance coverage</p>                                                                                                                                                                                                                                                                                                                                                   |
| Informal financial<br>resources | <p>'I am facing financial difficulties, I have to withdraw my savings to support my daily living.'</p> <p>39 years old, Malay, low-income, employment medical insurance coverage</p>                                                                                                                                                                                                                                                                                                                                                                                   |
| Financial<br>navigation         | <p>'A financial advisor. They [hospitals] should have a consultant, who can gather the patients and advise them on how to get money from SOCSO, or the government, or any charity organization ... to be able to advise the newly diagnosed patients on how to seek help financially ... maybe include a consultancy to advise you on career issues too.'</p> <p>41 years old, Chinese, high-income, personal and employment medical insurance coverage</p>                                                                                                            |
| Loss of income                  | <p>'I finished my radiotherapy and immediately I had to go back to work the next day. I wanted to rest before going back to work but they [employer] didn't approve [of her application] because I had already completed my treatment. They [employer] said there was no reason to give me more leave. The employer assumes that we are fully cured after [cancer] treatment, that we do not need extra leave.'</p> <p>A 41-year-old woman with breast cancer, paid work</p>                                                                                           |
| Dealing with side<br>effects    | <p>'I applied for a transfer to a different department just to reduce my workload and stress ... But my employer did not understand my situation. They compared me with older patients and ask me what my excuse was ... Almost every week I have to go outstation ... It is not that I do not want to work, just that my body cannot handle it anymore, like how I used to be. I can no longer work for long hours.'</p> <p>A 41-year-old woman with breast cancer, paid work</p>                                                                                     |
| Discrimination and<br>stigma    | <p>'For those who are working, I think that the doctor needs to give something [to the employer]. Like our bosses may not understand our situation as a cancer patient.'</p> <p>A 37-year-old woman with breast cancer, paid work</p> <p>'I applied for a new job. But upon doing a background check, they did find out that I have cancer. Although I satisfied all the requirements but my application was rejected because of cancer ... This is like discrimination towards us.'</p> <p>39 years old, Malay, low-income, employment medical insurance coverage</p> |

Adapted with permission from Kong YC, et al. Understanding the Financial Needs Following Diagnosis of Breast Cancer in a Setting with Universal Health Coverage. *Oncologist* 2020;25(6):497–504; and Kong YC, et al. Working after cancer: in-depth perspectives from a setting with limited employment protection policies. *J Cancer Surviv* 2021;15(5):706–12.

challenge, especially when undergoing active treatment, particularly chemotherapy and radiotherapy, when they had to frequently take time off from work. Some participants were entitled to paid medical leave, but this was often insufficient.

Many of the patients suffered complications of cancer, and the side effects of treatment, both short- and long-term effects, which affected their work performance. Cognitive limitations, such as attention and memory loss, as well as physical issues, such as fatigue, were common among breast cancer patients and may persist for a long time after treatment completion. Patients voiced the need for reasonable workplace accommodations that were perceived to be helpful in coping with cancer symptoms and the side effects of treatment. Examples of 'return-to-work wish list' that were cited include being assigned lighter duties or less stressful job tasks, having flexible working hours, having dedicated rest areas for short breaks, and being offered the opportunity to work from home. Regarding discrimination and stigma, patients reported being at risk of getting fired, being unjustly overlooked for a workplace promotion, or facing discrimination when looking for a new job because of their cancer diagnoses. Participants expressed the need to increase knowledge about cancer in the workplace. Importantly, the study highlights the unmet need for cancer-specific leave (of adequate length), workplace accommodations, destigmatization of cancer at the workplace, and financial protection against catastrophic income losses due to time off work.

## Policy implications

Breast cancer can lead to major financial burden, especially in low- and middle-income countries, because treatments are costly and out-of-pocket expenses are high. This was illustrated by the ACTION study: among the study's breast cancer population, almost two-thirds of families faced catastrophic expenditures for treatment, and one in four families experienced economic hardship within one year after diagnosis. Older patients and patients with greater levels of disadvantage (e.g. low income or education) tended to have a higher risk of financial burden. Interviews with patients in Malaysia, an upper-middle-income country, were in line with these findings and provide a better understanding of patient experiences, which is crucial to developing successful policies. The interviews suggest that even in settings that have made good progress towards universal health coverage, patients can face substantial out-of-pocket costs for treatment and also prostheses, bras, transportation, accommodation, and childcare, which increase household expenses. In addition, patients and caregivers see income reductions, and patients face challenges at work related to experienced side effects of treatment, but also stigma and discrimination. There is a clear need for governments to re-examine their health financing systems and extend financial protection through social health insurance and publicly supported cancer care to better protect citizens from the costs associated with cancer treatment. In addition, benefit packages of private health insurance, as well as the coverage of subsidized care in the public sector, need to be revised to not only keep up with the increasing medical costs, but also extended to include coverage for other supportive cancer care costs, as expressed by many participants in the focus group discussions. In view of its wider economic implications, returning cancer survivors to a supportive workforce should also be regarded as a priority intervention in any national cancer control effort, requiring multi-sectoral collaboration among major stakeholders catalysed by strong political will.

Early diagnosis followed by prompt treatment remains the hallmark of an effective cancer control strategy resulting in less invasive treatment, better health outcomes, and, thus, potentially lower household economic burden. Policymakers, payers, and healthcare providers in low- and middle-income countries have to work towards making the best use of available resources to provide timely access to optimal cancer treatment (5). In addition, it is crucial for governments to create social safety nets and put in place programmes to improve welfare support for cancer (e.g. income support, access to short-term credit, and disability insurance) and public transport services, which are beyond the scope of healthcare systems, *per se*. In conclusion, breast cancer must be recognized, prioritized, and seen as a cross-governmental issue affecting households, society, and the economy, rather than merely health.

Breast cancer among adolescent and young adult (AYA) patients (age 15–39) is also a relevant public health challenge. Between 1990 and 2021, breast cancer incidence rates among AYA patients rose across all Southeast Asian countries. As breast cancer screening programmes target women aged 40 and above, the rising incidence suggest the growing prevalence of hormonal and lifestyle risk factors, in the setting of socioeconomic transformations. These findings highlight the need for tailored interventions that address the unique challenges faced by AYA patients (6).

## Key messages

- Approximately two in three new breast cancer patients in Southeast Asia experience financial catastrophe within one year after diagnosis.
- Even in settings with good progress towards universal health coverage, patients often face out-of-pocket costs for treatment, transportation, and accommodation, and for products such as bras, prostheses, and dietary supplements.
- Patients experience reductions in income due to prolonged unpaid work absences or reduced productivity due to side effects of treatment.
- An advanced stage at diagnosis and living in lower socioeconomic status are significant risk factors for poor health and economic outcomes.
- Policies should aim to provide adequate financial protection from the costs (medical costs, non-medical costs, indirect costs) of cancer, requiring multi-sectoral collaboration and strong will.

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## Personalized care

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### Introduction

The recent *Lancet* Breast Cancer Commission states four approaches to achieve personalized breast cancer treatment and care (1). Those are precision, optimization, interpretation, and innovation. In this chapter, we will use these approaches as a starting point to move from 'one-size-fits-all' to personalized breast cancer care. The focus here is on precision, optimization, and interpretation, whereas innovation is covered in other chapters.

### Precision

**Precision**, which in this context means that the care and treatment of breast cancer patients, is based on molecular characteristics. This has led to targeted systemic therapies that are directed to tumours with the required molecular characteristics. In addition, it has also led to the development of molecular biomarkers that can determine the choice of (non-) targeted therapy. The use of these targeted treatments or biomarkers are two possibilities that could lead to personalized or tailored systemic treatments for patients.

### Targeted treatments for Breast Cancer

Hormonal therapies, mostly oestrogen receptor modulators and aromatase inhibitors, were some of the earliest effective targeted therapies, directed at oestrogen receptors. The newer agents in this class are the selective oestrogen receptor degraders (SERDs). Cyclin-dependent kinase 4/6 inhibitors (CDK4/6is) have recently been licensed for use both in metastatic and adjuvant settings. HER2-directed therapies have been one of the major success stories of the twenty-first century, and neoadjuvant trastuzumab (now in combination with pertuzumab) has been transformative (2). Also, the kinase inhibitors tucatinib, lapatinib and neratinib and antibody drug conjugates (ADC) against the Her2 receptor have now been developed, which are proving effective mainly in the metastatic setting (3). In addition, these trastuzumab-based ADCs have been tested and licensed in HER2 low breast cancer.



## Biomarkers for breast cancer

There are several different kinds of biomarker that are of value for selecting the right drug for the right patient.

- **Germline genetics:** e.g. *BRCA1/2*, in which breast cancer patients with *gBRCA* deleterious mutations, demonstrate important sensitivity to poly (ADP-ribose) polymerase inhibitors (PARPis). The same probably applies to *gPALB2* mutations (4).
- **Tumour genetics:** this includes single gene alterations up to increasingly complex multi-gene signatures: e.g. *ESR1* mutations, *HER2* amplifications/mutations, prognostic and predictive signatures, mutational, immune activation signatures and homologous recombination deficiency (HRD) states.
- **Tumour biomarkers:** includes substances produced by tumours or the body's responses to tumours during tumorigenesis, which are reliable, often validated, and used in daily clinical work to guide personalized treatments as prognostic and predictive indicators, e.g. the degree of tumoural ESR or PD-L1 expression.
- **Pharmacology/pharmagenetics:** one example is capecitabine used in both adjuvant and metastatic breast cancer, and dihydropyrimidine dehydrogenase deficiency (DPD). This deficiency leads to a lack of metabolism of fluoropyrimidines, which produces either severe (complete deficiency ~1% of the population) or moderate (partial deficiency—up to 8% of the population) capecitabine-related side effects.

The last often-neglected 'biomarker' is probably the most important. This is about considering all the personal circumstances of the patient and personalizing their treatment and care around their priorities and their lives; their preferences and choices. These are the features of personalizing care that are most difficult to quantify.

## Optimization

Optimizing breast cancer care means taking specific subgroups (e.g. elderly) and then taking certain comorbidities of patients into account. In addition, care can be optimized by offering patients the opportunity to express their preferences in consultation with the healthcare provider (shared decision-making) for equivalent treatment (e.g. surgical treatment). Finally, healthcare optimization relates to the pursuit of the most efficient possible use of care, in diagnostics (e.g. personalized follow-up after breast cancer and expanding pathologic examination with tumour-infiltrating lymphocytes (TILs) in triple-negative breast cancer (TNBC) (see Chapter 13)), and treatment (e.g. pharmacology in immunotherapy and optimal use of CDK4/6 inhibitors (see Chapter 8)).

## Identifying subgroups: the elderly

Cancer incidence increases with age. Given the important increase in general life expectancy, a 'silver tsunami' of cancer cases in older people is expected in the next decades (5). Breast cancer

is not an exception to the rule. Its incidence peaks currently at 65, and more than 60% of patients will soon be diagnosed after age 70 according to the projections for the next two decades.

Several studies have shown that management of breast cancer in elderly patients does not always reach high quality standard. Over- and under-treatments are indeed very common and reflect enthusiasm for futile or 'at risk' treatments (often found in oncology) and ageism, respectively. A crucial factor to integrate in treatment decisions are competing causes for mortality caused by multimorbidities, which increase in incidence and severity with age and can make non-breast cancer causes of mortality prominent. Older patients are at higher risk of side effects, especially for treatments with narrow benefit/risk ratios such as chemotherapy, especially in the more frail patients (6). This can be partially related to pharmacokinetic alterations, but it may also reflect increased sensitivity of ageing cells to toxic agents. Therefore, the main challenge is to prioritize health problems and adjust strategies to personalize treatment, which cannot be simply a copy of what has been developed and approved in young and middle-aged adults.

The first important step is screening for frailty through a short scale or questionnaire. Many tools exist, and debates regarding the selection of the best one are probably a waste of time. One of the most popular and disseminated tools in Europe is the G8 developed after the Oncodage programme in France (7). It is built with eight items derived mostly from the mini-nutritional assessment, added to some polypharmacy and self-rated health status assessments, and to an age strata. It has a high sensitivity and specificity for detecting geriatric problems (77% and 64%, respectively) that are present when performing a comprehensive geriatric assessment and requires only three minutes to be completed by a physician or nurse. When impaired ( $G8 \leq 14/17$ ), a detailed/comprehensive geriatric assessment is recommended. Comprehensive geriatric assessment allows review of many different domains of interest (nutrition, cognition, depression, functional status, and others). It predicts survival, therapy induced toxicity, functional decline, and discovers many age-related problems that oncologists are not aware of without comprehensive geriatric assessment. Estimation of life expectancy should be performed using a validated short term (e.g. Carey, Walter) or a long-term scale (e.g. Lee, Schonberg) depending on the clinical setting (metastatic or adjuvant, respectively) as found on the website: <https://eprognosis.ucsf.edu>.

For chemotherapy toxicity prediction, two scores have been developed and validated (CRASH score and CARG score). Both accurately discriminate the risk of serious adverse events with standard chemotherapy regimens, when the usual performance status (ECOG, WHO or Karnofsky index) are unable to do so. Several tools exist to predict the benefit of specific therapies in early breast cancer. PREDICT (<https://breast.predict.cam/>) is the most used in general breast oncology; it predicts the benefits of adjuvant chemotherapy, endocrine therapy, and anti-HER2 therapy on overall survival at 5–10–15 years. The major limitation of the PREDICT is that it does not take into account general health condition in older patients, which should be considered in the interpretation of risk estimates for the elderly (8). The AGE-GAP tool (<https://agegap.shef.ac.uk/>) was developed to calculate the benefit of surgery, endocrine therapy, and chemotherapy specifically in older patients, taking into account geriatric aspects, and is the preferred tool in the older early breast cancer population.

Most importantly, geriatric assessment allows identification of specific 'geriatric' defects that are 'targetable' by geriatric interventions in order to maximize the benefits of the selected anti-cancer treatment. Oriented interventions decided according to the geriatric assessment can then be extremely helpful to ensure access to the right care in safe and cost-respectful

conditions. Several recent prospective randomized trials demonstrated that geriatric interventions significantly decrease severe chemotherapy-induced toxicity. Indeed, as the molecular portrait of the tumour allows treatment personalization based on actionable targets, geriatric assessment allows treatment personalization based on a more holistic view of the patient.

This strategy is strongly advocated by the International Society of Geriatric Oncology (SIOG) as mentioned in its 10 priorities (9). Any treatment decision in older patients should take into account the absolute benefit of treatment on classical endpoints such as relapse and survival, but also integrate the patient's wishes, life goals, general health status, and competing risks of death. It should not be forgotten that treatments can also induce debilitating side effects, to which older/frail persons are more sensitive. The pros and cons of treatment should be discussed in depth with each individual patient.

On a broader scope, health economic evaluation, which systematically assesses (broad) health benefits in relation to the costs of therapies, should also be performed in order to use healthcare resources optimally.

## **Shared decision in case of equivalent treatment: e.g. surgical treatment**

The advent and adoption of oncoplastic breast surgery has helped women to achieve improved quality of life and pursue choice by participating in the decision regarding extent of surgery and reconstruction (see Chapter 15). Although access to radiotherapy can make it challenging for some patients to pursue the breast conservation surgery option in low- and middle-income countries (LMIC), these surgical techniques have allowed patients to avoid mastectomy, have optimum surgery with relatively quicker recovery period and preservation of form and function of the affected breast.

The timely access to direct breast reconstruction is however at best low, even in the developed world (10). A significant number of women are forced to undergo mastectomy without reconstruction. Barriers to high uptake of reconstructive surgery are the intensity of resources required, the impaired access to (direct and) delayed reconstruction, personal circumstances, and concerns about undergoing major surgery. However, the safety of these techniques, has been shown for years in medium to long-term follow-up cohort studies.

The axillary surgery has seen a paradigm shift over the last three decades. The standard of care has moved from axillary node clearances for all to sentinel lymph node biopsy to assess nodal status (AMAROS trial; <https://clinicaltrials.gov/study/NCT00014612>; ClinicalTrials.gov; ID NCT00014612) and limiting axillary node clearances to the node positive axilla. We now aim to limit axillary node clearances to those node positive axillae which do not respond to primary systemic therapy. This is primarily to reduce the exposure to risk of arm lymphedema which can be a debilitating complication. There are trials underway (ATNEC; <https://clinicaltrials.gov/study/NCT04109079>; ClinicalTrials.gov; ID NCT04109079) of further surgical de-escalation, with axillary radiotherapy for the responders. One recent trial has assessed the safety of omission of sentinel lymph node biopsy for small, good prognostic (cT1N0) breast cancers (SOUND trial; <https://clinicaltrials.gov/study/NCT02167490>; ClinicalTrials.gov; ID NCT02167490). Surgical de-escalation can sometimes be difficult for caregivers to adopt due to concerns around potential undertreatment; patients may therefore be not fully aware of their options. On the other hand, overtreatment poses significant risks

to impair quality of life of patients and is a financial burden for the patient, families, society and healthcare (see Chapter 14).

The importance of discussing all the surgical options with patients, including the risks and benefits, supported by prior multidisciplinary team discussion, allows choice and facilitates informed decision-making, taking into account patient preferences, beliefs, and personal/family situation (11).

## Personalizing follow-up: an example from the Netherlands

In most European countries, following primary treatment, women diagnosed with early breast cancer are invited to attend frequent follow-up visits in the hospital, generally every 3 to 4 months in the first 2 years, every 6 months from years 3–5, and annually thereafter (12). Follow-up can be divided into two parts: **surveillance**, with the aim of early detection of local disease recurrence or a second primary breast cancer and **after care**, aiming to provide information, detect late side effects, and provide psychosocial support.

In the Netherlands, a large variation in the organization of aftercare, particularly in timing, frequency, and disciplines of involved healthcare professionals (HCPs) has been seen. On a personal level, patients, and HCPs indicated a desire for personalization and more shared decision-making about the organization of surveillance. When there are multiple care options with similar outcomes from a medical perspective, patients indicated that for surveillance they agreed on the preference-sensitive nature of the decision. In such cases, patients' preferences for possible risks, benefits, and trade-offs between options play a crucial role in the decision-making process. According to HCPs, best practices centred on case management and collaboration between HCPs of different disciplines. Furthermore, HCPs were positive about less intensive surveillance for women with a low risk for recurrences. However, they highlighted the need for clearly defined surveillance schedules based on risk categories and cut-off values, information provision and communication support for patients and HCPs (13).

The need for frequent follow-up visits with clinical examination remains an issue of debate as studies have convincingly shown that it does not contribute to improved survival, may induce stress and anxiety because of the (perceived) risk of detecting a recurrence, and may fall short on meeting the needs of breast cancer patients in terms of physical and psychosocial support (14). Moreover, risk of recurrence is generally low and depending on the age, tumour characteristics, and treatment given. At the same time, intensive follow-up is associated with a significant cost burden. Therefore, nomograms were developed, such as the INFLUENCE nomogram first published in 2015. This prediction model was extended with contralateral second primary breast cancer in the INFLUENCE 2.0 version (15). Using this nomogram was cost saving in case of applying the nomogram. Similarly, it was estimated that offering follow-up care in line with individual preferences can reduce costs and improve satisfaction due to preference heterogeneity regarding frequency of visits and care provider.

The INFLUENCE 2.0-nomogram was incorporated in a patient decision tool ('Breast Cancer Surveillance Decision Aid' (BCS-PtDA, Figure 32.1) (12). The SHOUT-BC study revealed that using the BCS-PtDA reduced the anxiety and increased the feeling of shared decision-making. Participants in the post-implementation phase reported a more active role in decision-making, decreased decisional conflict, increased knowledge, decreased fear of

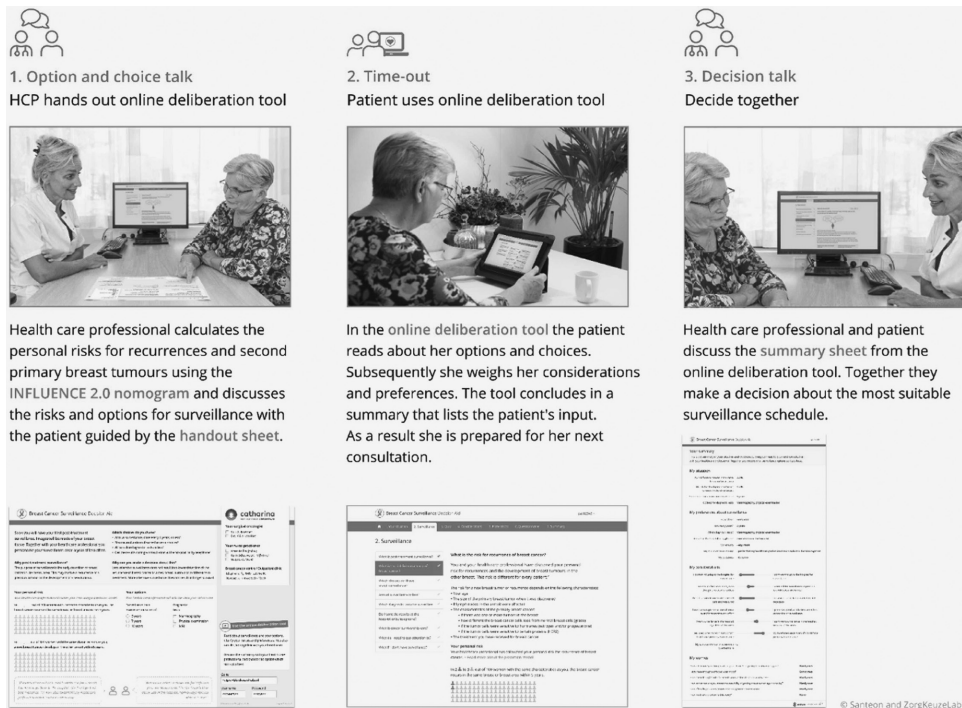


**Figure 32.1** The three components of the BCS-PtDA decision aid.

Reproduced with permission from Ankersmid. The use of outcome in shared decision-making about surveillance after breast cancer. ISBN (digital): 978-90-365-6115-0 (<https://doi.org/10.1016/j.ejca.2024.115107>).

recurrence, and a lower risk appraisal than patients in the pre-implementation phase. The patient-reported intensity of post-treatment surveillance schedules decreased slightly and the BCS-PtDA received highly positive evaluations.

In a subsequent study, the NABOR study (ClinicalTrials.gov; ID NCT05975437 (<https://clinicaltrials.gov/study/NCT05975437>)), the INFLUENCE nomogram has been further developed and includes a more recent patient cohort and patients with neo-adjuvant systemic treatment (16). Furthermore, a tool has been being developed in which the patient is supported in the choice for the aftercare plan focussing on the needs and goals of the patient (17). In the NABOR study cost-effectiveness of the use of the PtDA and the aftercare discussion tool as compared to usual care will be determined. Moreover, the guideline, which has already been adapted and advised a more personalized follow-up (18), will be implemented after the study.

## Pharmacology: making therapy more affordable

Personalization of breast cancer care also consists of optimization of pharmacology, which results in minimal burden for the patient but also takes the available resources into account. The registration dose and schedule of immune checkpoint inhibitors has largely used ‘maximum-tolerated’ rather than ‘minimum-effective’ dosing. Pembrolizumab pharmacokinetic studies have shown that 1 mg/kg every six weeks can be used rather than flat dosing of 200 mg every three weeks, which would reduce doses by 75% (19). In addition to this, adaptive patient

pathways in the neoadjuvant setting based on data from KEYNOTE 522 (ClinicalTrials.gov; ID NCT06418139; <https://clinicaltrials.gov/study/NCT06418139>) and pathological complete remission rates could be used. Patients with pathological complete remission (63%) could be spared the inconvenience, expense, and toxicity of continuing immunotherapy into the adjuvant setting. Then drug costs would be reduced by 86%. These reductions in drug costs would mean that these expensive new treatments would be much more widely available thus providing personalized medicine and better outcomes for patients across the world (20).

Similar reduction could be done with adjuvant antibody treatment in HER2 positive breast cancer, reducing the adjuvant treatment from 18 to 9 treatments, making it more affordable for many countries. Moreover, selective use of CDK4/6 inhibitors in second line instead of first-line treatment in metastatic disease, was also proven to be equivalent and cost-effective (SONIA-trial; ClinicalTrials.gov; NCT03425838; <https://www.clinicaltrials.gov/study/NCT03425838>, see Chapter 17).

## Interpretation

Interpretation, in the context of personalizing breast cancer care, specifically refers to gathering knowledge and understanding of prognostic and predictive biomarkers that provide insight into individual risks and benefits. The use of prediction models to support treatment decision-making for patients has been extensively elaborated.

A systematic review of the available prediction models aiming to support breast cancer treatment decision-making, published between January 2010 and December 2020, included 534 studies, reporting on 922 models. The 922 models predicted: mortality ( $n = 417$ , 45%), recurrence ( $n = 217$ , 24%), lymph node involvement ( $n = 141$ , 15%), adverse events ( $n = 58$ , 6%), treatment response ( $n = 56$ , 6%), or other outcomes ( $n = 33$ , 4%). In total, 285 models (31%) lacked a complete description of the final model and could not be applied to new patients. Most models ( $n = 878$ , 95%) were considered to contain high risk of bias assessed using the prediction model risk of bias (ROB; <https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials>) Assessment Tool (PROBAST; <https://www.probast.org/>). Moreover, a substantial overlap in predictor variables and outcomes between the models was observed. Most models were not reported according to established reporting guidelines or showed methodological flaws during the development and/or validation of the model. Development of prediction models with thorough quality and validity assessment is an essential first step for future clinical application (21). One of these is external validation, a prerequisite for implementation in clinical practice, has been performed for only a few models. Externally validation could be performed in 87 of the 922 published clinical prediction models using population-based data from the Netherlands cancer registry. It was revealed that of the 87 included models (predicting survival ( $n = 33$  (38%) overall,  $n = 27$  (31%) breast cancer-specific, and  $n = 3$  (3%) other cause-specific), locoregional recurrence ( $n = 7$  (8%)), disease free survival ( $n = 7$  (8%)), distant metastases ( $n = 5$  (6%)), lymph node involvement ( $n = 3$  (3%)), pathologic complete response ( $n = 1$  (1%)), and surgical margins ( $n = 1$  (1%)). Seven models (8%) showed poor ( $AUC < 0.6$ ), 39 (45%) moderate ( $AUC: 0.6-0.7$ ), 38 (46%), good ( $AUC: 0.7-0.9$ ), and 3 (3%) excellent ( $AUC \geq 0.9$ ) discrimination. Using the scaled Brier score, worse performance than an uninformative model was found in 34 (39%) models. It could be concluded that comprehensive registry data supports



broad validation of published prediction models. Model performance varies considerably in new patient populations, affirming the importance of external validation studies before applying models in clinical practice after careful impact evaluation.

## Innovation

**Innovation** must ensure equal access with the best use of resources for care/treatment and research. Innovation will proceed fastest if we work together with other disciplines, such as health technology and health economists. Implementation research and use of real-world data should complement information from randomized clinical trials. Artificial intelligence can support this. The aim is to allow access to personalized breast cancer care for all no matter where they live. Evidence-based guidelines for breast cancer treatment should be country and resource specific and the responsibility of the healthcare professionals on the ground in consultation with patients. This is further elaborated on Chapter 10. A modular approach could speed up the implementation as was achieved in the Netherlands.

## Key messages

- Personalized care involves the adoption of evidence-based and cost-effective management, which can be applied immediately, with care to pay attention to important patient preference and choice.
- As the molecular portrait of the tumour allows treatment personalization based on actionable targets, geriatric assessment allows treatment personalization based on a holistic view of the patient.
- The importance of discussing all the surgical options with patients, including the risks and benefits, allows choice, and facilitates informed decision-making, taking into account patient preferences, beliefs, and personal/family situation.
- It is time that current clinical practice guidelines for breast cancer follow-up are revisited to use a more risk-based, personalized approach, acknowledging patients' voices as well as costs to society.
- Guidelines for breast cancer treatment should be country- and resource -specific and the responsibility of the healthcare professionals on the ground in consultation with patients.

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**PART 9**

**PATIENTS, PHYSICIANS, AND THE MEDIA**



## How to manage the messaging

*Beth DuPree, Luis Lasalvia, Lopamudra Das Roy, Lisa Montel, Robyn Roth, and Shahla Masood*

### Introduction

‘You have breast cancer’, the four words that no woman or man wants to hear. A patient is faced with fear, feelings of being alone, and lacks the information to make intelligent decisions regarding their care. Breast cancer is an emotional emergency, not a surgical emergency. Often, there is ample time to obtain the opinions necessary for deliberative decision-making. However, from a patient perspective, the reaction seems to be universal: remove the cancer immediately. There is a sense of urgency in that moment, and decisions need to be guided by knowledge, not fear. They deserve and need a full understanding of their treatment options.

Evaluation and discussion from a multidisciplinary team is imperative to give patients the full picture of treatment options. Every decision has associated risks, benefits, and alternatives. Patients who face a diagnosis of breast cancer may find it challenging to wade through all of the media messages that swirl about them as they try to make treatment decisions and to weigh quality-of-care concerns.

Prior to the internet, physicians completely controlled the healthcare message. Currently, treatment options are more varied and patients must be included in shared decision-making. In the past few decades, patients relied heavily on the advice of their physician and now they have the ability to research treatments on the internet.

Currently, although treatment recommendations are often made with the assistance of evidence-based guidelines (for example, guideline-recommended post-lumpectomy radiation therapy or endocrine therapy for oestrogen-receptor-positive breast cancer), patients should still be invited to participate in the ‘shared decision-making’ process. In an era of patient-centric care, it is important to recognize that every patient is unique and different. Many patients try to understand everything and immediately turn to the internet for information, yet some rely on their physician to dictate their treatment. In small communities or in remote areas or environments underserved by multidisciplinary teams, gathering accurate information may be challenging. In certain cultures, diagnosed patients may be expected to make decisions based upon decades-old ‘traditions’ or are not expected to make decisions on their own behalf.

*‘We have the responsibility to educate and empower our patients to make decisions about their treatment based upon knowledge, not fear.’*

Beth DuPree, MD

## **The right to health: empowering patients to participate in decisions that affect them**

Everyone is entitled to ‘the enjoyment of the highest attainable standard of physical and mental health’ as protected by the International Covenant on Economic, Social, and Cultural Rights (‘the Covenant’) (1). Under this right, which all countries have committed to implement, patients have a right to access information that supports them in making decisions that affect their health (2).

Information should not only be available, but also accessible to all. This means that it should reach patients in their own language, including in minority languages or Braille when needed, and be easy to understand. For example, a woman with a nodule in her breast should have information, within the community where she lives, that she should seek help from her primary care physician and if needed undergo further examination for a potential early detection of breast cancer. Patients must also receive targeted information about their own case, so that they can participate in decisions about their care, including difficult decisions. To continue with the example of breast cancer, a woman should be informed about all possible options regarding partial or full mastectomy, breast reconstruction when available, and should participate in this decision with clinical and psychological support when available.

The right to access information and the right to participate in decisions affecting one’s health—both dimensions of the human right to health—are intricately linked to issues of power. Patient’s empowerment is ‘a process through which people gain greater control over decisions and actions affecting their health, which can be obtained through skill development, access to information and resources and influencing those factors that affect their health and well-being’ (3). Empowerment is both a process that enables patients to gain knowledge and an outcome, i.e. empowered patients who are able to make informed decisions.

The human right to health encompasses other principles that must be implemented by health facilities and physicians when delivering care (4). Physicians should not discriminate between patients, whether because of sex, age, disability status, religion, or ethnic group (Article 2.2 of the Covenant). There should be a continuous system of monitoring and evaluation to assess whether people’s right to health is respected. In terms of access to information, indicators could be collected to look at patients’ satisfaction with the way information is delivered to them and whether they feel they can adequately participate in decisions affecting their health (5). Continuous evaluation is crucial to establishing a system of accountability that ensures people’s right to health over time.

Acknowledging that patient empowerment is a human right creates a responsibility for Governments to support an efficient, robust, and fair health system. The economic and social structures in a country should encourage health providers to inform patients and include their voices in decisions. The right to health operates at a structural level and not just at the level of delivery of goods and services. It addresses patterns of inequality, power, and discrimination to give the voice back to people (6).

## The patient's right to know: implementation of appropriate strategies about breast cancer risk factors and the options for therapy

During the last several years, there have been significant changes in the diagnosis of breast cancer and the patient's options for therapy. In addition, advances in science and technology have contributed to better recognition of breast cancer risk factors and their relationship to the development of breast cancer. Currently, most breast cancers are associated with a favourable prognosis if detected early. Clinical breast exams, screening mammograms, advanced imaging technologies and molecular targeted therapies are now available for early breast cancer detection and optimal therapy (7).

Advances in genetic testing and increased awareness of the public about breast cancer risk factors are effective tools to better manage high-risk patients with breast cancer and provide them with the most effective risk reduction modalities such as bilateral prophylactic, mastectomy, bilateral oophorectomy, participation in chemopreventive measures, and close surveillance programmes. The impact of the progress made in breast cancer detection and therapy is best recognized if measures are in place to build trust between patients and their physicians. There is no doubt that the failure to obtain relevant personal information about a patient's risk of developing breast cancer is the first step in the failure of breast cancer detection and better control.

### Box 33.1 Case of a 28-year-old pregnant African-American woman

The patient was a 28-year-old pregnant African-American woman who felt a mass in her breast while showering. She was referred to her physician and was told that the mass is most likely the result of pregnancy. The mass persisted for four months after the birth of her baby. She then underwent a breast biopsy. The tumour was typical of a genetically mutated breast cancer that had already metastasized to the axilla. Based on the characteristics of the tumour, the patient underwent risk assessment and DNA genetic testing that identified the patient as a high-risk *BRCA1* mutation carrier. Despite aggressive therapy, the patient died within two years after her original breast cancer diagnosis. Upon review of her file it was found that the patient had a strong family history of breast cancer, the knowledge of which had not been recognized during her pregnancy visits. There is no doubt that if someone had asked her about her family history and she had known about her risk for breast cancer, she may have experienced a different outcome. She may have chosen to undergo risk reduction modalities a long time before she decided to become pregnant had she known about her high risk of breast cancer. But she did not know. There are examples of neglected high-risk patients with breast cancer who were unaware of their risk status and who are not counselled appropriately or in a timely fashion to guide their surgical treatments.

## Patient education

Patient education is a complex process and is the core component of the patient-physician relationship. There are studies suggesting that there is a direct relationship between the level of contribution by the physicians to educate their patients and the level of patient satisfaction and compliance with therapy (8). The physicians, particularly those ‘women healthcare gatekeepers’, such as primary care physicians, obstetric gynaecologists, and surgeons, should take the responsibility to properly educate their patients about breast cancer risk factors and the available options for follow-up management. Without this knowledge, a high-risk patient may not be referred for appropriate breast cancer risk assessment and possible DNA genetic testing. It is possible that if a neglected high-risk patient develops breast cancer, the failure of the physician to have informed the patient of his or her risk may lead to medical legal liability (see Chapter 34). Aside from medical liability, it is a social and moral responsibility for physicians involved in the care of their patients to familiarize themselves with the relevant breast cancer risk factors and learn about the most effective referral and management strategies. As an example, the specific morphologic features of triple-negative breast cancer of a high-grade breast cancer with geographic necrosis, frequent mitosis, and lymphoblastic infiltrate should alert the pathologists to the possibility of a genetically mutated breast cancer, followed by a recommendation for DNA genetic testing (see Chapter 23).

Similarly, with advances in the better understanding of the types of breast cancer and molecular characterization of breast cancer subtypes, the patients are entitled to know exactly what type of breast cancer they have and what their options are for therapy (9). Naturally, those patients with low-grade breast cancer can be spared from extensive cancer therapy versus high-grade multifocal and multicentric disease that requires more aggressive therapy. However, based on the experience with patients being referred for a multidisciplinary evaluation, the majority of the patients are often offered extensive cancer therapy regardless of the characteristics of their tumour. As an example, mastectomy is still offered to many women who are otherwise candidates for conservation therapy. It appears that low-income women, those who are less educated, or older women, are less likely to have breast-conserving surgery. One of the legitimate reasons for offering mastectomy instead of breast conservation therapy is the lack of availability of radiation therapy facilities in close proximity to patients. However, patients should have the right to learn about their options. In addition, patients with multifocal and multicentre ductal carcinoma *in situ* benefit from mastectomy as their initial surgical intervention. Therefore, it is essential to recognize that the physician’s recommendation based on the characteristics of individual patients remains the most influential factor in treatment choices. This consideration also holds true for the choice of sentinel lymph node biopsy versus total axillary dissection. This practice can spare many patients from the risks of lymphedema and other discomforts associated with total axillary dissection. It remains the responsibility of physicians to appropriately educate their patients. It is critically important that patients with breast cancer receive a great amount of specific information about the nature and extent of their disease and their options for therapy.

There are several possibilities to provide patient education; however, the methods of delivery of the information should be tailored to the patient’s health literacy. These include face-to-face communications, availability of online and printed breast health information that

has to be culturally sensitive, easy to understand, and multilingual (10, 11). There are also a variety of breast cancer education programs available on the internet; however, the websites might be difficult to navigate. There are also issues surrounding the quality and the accuracy of the information. More importantly, the internet may not be readily accessible to medically underserved populations. There is no doubt that online patient education may be a powerful tool that gives patients the knowledge and skills so that they can make their own treatment decisions (11, 12). However, those available currently to the public do not meet the criteria for readability, understandability, or actionability. The internet can offer unparalleled opportunities to increase public breast health literacy with assistance from knowledgeable experts in breast health education. Ultimately, breast health education remains the responsibility of healthcare providers.

## **Bridging disparities and ignorance**

There is a huge gap in breast cancer survival globally, with the death rate being significantly higher in developing countries due to taboo, ignorance, and lack of awareness leading to late detection, inaccessibility to healthcare facilities, proper guidance, and treatment management. Irrespective of socioeconomic status and education, the populace in urban sectors of the developing world are also reluctant to undergo breast cancer screening, as health is their last priority, even if their local centres provide free or subsidized screening. In the USA, many minority communities of diverse races and ethnicities delay early-detection screening processes due to the inherent culture of disregard for breast health, leading to late detection and death. Therefore, the challenges are not only about the rural populations poor access to the hospital system but also urban society's inertia to discuss breast concerns due to the ingrained ideology of shyness about breast health.

It is equally imperative to highlight the ground reality in the underprivileged sectors living in poverty. This populace is not only in financial constraints, struggling for daily food, with health taking a back seat, but due to geographical barriers, the hospitals equipped with cancer screening and treatment are in towns/cities, needing hours of travel for the villagers as they live in the remote far-flung areas, investing the full day to go back and forth, adding to their transport charges. It is hard for them to miss their daily wage, and since a family member needs to accompany the at risk individual, the monetary loss adds up, eventually delaying or skipping treatment. Many countries assist the underprivileged populace with their government schemes, but unfortunately, the villagers are unaware of these avenues, and even if they knew, their daily fight for existence surpasses the illness. The challenges of this population worldwide need to be addressed at the grassroots level with sustainable solutions, by taking care end to end.

Within urban sectors, we also see a disproportion in leveraging the resources available via the internet, social media, or support groups, as the educated target audience also come from diverse backgrounds, races, ethnicities, languages, and age groups, finding it difficult to access and comprehend the complex terminologies, leading to fear and negativity. Verifying the available educational resources is vital, requiring experts to generate awareness in the community about screening protocols and counsel the patients and caregivers, channelling them towards the authenticated resources available in native languages, and connecting them to the support groups that are supervised by professionals.

In today's world, advancement has touched our lives through technology, science, and medicine, yet our minds continue to perpetuate the stigma that has engulfed our society for ages. It is important to uproot the fundamental taboos in addition to executing sustainable programmes, which will help bridge the disparities existing in the same world we all live in.

## Online resources and support for patients

A cancer diagnosis can be a life-altering event, often accompanied by emotional, physical, and logistical challenges. Access to trusted resources and support can significantly improve the patient experience. Numerous organizations, operating across both developing and developed nations, are dedicated to providing free, compassionate assistance. This section highlights three noteworthy resources: Breast Cancer Hub (BCH), Macmillan Cancer Support, and Breastcancer.org—each offering unique, patient-centred approaches.

### Breast Cancer Hub

Founded in 2017, Breast Cancer Hub (BCH; <https://www.breastcancerhub.org>) is a non-profit organization committed to delivering 100% free services to underserved populations, particularly in countries such as India, Sierra Leone, and Nigeria. BCH adopts a comprehensive, grassroots model of care that includes:

- Cancer screening, diagnosis, and treatment assistance
- Counselling services and food support
- Door-to-door screening initiatives through village adoption
- Educational outreach using self-exam cards translated into 27 languages
- Survivor stories shared in local languages to offer encouragement and empathy

In addition to in-person services, BCH supports a private, multilingual Global WhatsApp Support Group that connects patients and caregivers across the globe. The group is moderated by healthcare professionals, ensuring full confidentiality and cultural sensitivity. This platform provides a safe, respectful space for emotional support, treatment guidance, and community connection—especially for those facing stigma in their local environments (Figure 33.1)

### Macmillan Cancer Support

Macmillan Cancer Support (<https://www.macmillan.org.uk/cancer-information-and-support/breast-cancer>), based in the United Kingdom, has been providing holistic cancer care for over a century. The organization focuses on supporting patients from the moment of diagnosis through every stage of the cancer journey. Recognizing that cancer affects more than just physical health, Macmillan addresses a wide range of patient needs, including:

- Access to medical information and breast cancer-specific guidance
- Emotional and psychological counselling





**Figure. 33.1** Education in the underserved population in India.

© Lopamudra Das Roy, Founder & President, Breast Cancer Hub (<https://www.breastcancerhub.org/>)

- Financial advice and social support
- Career and relationship impact resource

Macmillan's services are designed to empower patients to live as fully and independently as possible, tailored to individual experiences and needs.

## Breastcancer.org

Breastcancer.org (<https://www.breastcancer.org>) is a United States-based nonprofit that provides a comprehensive online platform tailored to the needs of a global patient audience. The organization emphasizes education, empowerment, and community through the following offerings:

- Expert-reviewed articles and evidence-based medical information
- Step-by-step guidance through diagnosis, treatment options, and recovery
- Online forums for peer-to-peer support among patients and caregivers
- Multimedia content, including videos and podcasts, to enhance understanding

Its easily accessible platform serves as a vital resource for newly diagnosed individuals seeking clarity, support, and connection in their healthcare journey.

These organizations exemplify how education, empathy, and access can empower patients worldwide. While some focus on digital communities and knowledge dissemination, others deliver hands-on, localized care. Their shared mission is rooted in the belief that every patient

matters, regardless of geographic or socioeconomic background. By offering free services and safe, inclusive spaces, these organizations ensure that no patient has to face cancer alone.

## Internet-generative AI, podcasts, media, and TV in patients' terms

Breast cancer patients need reliable information about their health. Patients are critical and promisingly active players in the management of their health. Their inclusion in the core breast cancer team involves their participation in making informed and, many times, decisive decisions about the management of their condition. As patient education is of paramount relevance, it needs to be reinforced and stimulated appropriately.

**Internet:** As of 2023, two-thirds of the world's population or roughly 5.4 billion people now have access to the internet. Increased internet access now means that information is widely available to patients directly, helping to mitigate the geographic and socioeconomic barriers to breast cancer care. One of the first things that many patients do after receiving a breast cancer diagnosis is to reach for their phone and look up their illness on the internet. A 2022 study from the Centers for Disease Control and Prevention (CDC) showed that over half (58.5%) of adults used the internet to look for health or medical information, with a higher prevalence observed among women compared to men. Patients, physicians, technology, and the media all play a role in healthcare messaging and what information is available.

There's a revolution in how breast cancer information is used, driven mainly by the explosive growth in the number of websites and online information available now. This massive overload of information has been fuelled by the global demand of patients for information on breast cancer on one hand, and on the other by the record number of people accessing the internet as well. In 2024, more than 5 billion people are using the internet, standing for 66% of the population, and the number continues to increase as we author this book (13) (see Chapter 24). In the United States, 92% of individuals accessed the internet the same year, and 80% of internet users searched for health information online (14). One in two Europeans goes online to look for health information, and over the last decade, the share of individuals seeking health information online has risen in European member states (15).

The volume of information has also increased significantly over the years. As we are authoring this book, an internet search using the phrase 'breast cancer' reveals 1.7 billion results, up from the 150 million available when the first edition of this book was written, five years ago. A Google search for 'shared decision-making in cancer' yields more than 83 million results, an increase of over 360% in the same period.

An amount of accessible information is transforming the way breast cancer information is being managed:

1. The physician is no longer the information gatekeeper in breast cancer
2. Information flows freely and is accessible directly to the patients
3. Patients are exposed to experience information overload, misinformation, misunderstanding, and unnecessary distress
4. Patients and families are challenged on where to look for reliable information
5. Patients may sometimes have even more updated information than the specialist

When searching for all their answers, podcasts, blogs, and resources:

1. Assess the authors' credentials
2. Confirm the authenticity and current value of the information by cross-examining with trustworthy references
3. Knowing the owner and sort of the internet site (i.e. websites ending in .edu, .gov, or .org aim to offer unbiased info) (financial gain/conflict of interest)
4. Checking if the information on the site is peer-reviewed
5. Avoid sites that employ exaggerated promises (too good to be true)

The physician plays an important role in proactively guiding the patient to find websites to mitigate patient information overload, bias in info, and unnecessary anxiety. Instead of telling patients to stay offline, or to leave it up only to them, the healthcare professional adds quality value to the management of breast cancer patients by directing their attention to credible and helpful websites, forums, or blogs.

Reliable websites for breast cancer information include:

1. <https://www.who.int> (Global breast cancer initiative implementation framework, different languages available)
2. [breastcancer.org](https://breastcancer.org) (US)
3. [www.nationalbreastcancer.org](https://www.nationalbreastcancer.org) (US)
4. [breastcancerhub.org](https://breastcancerhub.org) (India)
5. [breastglobal.org](https://breastglobal.org) (India)
6. <https://www.macmillan.org.uk>

Reputable medical institutions also have a robust online presence.

**Generative AI:** On top of that, the sudden rise in using generative artificial intelligence online is deeply transforming how breast cancer information is treated. Available in more than 120 countries, it includes the generation of snapshots with information that turns scrolling through endless results no longer needed. In addition, it adds conversational, patient-engaging, and personalized themes, with diversified content already included in the results. These provide patients with further opportunities for more access to the information available. However, at the same time, it calls for considering its potential to harm the accuracy of the information. Patients and healthcare professionals should interpret the results with caution, focusing on ensuring the quality, safety, and efficacy of the information. The potential bias in certain results and the increasingly realistic presentation of text that can blend genuine and fabricated information are two of the potential risks of generative AI.

**Podcasts:** A quick search of 'breast cancer' on Apple Podcasts reveals hundreds of podcasts from a wide range of hosts covering a wide range of topics.

Podcasts can be a valuable way to spread information to a large audience, especially to those who are navigating a breast cancer diagnosis. Similar to all information on the internet,

the source of the information should be considered and verified when being used to make important treatment decisions. It is relatively easy to start a podcast, given the increased accessibility of recording and editing equipment and platforms to distribute recordings. Conversations can be recorded on a phone or computer using Zoom, Riverside, or Zencaster (many of which offer free subscriptions), edited using software such as GarageBand, and distributed across all podcast platforms at the click of a button using websites such as RedCircle. Vetting the credibility of the podcast host and content can be the challenge.

**Media:** It is not uncommon to see breast cancer on the front page or top story of large international publications and news programmes. As the most common cancer in women worldwide, breast cancer affects millions of people across the globe who are media consumers. Advances in breast cancer screening and treatment are happening rapidly, and headlines often reflect that.

Like it or not, celebrities also play a major role in breast cancer screening and treatment decisions. In 2013, after Angelina Jolie wrote an op-ed for the *NY Times* regarding her decision to undergo *BRCA*-testing and prophylactic bilateral mastectomy due to her mother's history of ovarian cancer, there was a 64% uptick in the rates of cancer genetic testing in the two weeks following publication, which has since been referred to as the 'Angelina Jolie effect'. In addition, the number of women choosing mastectomy increased sharply.

The same can be said for Olivia Munn's 2024 bilateral breast cancer diagnosis, which was only discovered after she was found to be high-risk from the Tyrer-Cuzick calculator and received a breast MRI, which has led to a spike in breast cancer risk assessment and high-risk screening.

**Television:** Medical TV shows can be an effective means of imparting breast cancer-related information to the public. However, it's crucial to understand that not all information presented on TV is trustworthy and accurate, and that carries important risks. Some recommendations may have no evidence or even contradict evidence-based medicine, can misrepresent the relevance of potential benefits, or may not address conflicts of interest adequately. For these reasons, patients should evaluate the content they come across critically and consult breast cancer physicians to make informed decisions about their health. The TV content helps better when it integrates a balance between supplying accurate data and attending to emotional needs, as both aspects are key for achieving the patient's appropriate education and psychosocial support.

Patients need to seek out high-quality information and educate themselves about their health, but it's equally important to consult with experts to avoid any potential misinformation (16). With so much information available online and on TV, it can be difficult to know what's correct and what's not. Seeking advice from their physician about proper channels of information is a great way to ensure patients are making well-informed decisions about their health.

## Conclusion

### What can we do as physicians?

It is challenging to answer the questions of patients who are influenced by media messages about breast cancer treatment. The media is not always correct and not always wrong.

Physicians receive information from multiple sources and it is unrealistic to expect that patients will not consult 'DR GOOGLE' or online chat rooms, as well family and friends. Physicians are not the only source of health information, but they need to remain the most credible source. This presents a unique opportunity to impact patient education, but they must meet patients where they are searching for answers, which most often is online. We can suggest that quality online information can also create social media content, and can participate in online discussion groups and podcasts. Increased physician engagement can substantially improve patient experience for those patients actively seeking information and advocating on behalf of other patients with similar diseases (17).

One of the primary roles of a physician is to be a source of education and support to patients. Thackeray et al. studied the use of Twitter as an educational platform during Breast Cancer Awareness Month (18). The majority of users were individuals, though they found that organizations and celebrities posted more often and had the most online shares. Celebrity tweets primarily focused on fundraising, early detection, and diagnosis. Individuals primarily tweeted about wearing pink. This is an example of a missed opportunity by physicians to promote health literacy. Physicians who carefully and consciously engage in various social media platforms have a unique opportunity to provide credible medical information, support, and guidance to a large audience that is thirsty for this sort of information.

An often-overlooked aspect of physician participation in social media and engaging with patients in online forums is the benefit that physicians receive from these interactions. The current chapter authors, who participate in interactive online patient communities, feel there is a much deeper level of appreciation for what patients are going through. In-person patient interactions have changed the way they ask questions and gained a better understanding of the patient experience. Perhaps most importantly, by engaging on social forums, physicians may better learn what questions patients are asking when they are not sitting in examination rooms.

## Key messages

- Physicians play an important role in terms of directing patients to credible websites, forums, and blogs that are factually correct and non-threatening.
- Encourage patients to bring information found online to the attention of their physician and to discuss whether the information actually pertains to them.
- A constructive relationship between doctors and journalists, with understanding on both sides about their respective roles and responsibilities, can help promote good-quality health journalism that is accurate and fair but also investigative and independent.
- The media can play a valuable role in informing the public, holding healthcare providers and policymakers to account, and opening up informed discussion on how to improve standards of healthcare.
- Physicians need to truly understand that patients are receiving information from multiple sources.
- Physicians can direct patients to quality online information, create content, and participate in online discussion groups.

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## Medico-legal aspects

*Richard Linforth, Rudi Vermeiren, Cary S. Kaufman, and Robert Mansel*

### Introduction

Over the last 20 years, the number of medico-legal or malpractice claims against clinicians has risen.

In a review of claims in the UK administered by NHS resolution, clinical negligence claims doubled from 2006 to 2016 from 5,300 to 10,600. In 2018–2019, the annual cost of clinical claims was £2.4 billion, which represents about 2% of the entire NHS UK budget for that year. Breast makes up a small percentage of such claims and ranked 3.5% (224/6351) of all general surgical claims and 22.7% of plastic surgical claims (128/564). In 2023, total negligence claims against the NHS topped 12,000 at a cost of £8 billion pounds 6.7% of the NHS UK budget (Figure 34.1) (1, 2, 3).

The same worrying trend is seen across Europe; i.e. in the Netherlands (4) and Poland, the cost of closed claims nearly quadrupled between 2007–2021.

In the USA, misdiagnosis or delayed diagnosis accounts for nearly one-third of medical malpractice claims.

### Principles of civil liability

There are well-established principles in the law of civil liability. First, the clinician (defendant) must observe the standard of care for the patient (claimant), i.e. the clinician is responsible for delivering those usual efforts to the correct diagnosis or treatment as judged by professional standards. This is known as failure according to the standard of care. Third, the patient (claimant) has to show that he/she has been harmed in a measurable way, such as earlier death, more extreme treatment, increased pain, and suffering, as a result of additional treatment or financial loss. This is known as causality (harmed). If failure and causality are proven, then the court can award financial compensation to the claimant with the aim of restoring the individual to the position they would have been in if the failure had not occurred.

A delay in the diagnosis of breast cancer is one of the most common reasons for litigation against a breast specialist. The claim will usually involve the radiologist and or the surgeon and occasionally a primary care clinician.

In asymptomatic patients, this may mean failure to carry out the appropriate investigation, such as imaging, needle core biopsy, or arranging an appropriate follow-up. In screening, it usually means failure to detect the early signs of breast cancer or misinterpretation of

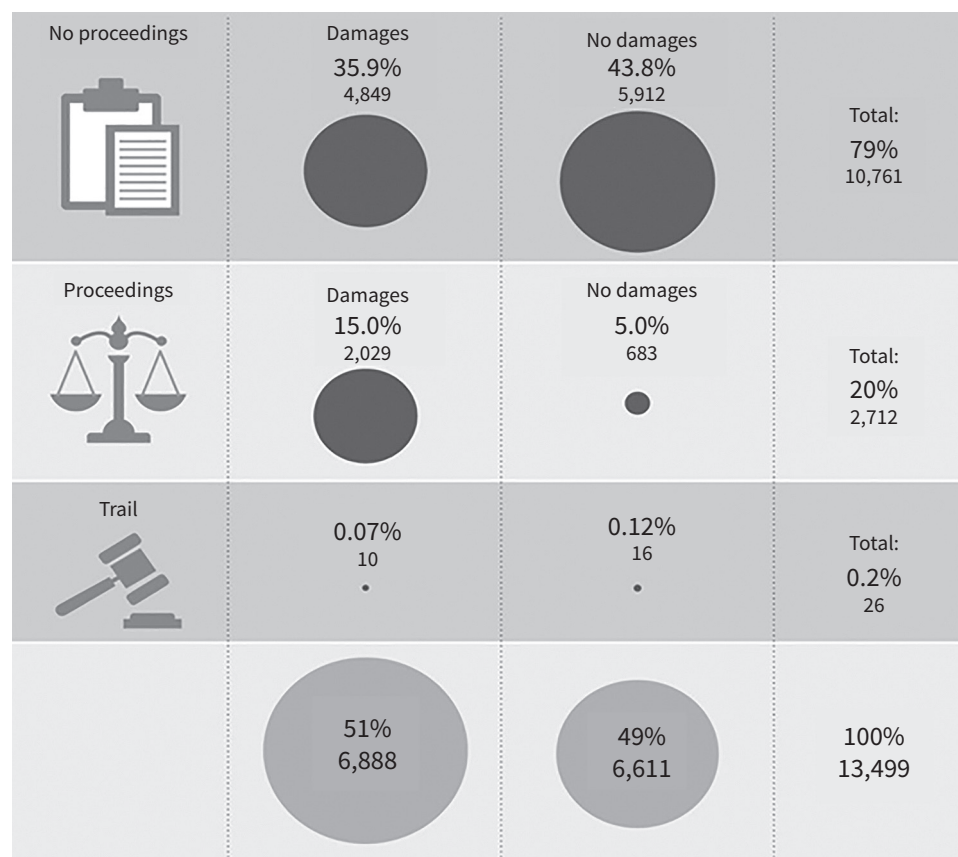


**Figure 34.1** Resolution of 13,499 claims settled in 2022/2023 by the NHS, showing a decreasing amount (–2,841) of proceedings and trials compared to 2016/2017.

imaging. The median age of the claimant is under 50, where mammographic interpretation may be significantly hindered by breast density.

Other causes of litigation include surgical site infection, cosmetic outcome dissatisfaction, implant-related issues, and lack of informed consent.

One established standard of breast assessment is known as triple assessment with physical examination (P1-5), radiological assessment with ultrasound (U1-5), and/or mammography (M or R1-5), and core biopsy (B1-5a/b). (Here, the grading 1–5 means from most likely benign (1) to most likely malignant (5) according to the examination modality.) In the absence of any palpable or radiological abnormality clear core biopsy is not performed (6).

Sensitivity of physical breast examination is clinician-dependant and ranges 44–66% predictability of cancer with the age of the patient being significant. Specificity, however, remained fairly consistent. In a retrospective review of 16,603 clinical breast examinations at the Cambridge breast unit, UK, Wishart et al. found that sensitivity increased with age, being as low as 11% in those <30, to 88% in those over 90 years (7).

Overall, clinical examination alone is correct in 60–85% of cases. The low sensitivity of clinical examination, coupled with the low frequency of breast cancer in women under 50



and the relatively high number of younger women in breast clinics with benign nodularity, may explain why the most common claimant for a delayed diagnosis is 46 years of age.

Mammography also has a sensitivity that increases with age due to breast density decreasing with age. Two-view digital mammography is the first-line imaging of women over 40 attending a one-stop clinic with ultrasound for any palpable abnormality.

The delay in diagnosis for breast cancer tends to arise when the claimant complains of a lump, and the clinical examination is considered normal or probably benign (P1-3). With clinical examination alone having a 30–40% inaccuracy, focal imaging of the P1 symptomatic area will, on balance, reduce the false-negative rate of a missed cancer.

If imaging is normal (M1/U1) or does not show a discrete focal mass, core biopsy may not be performed.

Guidance has been described for the management of a symptomatic lump showing an algorithm for clinical assessment, imaging and needle biopsy, and multidisciplinary team (MDT) discussion (6).

The other common error is when a P3-indeterminate lesion is felt, but imaging is normal, a clinical review with core biopsy of the palpable abnormality would significantly reduce the missed cancers, which may often be lobular in nature.

Accepting a failure in diagnosing breast cancer leads to a delay in diagnosis. Short delays of a few weeks may have no detrimental effects on treatment or survival.

Quantifying the impact of delay can be estimated using medical-legal tools such as Tumour volume doubling times (TVDT) to estimate the size of a tumour at first presentation.

Most publications on TVDT are taken from the screening programmes (8). Growth rates are known to vary from 28 days in young under 40 *BRCA1* gene carriers, 80 days in a woman under 50, 157 days aged 50–70, and 188 days over 70. Other biological features will also increase TVDT, such as high grade, ER negativity, HER2 positivity, and high Ki-67 expression (9). Knowing the interval between first presentation and diagnosis, plus the size of the cancer at diagnosis, allows the back calculation facilitated by online calculators using these doubling times.

Once the size of the tumour has been calculated, nomograms such as the Memorial Sloan Kettering tool for sentinel lymph node positivity can be used to estimate whether or not any axillary nodal disease would be present. Estimating the number of nodes is much more difficult as metastatic progression does not follow a linear relationship once the process of metastasis has begun.

## Quantification and prognostic tools

Prognosis and survival can be quantified by tools such as the Cambridge Predict model or Cancer Life Maths, which can also calculate potential years lost for quantum.

If a delay is more than a few months disease can progress from a small node-negative cancer to a large node-positive cancer, meaning not only additional treatments such as axillary dissection instead of sentinel node with a much higher rate of lymphoedema, or the addition of systemic chemotherapy, which may have been avoided in a smaller ER-positive node-negative cancer. These additional treatments with their associated morbidities each add to the quantum, along with any loss of years lost in prognosis.

In terms of prognosis, Hanna et al (10) reviewed mortality due to cancer treatment delays in a systematic review and meta-analysis. The review included 1,272,681 patients in 34 studies.

Surgery findings were consistent with a mortality risk for each four-week delay of 1.08 for breast surgery compared to 0.98 for breast radiotherapy after conservation surgery. Breast cancer mortality increased from a baseline of 12% mortality by 6–8% for each four-week delay. Delays of up to eight weeks and 12 weeks further increase the risk of death.

For example, an eight-week delay in breast cancer surgery would increase the risk of death by 17% ( $=1.08^{8\text{weeks}/4\text{weeks}}$ ), and a 12-week delay would increase the risk by 26% ( $=1.08^{12\text{weeks}/4\text{weeks}}$ ).

Such figures translate into significant excess mortality at the population level. A surgical delay of 12 weeks for all patients with breast cancer for a year (e.g. during COVID-19 lockdown and recovery) would lead to 1,400 excess deaths in the United Kingdom, 6,100 in the United States, 700 in Canada, and 500 in Australia, assuming surgery is the first treatment in 83%, and mortality without delay is 12%.

Delays to chemotherapy among patients with breast cancer also impacts on survival.

In a study of 24,843 patients on the California cancer registry, time to first dose of chemotherapy (TTC) was a median of 46 days, with a delay defined as 91 days or more from surgery. Adverse outcomes were similar with TTC of 31 to 60 or 60–90 days, whereas those treated after 90 days had a worse overall survival (HR 1.34) and worse breast cancer-specific survival (HR 1.53) (11).

In another study of 6,827 patients treated at the MD Anderson centre, Texas, USA, time to chemotherapy after 61 days was associated with adverse outcomes among patients with stage II or III disease. In addition, triple-negative and HER2-positive patients had worse survival (HR 1.54 and 3.09, respectively) compared to those who started treatment in the first 30 days after surgery (12).

Claims relating to treatment choice and informed consent are also significant.

## Informed consent

Consent has moved to the forefront of good medical practice and doctors are negligent if they fail to obtain truly informed consent (13).

A body of professional clinicians can no longer determine treatment (the former Bolam standard). Medical paternalism has been replaced by shared care and patient self-determination; patients are now partners in the decision-making process. (See Box 34.1).

Informed consent is the process in which a healthcare provider educates a patient about i.e. the risks, benefits, and alternatives of a given procedure or intervention. The patient must be competent to make a voluntary decision about whether to undergo the procedure or intervention. Informed consent is both an ethical and legal obligation of medical practitioners and originates from the patient's right to direct what happens to their body. Implicit in providing informed consent is an assessment of the patient's understanding, rendering an actual recommendation, and documentation of the process.

It is clear that this is a time-consuming process if done correctly and may take more than one outpatient visit. The General Medical Council has provided principles of decision-making and consent (14) (See Box 34.2).

### Box 34.1 Case study: Montgomery v Lanarkshire health board

It was the Nadine Montgomery case in 2015 which brought the law firmly into line with modern medical ethics (13). Many readers will be familiar with this landmark ruling from the UK Supreme Court. The claimant was a diabetic woman of small stature whose baby was known to be large. The birth was complicated, the baby suffering shoulder dystocia and subsequently developed cerebral palsy. The risks associated with a vaginal delivery in such a patient were: shoulder dystocia 10%, brachial plexus injury 0.2% and cerebral palsy 0.1%.

After two appeals, the claimant won substantial damages from her provider. The Supreme Court unanimously held that a patient has a right to be informed of 'material risks'. She should have been told about the risks of vaginal delivery compared to the alternative, so that she could have made an informed, consenting decision about her management and elected to have a caesarean section.

The test of materiality was whether, in the circumstances of the particular case, a reasonable person in the patient's position would be likely to attach significance to the risk. The court said that materiality cannot be reduced to percentages and the extent of disclosure should be fact sensitive and emphasized the importance of 'dialogue' over mere lists or consent forms.

*Source:* data from Montgomery v Lanarkshire Health Board [2015] UKSC 11 (11 March 2015) (13).

### Box 34.2 Proposed principles of decision-making and consent

- 1) All patients have the right to be involved in decisions about their treatment and care and be supported to make informed decisions if they are able.
- 2) Decision-making is an ongoing process focused on meaningful dialogue: the exchange of relevant information specific to the individual patient.
- 3) All patients have the right to be listened to, and to be given the information they need to make a decision and the time and support they need to understand it.
- 4) Doctors must try to find out what matters to patients so they can share relevant information about the benefits and harms of proposed options and reasonable alternatives, including the option to take no action.
- 5) Doctors must start from the presumption that all adult patients have the capacity to make decisions about their treatment and care. A patient can only be judged to lack the capacity to make a specific decision at a specific time, and only after assessment in line with legal requirements.
- 6) The choice of treatment or care for patients who lack capacity must be of overall benefit to them, and decisions should be made in consultation with those who are close to them or advocating for them.
- 7) Patients whose right to consent is affected by law should be supported to be involved in the decision-making process, and to exercise choice if possible.

The choice of treatments with de-escalation surgery after neoadjuvant chemotherapy, alternative treatments to the axilla after sentinel node biopsy such as no further treatment, axillary radiotherapy or axillary dissection alone can be confusing for a patient as are the choice of implant reconstruction versus autologous techniques, donor site morbidity, and aesthetic satisfaction.

It is the obligation of the provider to make it clear that the patient is participating in the decision-making process and avoid making the patient feel forced to agree to with the provider. The provider must make a recommendation and provide their reasoning for said recommendation.

In some facilities, delegation of the decision-making process is routinely used by multidisciplinary teams. In doing so it is the senior responsible clinician that must make sure that the person delegated to is:

Suitably trained and competent, has sufficient knowledge of the planned treatment or intervention and its associated benefits and harms, as well as alternative options for treatment and care and has the skills to have a dialogue with the patient.

When poor outcomes and medico-legal claims do occur, lessons may be learned and integrated into local governance frameworks by meaningful reflection and education. For example, the regular inclusion of medico-legal claims in local morbidity and mortality meetings would facilitate ongoing awareness and education both for consultants and trainees. However, though being aware of the underlying trends, causes, and injuries may enable clinicians to reflect on their own practice and enact change, a wider approach is needed. Several actions at an organizational level, including investing in staff and infrastructure, learning from and disseminating practices that result in clinical excellence, committing to high-quality professional education, and supporting system-wide safety improvements have been shown to improve clinical outcomes. An approach combining both improvement in local surgical care and higher-level system changes will be necessary to address the medico-legal burden.

## Key messages

- Breast cancer is a leading source of malpractice claims for radiologists and breast pathologists. Other disciplines are concerned, including surgeons, general practitioners, radiotherapists, medical oncologists, and reconstructive surgeons.
- The importance of breast imaging in screening and diagnosis means that breast radiologists are on the frontline for medico-legal actions.
- Once a failure to observe the standard of care has been established, the claimant must prove the measurable damage to the patient.
- All doctors present at the multidisciplinary breast cancer meeting and contributing to the decision-making process are accountable for decisions related to their area of expertise.
- A greater awareness of the responsibility of all disciplines will optimize outcome for patients and limit exposure of doctors to legal liability.
- Prognosis and survival can be quantified by specific tools.
- Informed consent has moved to the forefront of good medical practice.

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**PART 10**

**THE ROLE OF GOVERNMENTS AND  
EXECUTIVES**





## Europe

*Wim van Harten, Silvia Brotea-Mosoiu, Tania Cufer, Sabine Siesling, and  
Didier Verhoeven*



**Figure 35.1** Europe

'Shaping our future with resilient forests'.

Visceral landscapes by Pascale Pollier.

Breast duct cell cluster in carbon dust technique created by © Pascale Pollier MAAA, Registered Medical Illustrator, Artem Medicalis. Hallerbos background landscape image generated and edited in Adobe Photoshop AI.

## Introduction

In this chapter, we will cover the tasks and responsibilities of governments and agencies in the European setting, of professional societies, and of hospital executives. Specifically, we will

cover technology development, innovation, and differences in access related to system characteristics and to management choices. The European Commission (EC) has limited jurisdiction related to breast cancer care, as healthcare and social care system choices are defined as national competence in the EU treaty.

## Tasks and responsibilities of governments

Research and development (R&D) and market and consumer regulation are agreed to be the EU's competence. However, a strict delineation is not always possible, for instance, in case of for-profit- and private sector-based healthcare provision or managed competition type of care systems, such as is the case in the Netherlands. The European Medicines Agency (EMA) decides on access of drugs and devices to the European market, whereas national agencies have to decide on coverage and acceptability of prices and costs. As a consequence of this focus, EC R&D and market development programmes and subventions have commonly been much larger than subvention budgets related to healthcare provision.

The EC, through its Directorate-General for Health and Food Safety (DG Sante), is primarily responsible for protecting and improving public health, and this role has certainly gained momentum as a consequence of the COVID crisis. We see the DG exploring the limits of their mandate, such as cross-country travelling of patients and the quality and care provision for rare diseases (1). As part of their responsibility for quality, breast cancer was prioritized as a development domain, and from 2015 onwards an extensive project was conducted through the Joint Research Centre (JRC) structure on guidelines and a quality assurance scheme for the breast cancer care pathway in their European Commission Initiative on Breast Cancer (ECIBC) (2). The newly launched European Quality Assurance Scheme for Breast Cancer developed under the ECIBC is a voluntary instrument to implement European guidelines, monitor, and evaluate their compliance with European requirements. Important features are 64 evidence-based quality requirements developed with experts and patient representatives. Certification will be delivered by independent accredited certification bodies. For inquiries about the scheme: [JRC-CANCER-CARE-QA-SCHEMES@ec.europa.eu](mailto:JRC-CANCER-CARE-QA-SCHEMES@ec.europa.eu)

By the end of 2025, the Commission renewed its expert panel, appointing a new vice chair (Didier Verhoeven, lead editor) and new working group members. They will update the breast cancer guidelines and quality assurance scheme within the context of organized, population-based screening and follow-up care. For inquiries about the scheme: [JRC-CANCER-CARE-QA-SCHEMES@ec.europa.eu](mailto:JRC-CANCER-CARE-QA-SCHEMES@ec.europa.eu).

There are no reports on the degree to which this material has been used in practice after being formally published.

In recent years, the EC has decided to focus on cancer in its policies, resulting in the Beating Cancer Plan (3) in which a broad scope of preventive, services and research aspects and fields are covered, and many billions of Euros are to be spent. Part of this plan is a cancer mission on R&D funding on topics identified as relevant for cancer mission-related research projects (4). Many of these projects are not diagnosis-related and focus on training and capacity building, improving cancer services in general and stimulating the interaction of care and research in comprehensive cancer infrastructures. Breast cancer can, of course, be a topic in such a project or initiative, but will seldom be the sole subject.

Apart from obviously those countries that are not members of the EU, health system choices and related responsibilities are the competence of national governments. The three main variants are:

- ‘Bismarckian-like systems’ that have social insurances or sick-fund-like structures. The government regulates the system, but the insurance companies execute coverage and funding and negotiate budgets with often private providers (either profit or non-profit) (e.g. Germany).
- National Health Service variants have health systems that are completely administered by the government (UK) or regional authorities (Scandinavian countries). Often, providers are also public entities. In some countries, services not covered by the public authority or additional to the public services (in terms of faster access or extra amenities) can be accessed through private, additional insurance and private providers (Italy).
- Mixed systems with management competition. In Eastern Europe, we see mixed systems with limited public service offerings and extensive private sectors. In the Netherlands, there is managed competition in terms of both insurance companies having to compete for subscriptions (without the possibility to refuse patients) and healthcare providers competing for contracts with the insurers and patients. The government acts as a strong regulator of the system, especially to constrain costs.

Related to breast cancer, there can be national choices and priorities on screening and prevention, on investments in technology (when these are not within the competence of the provider) and on coverage of interventions and—especially—expensive new treatments. This can have an effect on the availability of magnetic resonance imaging (MRI) diagnostics and access to expensive drugs. Further in this chapter, data about these differences are provided.

Countries cherish and protect their national competence on healthcare provision and system choices, and so far, national choices on quality regulation, concentration, and networking are dominant. A certain degree of- and gradual alignment between countries is to be expected. Apart from the earlier COVID-19s experiences, the EU Beating Cancer Plan, with initiatives such as working on Comprehensive Cancer Infrastructures, the ECBIC, by the JRC, initiatives from professional societies such as EUSOMA and publications on differences in access, costs, and survival will inevitably have effect on a very gradual shift towards new balances in EU and national competences.

## **Differences in spending, availability of medical technology, and drug access**

Within-country differences in the supply of medical equipment have decreased over time, but unequal distribution of medical equipment remains, leading to unequal access to medical technologies, including diagnostic and clinical procedures, across population groups in a few countries in Europe. Shortages and unequal distribution of medical equipment can lead to delayed diagnosis and treatment of cancer, but investment in equipment is not always sufficient to ensure timely access. Countries need to invest not only in purchasing and renewing equipment but also in maintenance, adequate workforce capacity, and organization of cancer care delivery also need to be sought. To improve access to high-quality cancer care, countries are increasingly developing networks focusing on regions or specific cancer treatments such as radiation therapy (Figure 35.2).

Reflecting the growing trends of cancer incidence and prevalence, the availability of medical equipment has improved over the past decade. The volumes of radiotherapy equipment

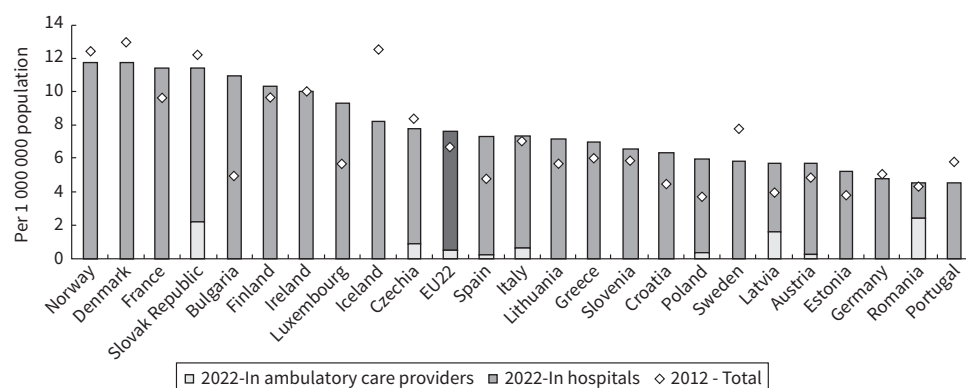


**Figure 35.2** Volumes of radiation therapy equipment per population vary three-fold across EU + 2 countries.

Notes: data refer to the nearest available year. Radiation therapy equipment includes linear accelerators, Cobalt-60 units, Caesium-137 therapy units, low to orthovoltage X-ray units, high-dose and low-dose rate brachytherapy units and conventional brachytherapy units.

Reproduced with permission from OECD (2024), *Beating Cancer Inequalities in the EU: Spotlight on Cancer Prevention and Early Detection*, OECD Health Policy Studies, OECD Publishing, Paris, <https://doi.org/10.1787/14fdc89a-en>.

per population have increased by 14% on average in EU countries over the last 10 years. The most notable increase was in Bulgaria, where the volume more than doubled between 2012 and 2021, becoming one of the highest in Europe after Norway, Denmark, France, and the Slovak Republic.

Innovations in cancer screening and early diagnosis have the potential to improve the chance of early cancer detection. For breast cancer screening, a few countries, including Estonia and Germany, have started to use a stratified risk approach based on individual characteristics, including family history. Research is underway to develop image-based risk prediction using machine learning (ML) algorithms on mammograms and MRI. Use of artificial intelligence (AI) technology in breast cancer screening is in the early stages of development in countries such as Cyprus, Finland, Hungary, and Luxembourg, while further work needs to be undertaken on regulatory, legal, ethical, clinical and economic aspects, including ensuring implementation without exacerbating existing inequalities.

Innovations in cancer treatment are also underway. According to the 2023 Organization of Economic Cooperation and Development (OECD) Policy Survey on Cancer Care Performance, 21 of the 26 responding countries in Europe used robotic or robot-assisted surgery that utilizes AI. For example, in France, surgical robots have been used for breast cancer, among other cancers (4).

## Cost of cancer care in European countries

There is a significant variation in per capita expenditure on cancer care across European countries, with Switzerland, Denmark, and Norway having among the highest expenditures in the EU. This reflects differences in healthcare systems and the adoption of new cancer medicines, highlighting the diverse financial challenges faced by countries in managing

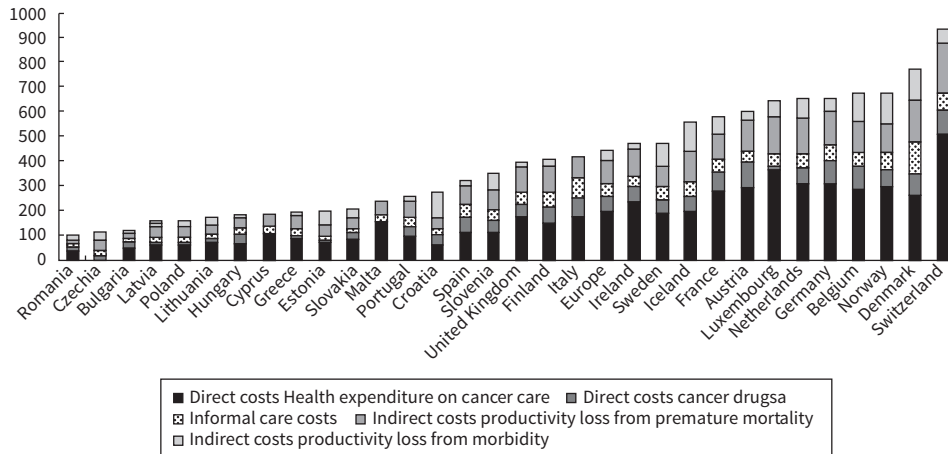


**Figure 35.3** Total cost of cancer per capita (in €) in Europe in 2018, by country and component.

Notes: Total costs do not match sum of costs because of rounding. No adjustment for price differentials. Cancer drug expenditure do not include confidential rebates. Data on cancer drugs for Cyprus and Malta could not be obtained for Estonia, Greece, and Luxembourg, and they only include retail sales but not hospital sales.

Source: data from Hofmarcher T et al. The cost of cancer in Europe 2018. *Eur J Cancer*. 2020 Apr;129:41-49.

cancer care. In earlier OECD reports, it was established that in oncology, system performance and relative spending were positively related.

European countries employ various strategies to control the costs of cancer care, such as systematically including health technology assessments and impact evaluations in countries like Germany and Ireland or risk-sharing mechanisms and price ceilings for pharmaceuticals in Italy. However, the effectiveness of these strategies varies, with some countries still facing challenges in ensuring sustainable access to new oncology drugs (Figure 35.3).

## Oncology drugs

Across Europe, the cost of new oncology drugs represents a major financial burden, contributing significantly to the growth in cancer care expenditure. Countries like the Netherlands, Belgium, France, and Spain particularly note the increasing costs of hospital cancer medicines as a threat to the financial sustainability of their health systems.

There is a three-fold difference in public coverage of cancer medicines with a high clinical benefit across EU countries. An OECD analysis of a sample of indications in breast and lung cancer with the highest clinical benefit scores and with EMA market authorization after 1 January 2016 shows that the proportion of indications reimbursed/covered varied substantially across countries. Germany reported that all indications were covered, followed by the Netherlands (92%) and Bulgaria and Sweden (both 85%) (Figure 35.4).

Recent research also showed that actual patient access to innovative cancer drugs varies considerably between countries and can vary up to eight years within countries between hospitals; after EMA access, coverage takes an average of 2 years to be achieved and again differs considerably between countries. Differences in early access schemes, selective launching by Pharma and differences in the filing and decision process leading to coverage are responsible factors and should be taken up by the relevant agents to diminish inequalities.

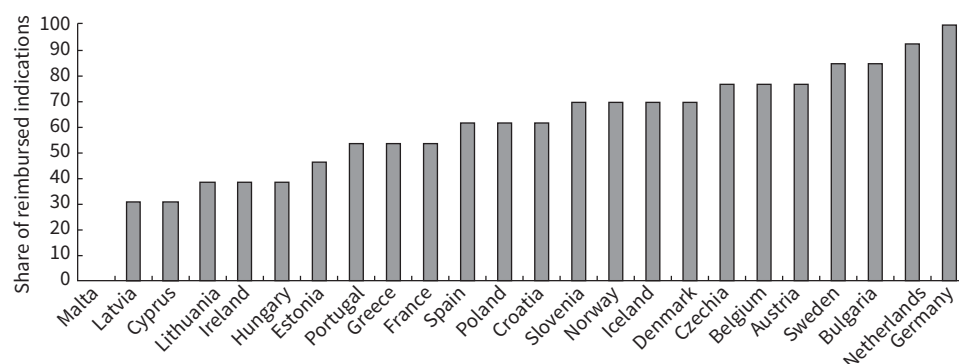


**Figure 35.4** The share of selected indications of newer cancer medicines with public reimbursement/coverage varies widely.

Notes: A total of 24 countries responded to the pilot data collection. Thirteen indications of ten cancer medicines used in the treatment of breast cancer and lung cancer with marketing authorization by the EMA after 1 January 2016 and active authorization on 26 March 2023, and with the highest clinical benefit according to the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) scoring system (scores of A and 5), were included in the analysis. The shares show the inclusion status of the indications in the public reimbursement list on 1 April 2023.

Reproduced with permission from OECD (2024), *Beating Cancer Inequalities in the EU: Spotlight on Cancer Prevention and Early Detection*, OECD Health Policy Studies, OECD Publishing, Paris, <https://doi.org/10.1787/14fdc89a-en>.

Encouraging the entry and use of generics and biosimilars when the originator product has gone off patent or lost market exclusivity is becoming increasingly important in lowering prices for oncology treatments, helping to redirect financial resources to pay for newer medicines and to improve financial sustainability (5).

## Cancer registries

National cancer registries in EU countries offer world-class population-based cancer registration (4), yet their utility varies due to differences in information scope and data quality (see Chapter 1). While most registries cover entire populations and are crucial for cancer surveillance, enhancing them to include broader data such as survivorship and socioeconomic factors could improve insights into cancer disparities. Overcoming challenges in data-sharing and strengthening these registries is vital for advancing cancer policy (6).

## Disparities between Eastern European and Western European countries

Cancer care disparities are especially present between Western European (WE) Eastern Europe (EE) countries and can be attributed to various factors. While in principle the role of governments and executives in EE countries is similar to their peers in WE, there are important discrepancies regarding their functioning and efficiency, due to a range of factors including healthcare systems, socioeconomic conditions, financial resources, cultural norms, and cultural attitudes towards cancer screening and treatment, and historical contexts (7).



One indicator of disparities between EE and WE countries lies in cancer survivorship. According to EUROCare 5, the five-year relative survival for breast cancer in Europe is 81.8% (95% CI 81.6–82.0), which drops to 73.7% (95% CI 73.2–74.1) for EE countries, with the lowest survival rates reported in Latvia and Lithuania (69.5% and 66.7%, respectively). Although sharing the same political background, Slovenia and the Czech Republic improved cancer survival rates in recent years, approaching the general European mean of survival for breast cancer, of 78.7% and 78%, respectively. They are referred to as Central European countries (8).

Taking this into consideration, to improve the quality of breast cancer care, governments and executives should focus on improving the efficacy of the health systems and their components, as the current structure is ill-suited and not flexible enough to serve the present requirements of multidisciplinary breast cancer care. Besides underfunded healthcare systems, EE countries struggle with an outdated pyramidal structure of their health system, inherited from the communist era, where healthcare services are organized and delivered in tiers or levels of increasing complexity and specialization (9). As in many EU countries, this traditionally consists of three main tiers: primary care (typically provided by family doctors who offer preventive care, basic medical treatment, and referrals to specialized services when necessary), secondary care (specialized medical services such as diagnostic imaging, laboratory testing, outpatient surgeries, and specialist consultations provided by hospitals and outpatient clinics) and tertiary care (specialized hospitals, academic medical centres, and research institutions with advanced medical technologies, specialized medical personnel, and comprehensive resources to manage severe or rare medical conditions, perform complex surgeries, and provide intensive care for critically ill patients).

Due to specificities of breast cancer care, the primary care physician is seldom involved in the management of breast cancer cases. Secondary care units provide basic diagnostic procedures such as mammography and ultrasound, but in fact, the large majority of breast cancer patients in EE agglomerate tertiary centres, which do not have the capacity to provide all services that are needed, or rely on private clinics. This is particularly noted in Romania and Bulgaria, where outpatient care is underutilized, also due to migration of the primary care workforce (family doctors and general practitioners) to Western and Northern European countries and patients relying on emergency rooms and hospitals instead of ambulatory care, in non-urgent situations (10). This has severe consequences on availability and access, leading to inefficient use of public funds to pay for services that would be much more affordable for the system if provided in the outpatient setting (11). Another gap in cancer care is a lack of comprehensive cancer centres in many EE countries. There are still countries without a single Organization of Cancer Institutes (OEI)-accredited cancer centre in the country, such as Bulgaria, Croatia, Poland, Slovakia and Slovenia (12).

**Screening.** A major cause of disparities in EE countries is access to screening for various types of cancer. In Romania, in 2019, only 9% of women aged between 50–69 had had a mammogram performed compared with 59% in the EU. Pilot programmes of regional screening were recently implemented and some screening programmes have been active since 2000 in EE, but the rate of early diagnosis is still very low (13).

**Costs.** All direct cancer costs are covered by the state, and different national oncology programmes assure wide and free access to medical care and drugs for cancer patients after diagnosis, regardless of a valid health insurance, for example, in Romania, as opposed to Bulgaria or Croatia. In later years, direct out-of-pocket payments increased, either for oncology drugs,

access to private healthcare units or diagnostic procedures, and reached 20% of total health expenditures in Poland and 18.9% in Romania in 2019, in contrast with the EU average of 15.4%. The cost of cancer care reported in 2018, in Romania, is the lowest in the EU, at 160 EUR per capita, versus the EU average of 326 EUR per capita (5). Nevertheless, more than 50% of cancer costs go directly to drug expenditure, threatening the financial sustainability of the health system (14).

**Access to drugs.** Compared to WE, time to reimbursement by local governments of novel anticancer drugs is lengthy. This is particularly caused by limited budgets, national health technology assessments, and close monitoring of drug effectiveness. In recent years, fundamental improvements were achieved, favouring countries with higher incomes, such as Czechia and Slovenia (Figure 35.4). As an example, it took 8 years to reimburse Trastuzumab in the metastatic setting in Romania, compared to only 84 months for Pertuzumab in the early breast cancer setting, since EMA approval in 2018, in the same country. Drug shortages, especially in essential medicines, are commonly seen in the least expensive drugs due to parallel trade or production disruptions (14). A critical issue is also a lack of medical oncologists in EE, making their workload and waiting times substantially higher than in WE (15).

To decrease disparities in breast cancer care in EE governments and policymakers should focus on securing funding for essential diagnostic and treatment procedures, stimulating research activities, and establishing modern high-technology capacities for specialized breast cancer centres. This can be done by implementing quality assurance schemes for centres treating breast cancer, with the ultimate goal of developing networks of certified breast units connected with ongoing initiatives to provide breast cancer research and screening across Europe (16).

## **The role of societies: ECIBC, EUSOMA, ESMO, OECD, Europa Donna**

In most countries, hospitals and physicians are organized to propagate the interests of their institutions and professions. Specifically for breast cancer, usually sub-branches of professional societies are active, and hospital associations seldom focus on a specific diagnosis, unless there is a specific issue of main importance. Most countries have patient associations or advocacy groups focusing on breast cancer, and these are increasingly influential, for instance, in lobbying for coverage of advanced genomic diagnostics or of innovative drugs.

As indicated earlier, the EC JRC has issued an accreditation scheme for breast cancer. It seems, however, that professional agencies are not very keen to implement this, risking a dated system that is not kept up to date. Nevertheless, to evaluate the performance of cancer care in the different EU countries, quality indicators were defined and recently published in the EU Country Cancer Profiles Synthesis Report 2025. This work is published under the responsibility of the Secretary-General of the OECD and the President of the European Commission. Special attention goes to breast cancer. The minimal, maximal, median, and trend over time of the individual EU countries can be compared (% breast cancer screening, breast cancer mortality, breast cancer five-year survival, prevention strategies, and cancer care capacity) (17).

EUSOMA, the European Society of Breast Cancer Specialists (<https://www.eusoma.org/>)



is accrediting specialist breast cancer units using an updated set of requirements that was published in 2020 (18). They are not yet working with an open register of accredited centres. The European Society for Medical Oncology (ESMO) operates an accreditation scheme for palliative oncology that involves 222 European and worldwide centres.

The European Organization of Cancer Institutes (OECI; [www.oeci.eu](http://www.oeci.eu)) has a membership of 150 (mainly) European Cancer Centres, either free-standing or as an identifiable entity within a larger (University) Hospital. The accreditation and designation programme focuses on institution-wide quality and integration of care and research. Presently, about half the membership is involved in the A&D programme, which covers all oncology served by the centres and leads to a designation of 'Comprehensive Cancer Centre' or 'OECI Cancer Centre'. In some countries, such as Italy, this designation is conditional on national research funding (19).

It is known from literature that participating in accreditation schemes can help to improve services, especially in the first three rounds. After a number of rounds, verifying the standards is of course relevant, but for the involved professionals the added value can diminish and bureaucratic demand may seem to dominate. It becomes a challenge for these programmes to also offer added value for professionals in the long run, and some change to appreciative enquiry methods and benchmarking to maintain their relevance.

Patient advocacy is of growing importance. Apart from national associations of breast cancer patients (and their relatives) on the European level, Europa Donna ([www.europadonna.org](http://www.europadonna.org)) is the organization that represents the interests of European women on all relevant political levels. They co-organize conferences, have an active advocacy programme, and provide patient-level input in many European initiatives and projects.

## Executives' roles and responsibilities

The responsibilities of healthcare providers differ in various health system types. Hospitals can be responsible for the whole pathway from screening to follow-up and survivor care in a capacity-based system. When there is a national health system, stakeholder management and dealing with political decisions and appointments are a challenge. Sometimes screening is organized as a prevention type of service, so there is no direct responsibility from hospital executives for these services. When a health system allows private practices or free-standing specialty clinics that focus on breast cancer outright competition is an issue. Breast cancer is often a frontrunner in service innovation in oncology; in recent years, working with multidisciplinary and dedicated teams have become the standard. Often using organizational principles from value-based healthcare, care pathways are redesigned to become more patient-centred and efficient. Often offering one-stop-shop diagnostics, shared decision-making, specialist nurses to work as a contact point and to ensure coordination. Hospital executives have the responsibility to ensure investments and pathway innovation in breast cancer.

However, an EU benchmark project comparing breast cancer services against value-based healthcare (VBHC) principles showed large differences in development and implementation. Differences in breast cancer pathway organization are especially visible in giving responsibility to the physician over the whole pathway, involving costs as a factor in team decision-making, a comprehensive approach towards patient involvement and survivorship and

especially in measuring outcome data and relating these data in dashboards for team evaluation and team decision-making (19).

When different providers have roles in screening, diagnostics, and follow-up/survivorship care, this requires coordination in quality across individual providers' responsibilities. Building expertise in this domain of quality management is especially important as cancer care is increasingly organized and provided in networks and with an explicit executive responsibility.

Networks are becoming increasingly important in view of growing demands in minimum volume norms, differentiation and centralization of molecular diagnostics and close cooperation with radiotherapy and integration with translational research. When academic centres are not active in breast cancer, in view of its less complex interventions, the research role should still be organized in the network. When the system allows for different types of providers and competition, from the viewpoint of the patient, smooth services and handovers should be organized anyway. Increasingly patient representatives demand transparency on service and outcome data and this in turn stimulates organizational improvement, especially in complex clinical environments (20).

Especially after COVID-19, digital medicine and digital care provision have really taken off. In most countries, hospitals work with electronic medical records (EMR) in different degrees of development. In general terms, this allows increasingly for digital check-in and contact, allowing patients to check in at home, to enter patient-reported experience measures (PREMs), and patient-reported outcome measures (PROMs), and to have follow-up contacts through video consult and survivorship programmes through e-health. Executives have to be aware that the investments in digitalization are increasing. Moreover, the potential of AI to identify subgroups or individuals at risk or in need of specific attention is still in its initial stages. Network development asks for innovative routes and infrastructure for data exchange, and the EMR-based data are increasingly in demand to assess 'real-world effectiveness' of treatments. The smaller hospitals or clinics are, the more difficult to free the needed funds and—especially—to hire the scarce expertise for all these developments; smart cooperation with other providers is a way to deal with this problem.

## **Future challenges: inequal access and disparities**

It is inevitable that the developments, both those that require serious investments on the national system and on the individual provider scale, will be different in various EU countries and are often related to the development of the gross domestic product. The available amounts for investments in MRI, PET-CT, and genomics will differ—as shown—and inevitably lead to differences in access. But also, the pharmaceutical market in Europe leads to strategic launching and pricing behaviour related to new cancer drugs. Reducing inequality requires more uniform use of RCT data in national requirements for coverage decisions. Uniformity in early access schemes over EU countries, and regulations on market introduction of drugs within a limited timeframe after obtaining market access from EMA are other factors that need to be adapted. Better access to novel drugs and treatment approaches could also be achieved with better access to clinical trials across borders, which would also facilitate breast cancer research in Europe.

As mentioned earlier, with the trend towards further digitalization, the use of real-world data, working with AI, and forms of digital care will only become stronger. Apart from investments in technical infrastructure and specific expertise, the digital skills and awareness of every member of the multidisciplinary team (MDT) will be challenged. Breast cancer patients as a group are often well able to advocate for their rights and improvement of digital services, but we have to be aware that there is always a subgroup that cannot follow this trend.

Although the European Union has no formal competency in care delivery, especially with the Beating Cancer Plan, more uniformity across countries is stimulated, and inequality in access is defined as an important action point (21).

## Key messages

- Although the European Union has no formal competency on care delivery, especially with the Beating Cancer Plan more uniformity over countries is stimulated, and inequality in access is defined as an action point.
- Eastern European countries especially struggle with less well-financed and organized systems, showing in challenges in investments and access to screening, treatment, and drugs.
- Professional associations and patient advocacy groups like Europa Donna have an important role in stimulating improvements and exposing inequalities.
- Challenges for executives depend on specific system characteristics, such as market elements, dealing with political stakeholders, and securing funds for state-of-the-art investments. In the coming years, especially when dealing with IT-related developments, such as digital access, digital care, working with AI, and using real-world data will determine the capacity of institutions to meet patients' demands.

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## India

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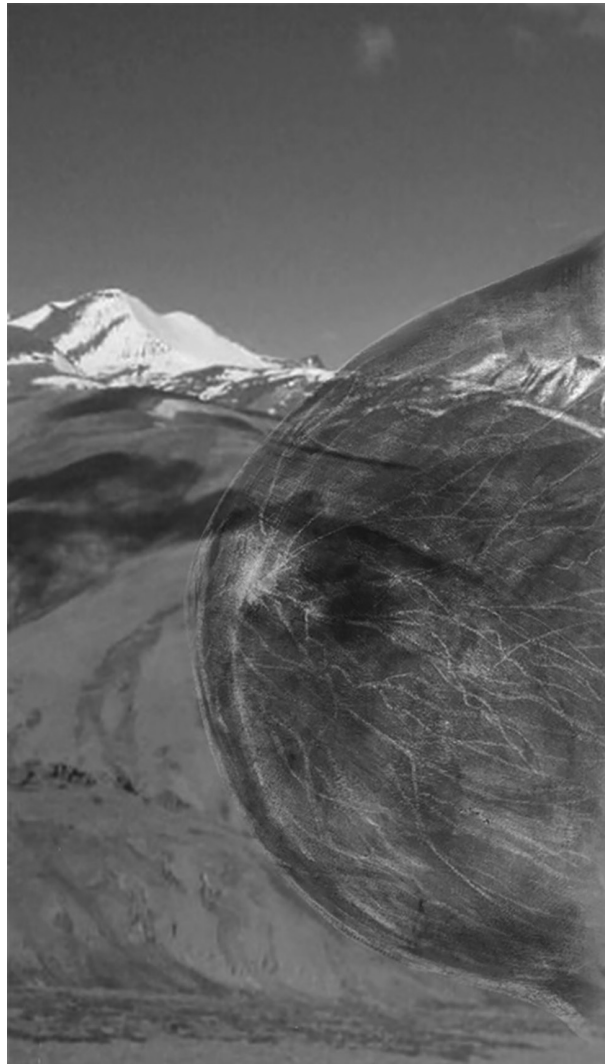


**Figure 36.1** India—‘Himalayas—Abode of Snow—shaping the culture.’

Visceral landscapes by Pascale Pollier.

Mammogram in carbon dust technique created by © Pascale Pollier MMAA, Registered Medical Illustrator, Artem Medicalis. Background photograph Himalayas with permission from Johan Van Ransbeeck. Collage edited in Adobe Photoshop.

## Introduction

Globally, breast cancer is the most prevalent malignancy among women. It is the second leading cause of cancer deaths and fifth leading cause of death in women worldwide. GLOBOCAN (1) statistics as well as data from the Indian Council of Medical Research through regional cancer registries show a rising incidence of breast cancer in India, documenting a surge of nearly 50% between 1965 and 1985. Further analysing data from 1988 to 2013, there was a substantial rise in breast cancer across all population-based cancer registries, replacing cancer of the uterine cervix as the most common cancer of the country, among women and in the overall population. There is a stark rural-urban divide in the incidence of breast cancer in the country, suggesting the etiological role of westernization of lifestyle including the changed dietary and reproductive habits of the Indian urban population. The current incidence is estimated to be 30–35 per 100,000 women. The landscape of breast cancer in India is further conspicuous by overall lack of awareness of early symptoms, an advanced stage at presentation, a higher proportion of younger patients, and poor compliance to treatment due to socioeconomic factors. Breast cancer now poses a substantial public health concern. The survival statistics of breast cancer in India suggest inferior long-term results as compared to the western benchmark due to inequitable distribution of healthcare resources, lack of standardized management guidelines, socioeconomic issues leading to delayed initiation of treatment and poor compliance rate. Another major issue in India is the prevalence of triple-negative breast cancer (TNBC), which is significantly higher than in western populations (2, 3). TNBC is a particularly aggressive form of breast cancer, characterized by poor prognosis and few treatment options. In India, most TNBC data comes from tertiary care hospitals, with prevalence rates reported between 10% and 43% in various cohort studies over the past decade. A recent meta-analysis revealed that the overall pooled prevalence of TNBC in India stands at 25.04%, highlighting the urgent need for focused research and improved therapeutic strategies.

Notably, the incidence of breast cancer in India is predicted to escalate further in future, emphasizing the urgency of addressing this burgeoning issue. Early detection and timely intervention are pivotal in formulating comprehensive strategies to mitigate the rising burden of breast cancer in the country

## Promotion of early diagnosis

A high uptake of mammographic screening is prevalent in the western countries whereas there is no systematic population-based or opportunistic screening programme for breast cancer in India. India is the most populous country in the world with a population of 1.46 billion in 2025 having a median age of 28 years. An estimated 32.4 crore women are above 40 years (4). The median age at presentation of breast cancer in India is 50 years, a decade younger than the western counterpart (5). India has one radiologist per one lakh population as compared to one per 10,000 in the USA and majority are concentrated in urban India. The younger age of onset of breast cancer, limited availability of radiologists, and mammography machines make mammographic screening a practically humongous task, if not impossible. Also, the likely overdiagnosis that may happen due to mammographic screening would put

huge stress on the healthcare system which is trying to cope with the current explosion of breast cancer incidence. There is no overall or breast cancer specific mortality benefit of breast cancer screening in women less than 50 years of age and there is a modest breast cancer specific mortality benefit in women above 50 years of age. The CNBSS-II study suggested no additional benefit of mammographic screening over and above clinical breast examination (CBE). CBE is easy to perform, less invasive, and is less likely to overdiagnose cancers. CBE is a more cost-effective method for breast cancer screening in India when performed biannually by trained Health Care Worker (HCW). Two large randomized controlled trials conducted in India have shown significant downstaging of breast cancers when CBE was conducted by trained healthcare workers and a 30% reduction in breast-cancer-specific mortality in women aged 50 years and above. The National Cancer Grid (NCG) of India recommends CBE for women aged > 40-50 years at least 1-3 times in their lifetime, or every two years.

A mammography may be added to CBE in high-risk or high-resource setting. Opportunistic screening with CBE and/or mammography is also recommended for women who visit breast clinics with breast symptoms (6).

Currently, cancer screening in India is clubbed together with other non-communicable diseases as part of the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases, and Stroke (NPCDCS). The NPCDCS includes guidelines for population-based screening of all women aged 30 to 65 years for breast, cervical and oral cancers by Accredited Social Health Activists (ASHA) and Auxiliary Nurse Midwives. The programme has 5,541 non-communicable disease clinics in 707 districts (out of 766) in India. In 2022–2023, an estimated 5 crore women have been screened and 1,61,308 (0.31%) cancers have been diagnosed. However, the uptake of breast cancer screening was far from satisfactory. Only 969 per 100,000 women aged between 40–49 years were screened as per the NFHS survey. Screening uptake was better among the rich, educated, and women in southern and western India. The low uptake of screening is due to many reasons, like lack of awareness, stigma of diagnosis, fear of treatment, fatalistic attitude towards disease, and lack of socioeconomic support. However, training of healthcare workers, promoting breast health awareness, and robust monitoring have been shown to improve screening rates. 91% of women with abnormal findings on CBE by HCW completed diagnostic workup. Tools like thermal imaging and handheld ultrasound sonography (USG) devices have been shown to be feasible low-cost alternatives with acceptable sensitivity and specificity in various pilot projects, however their efficacy is yet unproven. The road forward for India is to build a sustainable awareness programme and screening programme with CBE by trained HCW with robust monitoring and performance indicators and quality assurance of CBE. The use of low-cost innovations to supplement CBE in low-resource settings and mammography in >50 years of age in the optimal resource setting will be ideal.

## **Management of breast cancer: thinking globally, acting locally**

### **Surgery**

#### **Management of primary**

Surgery remains the mainstay of treatment for breast cancer. The diagnostic triad of clinical examination, breast imaging, and pathological evaluation remains the backbone of diagnosis



and treatment planning. Trucut needle biopsy is the standard diagnostic procedure, and excision biopsy for diagnosis should be avoided. Inappropriately placed scars and postoperative changes due to excision biopsy of large-sized tumours lead to a higher chance of mastectomy, higher nodal positivity, and worse survival. The percentage of women receiving breast conservation surgery (BCS) is between 20% and 30% across the country, with the exception of tertiary care cancer centres. The reasons for the higher rate of mastectomy are an overall lack of awareness about the safety of BCS across patients and doctors, irrational fears regarding breast conservation, traditional gender roles of women with a lack of autonomy, a male egalitarian society leading to a general apathy towards women's health, a lack of radiation centres, and financial issues. Earlier quality of life (QOL) studies showed that there was no difference in global QOL between women who have had a mastectomy versus BCS (7). However, the picture is rapidly changing with more patients demanding breast conservation and good cosmesis. Oncoplastic breast surgery is an evolving field. Aesthetic modulation of the remaining breast after partial resection of the breast helps in restoring a woman's quality of life. Specialist breast surgeons across the country have improved the quality of breast surgery. Safety and efficacy of various oncoplastic techniques like therapeutic mammoplasty and chest wall perforator flaps has been studied and published in last few years, in upfront as well as neoadjuvant setting, including the largest Asian cohort of TM published by Koppiker et al. (8).

With these promising oncoplastic techniques and multidisciplinary management, Indian oncoplastic breast surgeons who are often dealing with advanced tumours, are challenging the traditional indications of mastectomy such as central quadrant tumours, MCMF and large operable tumours (9, 10, 11, 12).

Mastectomy remains the surgery of choice in many patients either for tumour or patient related factors. Post-mastectomy reconstruction of the breast has low uptake across the country with a dismal 5% receiving either implant-based or autologous reconstruction. In a KAP analysis, 12% women who have had mastectomy, when contacted in follow-up, said that they would have opted for a post-mastectomy reconstruction if an option was given (13, 14).

### **Management of axilla**

Axillary treatment in India has similarly evolved towards a more conservation approach. Identifying a node-negative axilla is crucial to avoid overtreatment and complications such as lymphedema and shoulder morbidity. A clinically node-negative axilla should be staged using sentinel node biopsy (SNB) or a low axillary sampling (LAS) procedure, with at least three nodes sampled intraoperatively. Alongside established procedures like the blue dye method and scintigraphy, newer methods for node identification like fluorescent dye indocyanine green (ICG) should be incorporated for greater efficiency (15). If node-negative, no further axillary lymph node dissection (ALND) is necessary. In presence of micro-metastatic disease in the lymph nodes, one need not complete ALND. However, in macro-metastatic axillary disease, there is a 27% likelihood of having further positive nodes. Hence, a positive SNB mandates a complete ALND up to level II or III in our setting because of the general higher stage at presentation. The level III axillary nodal involvement is 15–25% (16).

The standard treatment for axilla after neoadjuvant chemotherapy (NACT) is a complete ALND. In a retrospective analysis, 50% of the axilla was negative in post-NACT ALND. If NACT is used for early breast cancer or if the axilla is radiologically proven to be negative before starting NACT, then post-NACT SNB can be performed. In a node-positive axilla, SNB



alone after NACT has not met the desired false-negative rate (FNR) of <10% and hence, the international standard has shifted to targeted axillary dissection, which mandates marking the positive node before starting chemotherapy. Different methods of marking the node, such as clipping, carbon tattooing, insertion of a radioiodine or ferromagnetic seed, are described, each with its own pros and cons. None of the newer markers are available in India; however, clipping of the positive node may be done before starting chemotherapy. LAS has met the FNR of 8.9% in the post-chemotherapy setting and is a good alternative in resource-constrained settings. The safety of post-chemotherapy axillary conservation in node-positive and locally advanced settings needs to be tested with prospective randomized and non-randomized studies regarding its impact on long-term survival outcomes.

### **Chemotherapy and targeted therapy**

Adjuvant chemotherapy protocols for early breast cancer are the same as in the west, with all high-risk tumours (node-positive, triple-negative, HER2 enriched, high grade, higher Ki67) receiving chemotherapy. Conventional chemotherapy such as anthracyclines, taxanes, and cyclophosphamide remain the backbone of systemic therapy in India. Trastuzumab availability and cost constraints have improved significantly with biosimilars, government support for cancer treatment and philanthropic efforts from non-governmental organizations. However, compliance with treatment, especially multidisciplinary treatment protocols, is suboptimal. Affordability for targeted anti-HER2 therapy, mainly pertuzumab, trastuzumab emtansine, CDK4/6 inhibitors, and immunotherapeutic agents such as pemrolizumab, is poor. Multimodality plays an important role in the Indian context, given the fact that factors which influence the need for multimodality treatment, like young age at onset, premenopausal status, locally advanced breast cancer, and triple-negative subtype are more prevalent when compared to the west (5). Indications for NACT are molecular subtypes like triple-negative, HER2 enriched tumours, high-grade, node-positive tumours for down-sizing for BCS and in locally advanced breast cancer. A conservation rate of 50% can be achieved in locally advanced tumours by effective use of neoadjuvant treatment (9, 17).

Systemic therapy accessibility is being addressed by strategies like government-sponsored health insurance programmes, using biosimilars, pooled procurement drives, and using abbreviated regimes. National Cancer Grid has tested pooled procurement across multiple centres as a strategy to improve negotiability of oncology medicines. By pooling demand for 40 drugs from 23 centres, equivalent to 15.6 billion Indian rupees (197 million United States dollars (US\$)), 13.2 billion INR could be saved (US\$166.7 million). The savings ranged from 23% to 99% (median: 82%). Biosimilar trastuzumab has shown similar pCR rates, like innovator trastuzumab. Triaging to at least three months of adjuvant trastuzumab has shown 66% five-year disease-free survival and 76% five-year overall survival. The uptake of anti-HER2 therapy has improved to 57% in 2016 from 8% in 2008. Pradhan Mantri Jan Arogya Yojana (PMJAY), is a National Health Protection Scheme which provides coverage for basic cancer treatment in India. 86,000 admissions for breast cancer were made in 2019–20 under this scheme. Overtreatment also remains a common problem, particularly in hormone-positive early breast cancers who are candidates of de-escalation. There is a lack of validation for oncotype-DX in Indian patients and cost of testing is a hindrance. CANASSIST, is a promising tool which has been developed and validated in the Indian setting. It is an immunohistochemistry based prognostic test for early-stage hormone-receptor-positive

breast cancer patients using expression levels of five biomarkers (CD44, ABCC4, ABCC11, N-Cadherin, and Pan-Cadherin) and three clinical parameters, such as tumour size, grade, and node status. However, prospective trials are needed to test its predictive efficacy.

### **Radiation therapy**

Radiation therapy is indicated in all breast conservation surgeries, mastectomy in node-positive, larger than 5 cm, and locally advanced tumours. Radiation penetration in India is 0.4 per million population, which is less than the WHO recommendation of 1 per million. However, the trend is getting better with 545 LINACS in 2019 to 779 in 2023 (18). However, 56% of these centres are in tier one cities, whereas 70% cancers occur in rural areas. Widespread adoption of hypo-fractionated radiotherapy can improve access to radiation. Outcomes in Indian patients with moderately hypo-fractionated radiotherapy are similar as compared with stage-matched patients from the west. Although retrospective-prospective studies have established feasibility and safety to certain extent, the ongoing HYPOR trial is currently exploring the same in a randomized setting. Data regarding APBI in India have also shown favourable clinical and cosmetic outcomes (19).

### **Endocrine therapy**

Adjuvant endocrine therapy is recommended in all hormone-receptor-positive patients with pre-menopausal women receiving 5–10 years of tamoxifen with or without 2–5 years of ovarian function suppression, depending on risk-based assessment. Aromatase inhibitors are recommended in post-menopausal women for a duration of 5–8 years, again based on stage. The efficacy of CDK4/6 inhibitors is like that in western population in the metastatic setting (20), however its use in the adjuvant setting is not yet widespread due to cost constraint.

### **Special situations**

The number of patients presenting with metastases is higher in India with a higher recurrence rate owing to the higher overall TN stage at presentation. Options in the recurrent setting may be limited due to financial constraints and non-affordability of personalized targeted treatment options in all subtypes of breast cancer. Owing to the population pyramid of the country, there is a higher absolute number of young breast cancer which demands multidisciplinary involvement, fertility preservation methods, germline testing, and reconstructive surgery (21). A nationwide pregnancy-associated breast cancer (PABC) registry has been established to identify clinical and translational loopholes of research in this unique setting that need special attention and guidelines. Male breast cancer (MBC) and phyllodes tumours each account for roughly 1% of breast malignancies. MBC is managed in accordance with standard guidelines used for women's breast cancer. Phyllodes tumours commonly present after inadequate prior surgeries or as advanced recurrences due to low awareness, and their primary treatment is surgical excision with wide margins. Radiation therapy is considered for large or recurrent tumours where adequate margins are challenging, while chemotherapy is reserved only for metastatic phyllodes tumours.

### **Training, education, and research**

In India, the shortage of dedicated specialist breast surgical training programmes, particularly in oncoplastic surgery, presents a significant challenge. Only a few esteemed institutions such as Tata Memorial Hospital (Mumbai), Postgraduate Institute (Chandigarh), Tata Medical Centre (Kolkata), Max Super Speciality Hospital (New Delhi), Manipal Hospital (Bangalore), HCG Hospital (Bangalore), and Sri Shankara Cancer Hospital and Research

(RGUHS Karnataka) offer breast surgery fellowships focusing on the multimodal management of breast cancer. Surgical oncology training, recognized by the National Medical Commission (NMC), is available through Diplomate of National Board (DNB) and MCh degree programmes, covering various cancers, including breast cancer. The recently introduced MCh in breast and endocrine surgery as a super-specialty provides another pathway, with institutes like Sanjay Gandhi Postgraduate Institute (Lucknow) and All India Institute of Medical Science (Delhi, Rishikesh) offering admissions to this course. There is a definite need of dedicated training programmes exposing to complex oncoplastic breast surgical techniques. Prashanti Cancer Care Mission's International School of oncoplastic surgery (PCCM-ISOS) and the Homi Bhabha National Institute (HBNI) along with a few other tertiary care centres offer dedicated breast fellowship programmes to address these needs. ISOS, in collaboration with the University of East Anglia (UEA), UK, has introduced an innovative oncoplasty programme to India. The ISOS-UEA programme offers a comprehensive three-year MS degree in oncoplastic breast surgery. The theoretical modules are delivered entirely online by UEA and comprise six modules. Face-to-face interactions occur during ISOS's hands-on training workshops held a few times a year in the city of Pune, covering both clinical and surgical aspects. Though the UEA online programme is entirely virtual, ISOS brings a significant advantage through hands-on training and observership opportunities (10, 12).

Similar to focused breast-specific training programmes, India's translational oncology research landscape also suffers from a critical gap: the lack of a bench-to-bedside approach is evident. However, visionary initiatives such as the Indian Cancer Genome Atlas (ICGA), launched in 2020 by the Prashanti Cancer Care Mission's (PCCM) Centre for Translational Cancer Research and its partner institutions, aim to address this shortfall. Modelled after the successful NCI's The Cancer Genome Atlas (TCGA), ICGA aims to create a pan-India consortium, fostering collaboration between clinicians and researchers to tailor cancer management strategies to India's unique needs and to create an indigenously developed, openly accessible, comprehensive multiomics database of cancers prevalent in the Indian population (22, 23, 24).

ICGA's pilot project targets sequencing 1,000 breast cancer samples, addressing the higher prevalence of TNBC in India, which ranges from 10% to 43%, significantly higher than in western populations (3). By recognizing the influence of environmental factors, dietary habits, health issues, and genetics on cancer profiles in India, ICGA which now stands as an independent company, plans to collaborate with hospitals nationwide. With ethical approvals, high-quality genomic and clinical data will be collected to establish an open-source database, accessible to the global scientific community.

## **Key messages: strategic imperatives for advancing breast cancer care in India**

1. **Breast cancer is the most common cancer among Indian women**, with a rising incidence in younger age groups and peak presentation between 40–50 years.
2. **Awareness campaigns and CBE-based screening** have proven effective in downstaging disease and improving early detection, particularly in low-resource settings.
3. **Surgical de-escalation and tailored adjuvant therapy** improve survival outcomes while minimizing treatment-related morbidity.

4. **Oncoplastic surgery** enhances cosmetic outcomes and quality of life in both breast-conserving and reconstructive settings but remains underutilized due to lack of trained specialists.
5. **Training a dedicated workforce** in breast surgical oncology and oncoplastic techniques is critical to expanding access to modern, patient-centred care.
6. **Multidisciplinary breast units (MBCUs)** are essential to deliver integrated, evidence-based care, and should be scaled across healthcare tiers in India.

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## Latin America

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**Figure 37.1** South America

‘Biodiversity, critical role on the global system.’

Visceral landscapes by Pascale Pollier.

Migrating Breast cancer cell in carbon dust technique created by © Pascale Pollier MMAA, Registered Medical Illustrator, Artem Medicalis. Hallerbos background landscape image generated and collage edited in Adobe Photoshop AI.

## Introduction

Breast cancer is a significant public health issue worldwide, including in Latin America, with more than 160,000 new cases year and 40,000 deaths. Brazil, Mexico, Argentina, and Colombia have 68% of the population and 60% of cases of breast cancer (1). The incidence rates vary across countries, but the rates have been increasing in Latin America over the past few decades (2). The mortality is high and variable (45–60%) over 10 years according to the age of patients, clinical stage, and time to diagnosis and treatment (3).

Latin America, with its diverse healthcare systems and socioeconomic disparities, faces unique challenges in delivering quality care for breast cancer patients. One of the major challenges in Latin America is inequities in access to treatment and healthcare services (4).



The countries have predominant populations of low and middle income with many barriers to accessing quality diagnosis and treatment. This leads to a higher proportion of breast cancer cases being diagnosed at advanced stages, resulting in poorer outcomes and higher mortality rates. There is a significant disparity between the public and private healthcare sectors, with the latter offering better resources and services. This disparity in access to care further exacerbates the inequalities in breast cancer outcomes. Additionally, there is a lack of standardized treatment guidelines and protocols in many Latin American countries (4).

Despite these challenges, there have been significant efforts to improve the quality of care for breast cancer patients in Latin America. Many countries have established national cancer control programmes that focus on early detection, diagnosis, opportunistic screening, and treatment of breast cancer. These programmes aim to increase awareness, improve access to screening, and provide comprehensive treatment services (5).

International collaborations and partnerships have also played a crucial role in improving breast cancer care in Latin America. Organizations like the American Cancer Society (ACS), Breast Health Global Initiative (BHGI), and the World Health Organization (WHO) have been actively involved in providing technical assistance, capacity building, and knowledge exchange to strengthen breast cancer control programmes in the region (6).

## Epidemiological burden

Latin America is experiencing demographic changes, with a growing proportion of older adults, obesity, an increase in alcohol consumption, and a sedentary lifestyle, which could contribute to the rising incidence of breast cancer. The countries have varying rates of breast cancer incidence and mortality (6–8).

There is evidence that breast cancer in Latin America affects women at a younger age compared to developed countries. Differences in disease incidence among young individuals may be attributable not only to inherited genetic factors but also to modifiable risk factors, such as smoking and alcohol, and exposure to carcinogens (9).

Data from the Brazilian Cancer Institute (INCA) reveals 4.4% of patients with breast cancer are younger than 35 years and 20.6% under 45 years. The prevalence of regional and metastatic diseases is even higher among young patients (10). Additionally, there was a higher proportion of luminal-B and triple-negative tumours among young patients (11).

One of the key challenges in addressing breast cancer in young women is the lack of awareness, screening ineffectiveness, and consequently delay in diagnosis and treatment. Breast cancer is often not on the radar of young women and doctors, and they may delay seeking medical attention or dismiss symptoms as unrelated to cancer (8). These include initiatives to promote breast self-care because most breast cancer in young women are self-detected, are fast-growing tumours, and more than 20% triple-negative (12).

Community outreach programmes and research collaborations to explore targeted therapies and personalized treatment approaches for triple-negative and Her2 positive breast cancer are necessary to reduce mortality. It is important to note that more research and data are needed to better understand the specific characteristics, epidemiology, and outcomes of triple-negative breast cancer (TNBC) in Latin America (9).

Certain genetic mutations, such as *BRCA1*, are associated with an increased risk of TNBC but data on *BRCA1* mutations in Latin America is limited. Improved data collection and

surveillance systems are needed to accurately monitor the burden and implement effective prevention and control strategies (9).

## **Access to diagnosis and treatment**

Access to timely and affordable breast cancer treatment is crucial in mitigating the social and economic burden of the disease. While healthcare coverage has expanded in recent years, it is important to note that not all dimensions of access have improved equally. Although several Latin American countries have created public policies and action programmes for the prevention and control of breast cancer, the effectiveness and impact of implementation are little known. Costa Rica, Chile, Colombia, and Brazil have implemented universal healthcare systems with high oncological coverage, more focused on early detection and opportunistic screening (12). Framework of care with some key aspects of access to treatment

## **Health insurance coverage**

In a universal health system like Brazil, there are difficulties in access and diagnostic resolution of suspected cases of malignancy and a lack of structure and integration of public oncological references in the north and northeast regions, leading to delays in treatment and consequent migration of patients to the southern and southeastern states (13, 14).

Even with health insurance coverage, out-of-pocket costs for breast cancer treatment can be significant. High deductibles, co-pays, and co-insurance can create financial barriers for patients, leading to delays or avoidance of necessary care. This can have detrimental effects on treatment outcomes and overall well-being. However, not all individuals have equal access to coverage, and there are still gaps in insurance coverage, especially for those who are uninsured or underinsured (5, 6, 7).

## **Geographic disparities**

Access to breast cancer treatment can vary depending on geographic location. Rural areas may have limited access to specialized healthcare facilities, leading to delays in diagnosis and treatment. Rural areas, mainly in the Amazon, are often underserved in terms of healthcare facilities and providers (6). People living in remote or isolated regions may have to travel long distances to reach a healthcare facility, making it challenging to access timely with a team trained for resolute primary and secondary care. Investment in mobile mammography for screening without trained teams to perform outpatient biopsy and pathological examination are not cost-effective for low- and middle-income populations (13, 14).

## **Early detection—mammographic screening**

Early detection of breast cancer is crucial for improved outcomes and particular in population with more than 30% of advanced disease. Access to timely and affordable screening



services, such as mammograms, can be limited, particularly for individuals without insurance or those living in underserved areas. Lack of access to symptomatic patients with fast-growing tumours can result in later-stage diagnoses and more extensive treatment regimens. Delays from clinical symptoms to diagnosis (biopsy) over 3 months are associated with advanced stage and poor survival. In high-income populations, the time is usually less than 30 days (13, 15).

The diagnosis of symptomatic disease should be a priority for low- and middle-income populations to decrease mortality. Improving access to breast cancer treatment in underserved areas and improving timely diagnosis, efforts should be focused on increasing awareness about the importance of regular breast clinical examination and secondary references to perform the biopsy and promoting programmes that provide free or low-cost screening services. Ensuring access to multidisciplinary care requires coordination among healthcare providers and the integration of services. This can be achieved through the establishment of breast cancer care teams, telemedicine initiatives, and collaborations between different healthcare facilities (16, 17).

In conclusion, while healthcare coverage has expanded in recent years, access to breast cancer treatment and the framework of care are still not equitable across all dimensions. Efforts are needed to address disparities in insurance coverage, geographic access, financial barriers, timely diagnosis, multidisciplinary care, and supportive services. By implementing targeted policies and initiatives, we can work towards ensuring that all individuals have timely and affordable access to comprehensive breast cancer treatment and care.

## **Importance of national cancer control programmes**

One significant factor contributing to disparities in access to care is the absence of national cancer control programmes. These programmes are essential for coordinating and implementing comprehensive strategies to prevent, detect, and treat cancer. Unfortunately, not all countries have established national cancer control programmes or have limited resources allocated to cancer control efforts. This results in disparities in access to cancer prevention, early detection, and treatment services. Individuals living in countries without comprehensive cancer control programmes may face challenges in accessing necessary screenings or may experience delays in diagnosis and treatment, leading to poorer health outcomes (5, 14, 16).

## **Guidelines**

Key recommendations for low- and middle-income populations are the early detection with clinical breast examination in symptomatic patients with biopsy and treatment in a short period of time (16).

These guidelines provide evidence-based recommendations for diagnosis, and treatment, with collaboration between healthcare professionals, policymakers, and international organizations. By working together, countries can ensure that treatment guidelines are effectively implemented, leading to improved access to quality cancer care for all individuals.

Data are crucial for understanding the challenges and local barriers to implementing treatment guidelines effectively for guideline adherence to treatment. Patient survival rates and quality of life measures can provide insights into the impact of guideline implementation on patient care and help identify areas where guidelines may need to be revised or improved (5, 12).

Resource allocation and socioeconomic data are fundamentals to conduct research specifically focused on the implementation of treatment guidelines to provide valuable insights into the barriers and facilitators of effective implementation. This research can help identify strategies and interventions that can improve guideline adherence and patient outcomes.

## Health systems and breast cancer care in Brazil

Although approximately one-quarter of the population can afford private healthcare, or supplementary health (SH), 75% of Brazilians depend exclusively on the public health system. The latter, 'Sistema Unico de Saude' (SUS), is universal with important advancements in health coverage in diagnosis and treatment of high complexity diseases (13, 14). However, important differences are identified between the two systems, reflecting inequality and directly affecting cancer care and patient outcomes (18). In 2004, Brazilian government guidelines included clinical breast examination and opportunistic mammographic screening, recommending biennial mammography for women aged 50–69 (14, 17) (see Chapter 8).

Brazil has more than 5,000 mammographs in the public references but they are heterogeneously allocated and underutilized. The percentage of women who undergo opportunistic mammographic screening varies from 43% in the north and northeast regions to 65%, in the south and southeast of Brazil (13, 14, 18).

The persistent high proportion of late-stage breast cancer at diagnosis in North and Northwest States of Brazil implies that early detection policies with a focus on mammographic screening have little effect on mortality. The priority for the low- and middle-income population is to improve the management of symptomatic disease before an effective screening programme, reducing late-stage diagnoses (13).

In May 2013, a federal law was passed in Brazil, the 60-Day Law (12.732/12), which mandates that patients with cancer begin treatment in the Public System of health within 60 days of a confirmed breast cancer diagnosis. Despite the law, some regions of the north and northeast of Brazil don't have trained teams or infrastructure for diagnosis and poor integration with oncological hospitals. Consequently, only 65% of patients are treated before 60 days (14, 18).

The experience of the One-Stop Clinic with an integrated diagnostic centre (radiologist, gynaecologist, pathologist nurse, and oncologist) with biopsy in the first consultation in the Women's Reference Centre in São Paulo, Brazil was an important outpatient model to reduce the time for diagnosis and treatment. They observed downstage with reduction of 30% of advanced disease (16).

Secondary references with resolute diagnosis with integrated oncological hospitals to start the treatment, are essential for downstage and reduction of mortality in populations with access and transportation difficulties in big cities and rural areas (15, 16).

## Argentine national breast cancer programme

The National Breast Cancer Control Programme (PNCM) has developed objectives and an action plan from the diagnosis of the situation carried out in 2010.

The axes are: quality control, coverage, and monitoring.

The objectives of the programme are:

- Ensure the quality of early detection, diagnosis, and treatment services.
- Establish a strategic information system that includes epidemiological surveillance, monitoring, and evaluation of the programme's quality and impact.
- Establish efficient reference and counter-referral systems that ensure the correct and timely diagnosis and treatment of women with breast cancer.
- Strengthen the work of regional cancer registries, implementing the necessary measures to achieve adequate validity and completeness of the data obtained.
- Achieve screening coverage that exceeds 70% of the target population.

Quality implies that the detection, diagnosis, and treatment procedures required by women at risk, suspected or with confirmed cancer training scholarships in reference centres for breast surgeons and imagers, mammography quality awareness workshops (for doctors and technicians), awareness workshops on clinical breast evaluation (for PHC doctors, gynaecologists, health agents), training of technicians in service, and evaluation of centres within the framework of the mammography quality control plan.

Coverage is the ability of a programme to reach the people who need it. The programme develops different communication and awareness strategies about breast cancer aimed at informing the population and strengthening women regarding their healthcare and patient navigation project.

The third axis targeted by the programme is the implementation of a monitoring system that provides data on the performance of the programme, including the number of mammograms performed, age, and the number of cancers diagnosed. This information is essential to achieve quality in mammography studies.

There are many difficulties of access to radiation facilities in low and middle-income populations. Equipment, human resource distribution, and geographical disparities result in rural areas being underserved. The recent hypo-fractionated techniques have made great progress in allowing a reduction in the number of sessions, increasing access to low- and middle-income populations. However, it requires modern equipment with new technologies to perform the treatment safely. The lack of access to radiotherapy treatment excludes the conservative surgery in some regions (19).

## New drugs and new protocols

Clinical trials play a vital role in the development and evaluation of new treatments. These trials test the safety and effectiveness of new drugs or treatment approaches before they are approved for widespread use. Participation in clinical trials provides patients with access to cutting-edge treatments and contributes to advancing cancer care.

In Brazil, the National Commission for Incorporation of Technologies (CONITEC) evaluates the cost-effectiveness and budget impact of new drugs before they can be included in the public healthcare system. This evaluation considers factors such as the drug's efficacy, safety, and cost compared to existing alternatives. CONITEC also takes into account the disease burden and the potential impact on the healthcare budget (20).

Argentina has a similar approach through the National Institute of Health Technology Assessment (IETS). IETS conducts health technology assessments to evaluate the clinical and economic impact of new drugs and treatments. This assessment includes a cost-effectiveness analysis, taking into account the drug's clinical benefits and the costs associated with its use.

These assessments also provide valuable information for healthcare professionals, patients, and decision-makers in determining the most appropriate treatment options. They promote transparency and evidence-based decision-making, contributing to the sustainability of the healthcare systems in Brazil and Argentina.

The use of new technologies in low and middle population may reduce morbidity and cost of treatment. Mattar et al (2021) demonstrated the clinical utility of the 21-gene test to help guide treatment decisions in patients with T1/T2 breast cancer with node-negative or node-positive, ER+, HER2-negative. The assay allowed physicians to reduce chemotherapy (CT) in the Brazilian public healthcare, reducing CT recommendations from 91% to 31%. Despite the cost of the exams, they observed cost reduction with chemotherapy and less morbidity for patients (21).

Overall, the value for money assessments carried out in Brazil and Argentina contribute to evidence-based decision-making and help ensure that limited healthcare resources are used efficiently and effectively.

Executive leadership, organizations, and governments play important roles in addressing breast cancer in Latin America (LATAM). Here are some ways in which they can contribute to creating awareness about breast cancer and advocating for policies and initiatives to address the disease. Strong executive leadership can use their influence to prioritize breast cancer research, funding, and the development of comprehensive strategies to improve prevention, early detection, and treatment (22).

Non-profit organizations, patient advocacy groups, and healthcare organizations have a significant role to play in supporting breast cancer patients. Governments have the power to shape policies, allocate resources, and implement programmes to address breast cancer. They can prioritize funding for research, improve access to diagnostic and fast treatment, as the law of 60 days for oncological treatment in Brazil (14).

Executive leadership, organizations, and governments can support and promote research initiatives focused on breast cancer in LATAM. to the region, improve understanding of the disease's biology, and develop targeted therapies. Overall, the role of executive leadership, organizations, and governments in addressing breast cancer in LATAM is multi-faceted. By working together, these stakeholders can create a comprehensive and coordinated approach to prevent, detect, and treat breast cancer, ultimately improving outcomes for patients in the region.

## Future perspective

Incidence and mortality from breast cancer in Latin America will increase significantly in the coming years. Breast cancer in LATAM requires the active involvement of

executive leadership, organizations, and governments to immediately implement a cost-effective programme to promote free access to symptomatic patients to reduce advanced cases and mortality.

Improving the quality of care for breast cancer patients in Latin America requires addressing the unique challenges faced by the region. Efforts should focus on increasing access to early detection and screening programmes, reducing socioeconomic disparities in access to care, and developing standardized treatment guidelines. Collaborations and partnerships, both within the region and internationally, will be essential in achieving these goals and reducing the burden of breast cancer in Latin America.

Public awareness and destigmatization campaigns are crucial in encouraging early detection, promoting screening, and reducing barriers to care. Considering the most cost-effective strategy for rapid mortality reduction is early detection in symptomatic patients (palpable tumours) through the downstaging. Stakeholders play vital roles in advocating for increased funding, promoting collaboration, raising awareness, and implementing policies and programmes to reduce mortality.

Management of breast cancer in Latin America represents a challenge, particularly in the public system. The CBreast cancer Revealed initiative proposed a strategy to improve outcomes. (See Figure 37.2) (23).

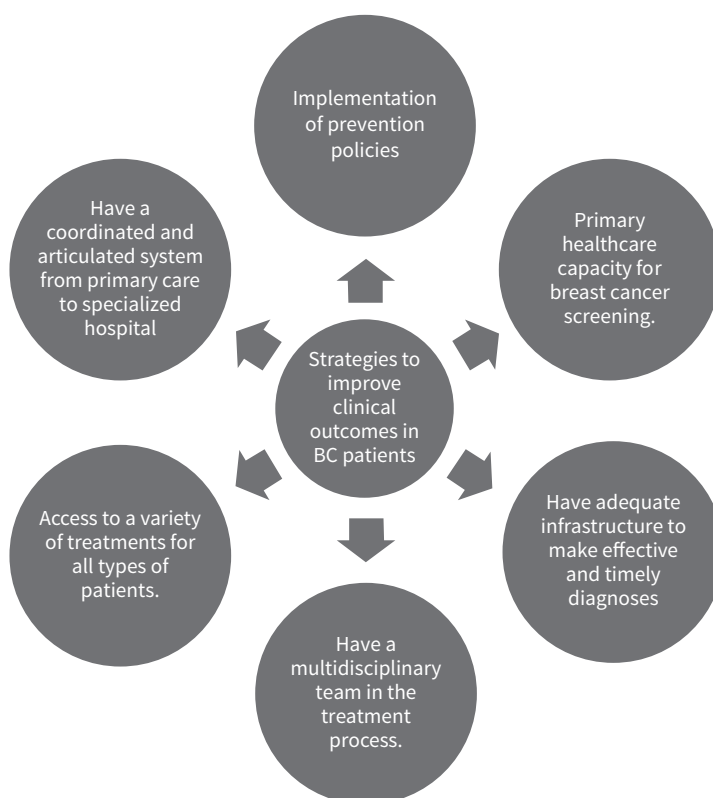


**Figure 37.2** Strategies to improve the clinical outcomes of breast cancer in Latin America.

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## Key messages

- Breast cancer is the most frequent cancer and kills more women than any other cancer in LACs.
- Latin America is experiencing demographic changes, with a growing proportion of older adults, obesity, an increase in alcohol consumption, and a sedentary lifestyle.
- Prevention plays a fundamental role, but several additional measures such as health education and behaviour modification, breast self-awareness, and clinical breast examination should be considered.
- Universal healthcare coverage is still not the rule in LACs.
- Data on survival are scarce and fragmented, but outcomes have improved over the past decade.
- The majority of breast cancer cases are self-detected (T2 and T3 tumours) following symptom onset.
- Initiatives to increase awareness of breast cancer are fundamental.
- Early detection with downstage is more feasible and has more impact in the reduction of mortality than mammography screening.
- Training and qualification are needed for technicians, nurses, general practitioners, or gynaecologists for clinical breast examination in primary care.
- Secondary references are needed for quick access to symptomatic patients with trained and integrated teams for diagnosis with core biopsy and availability of immunohistochemistry in up to 15 days.
- Public–private partnerships are essential, including telemedicine, navigation programmes for patients, and especially radiotherapy references.
- Programmes with individualized mammographic screening in medium and big cities must be implemented.
- Access to start treatment (surgical or neo-adjuvant chemotherapy) within 60 days is important to reduce mortality.
- Continued investment in research, artificial intelligence programmes, and database centres is important for follow-up and treatment adherence.
- Replicating successful experiences between Latin American countries is important to create a strategic model of cooperation between Latin American countries.

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## Sub-Saharan Africa

*Carol Benn, Cassandra Mbanje, and Dominic van Loggerenberg*

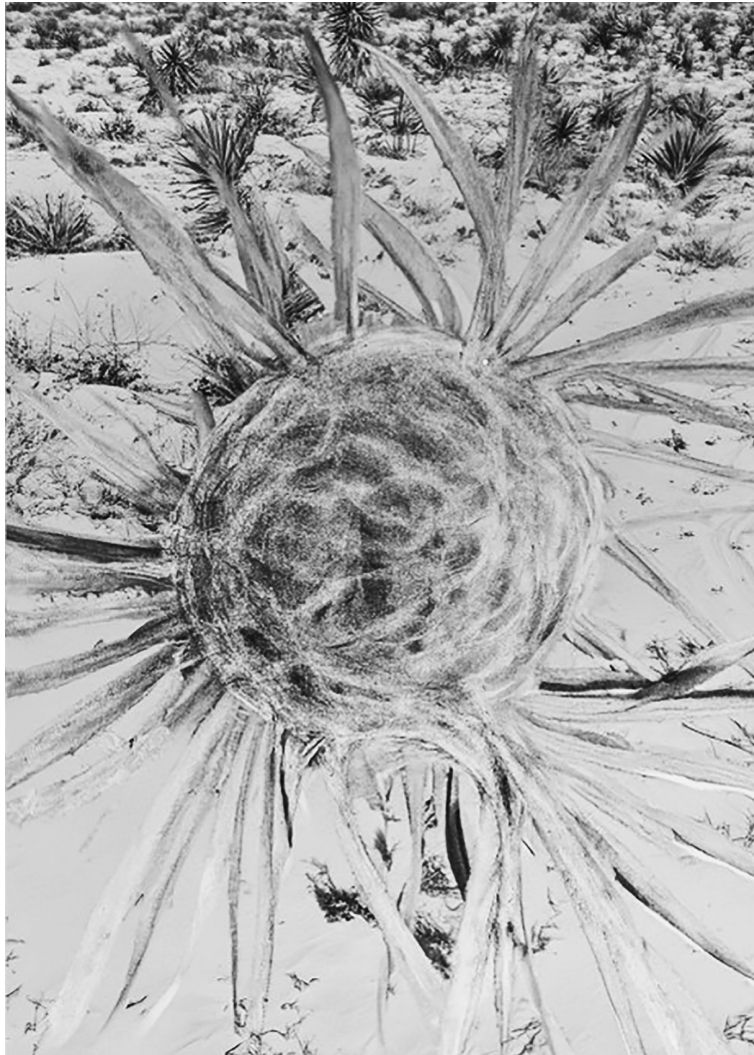


**Figure 38.1** Sub-Saharan Africa

‘Sahara-Sahel, key in the global climate system.’

Visceral landscapes by Pascale Pollier.

Breast cancer SEM cell in Carbon dust technique created by © Pascale Pollier MMAA, Registered Medical Illustrator, Artem Medicalis. Sub-Sahara desert background landscape image generated and edited with Adobe Photoshop AI.



## Introduction

The first edition of this comprehensive book that provided value to specialists and patients around the world was, surprisingly, not purchased by clinicians from LMI countries. This poses the question of why: was it due to cost or was the content not applicable? However, the local chapters were (for once) written by local specialists. The new updated version is also available for free online. Removing all possible concerns or barriers, we encourage all to read it.

The big five in cancer care across Southern Africa (awareness, access, standardized treatment guidelines, integrated supportive care, and equitable service delivery) remain elusive in isolated pockets across the subcontinent (see Box 38.1).

Since the last edition, the current pathology-based breast cancer incidence has gone from 1 in 27 to 1 in 30 women in South Africa (SA) (1). In 2014, the SA national burden of breast cancer accounted for 21% of all cancers. This burden increased to 23.25% of all cancers in 2020 (1).

### Case scenario

*A 30-year-old female of African descent, with clinically T2 N0 tumour and no family history of breast cancer, presented to our breast unit after repeatedly being told that she is too young to have breast cancer. She was triaged as a 'RED' patient (suspicious for breast cancer). Ultrasound, mammogram and core needle biopsy results confirmed a breast cancer diagnosis (Radiology: T2 N1; Pathology: luminal B, Ki 75%).*

*The tumour board decision: primary chemotherapy. Her booking date for oncology was for 4 weeks later at a location far from her. Her family advised that she seek counsel from the elders before commencing treatment. She returned 3 months later after attending spiritual cleansing ceremonies as advised by her elders—clinically now with T3 N1 breast cancer. Navigation counselling by community navigators explained the implicated cultural issues to the clinicians and the importance of being non-judgemental.*

*She eventually underwent primary chemotherapy and achieved a complete clinical response. She had not been examined during her treatment, and no markers had been placed. She was sent back home after her last chemotherapy session, resulting in the ideal window of 3 to 6 weeks for surgical booking being compromised. On return, she was referred to radiology, where little documented evidence of her breast cancer was seen.*

*After much debate, a breast-saving surgery was performed—including an immediate local parenchymal flap. It took 6 weeks to receive the final histology results, and she was then referred for radiation. The centralized radiation department promised to call her, but they did not. A year later, she returned to our breast unit with nodal breast recurrence. Further, her meta-static workup revealed disease in the lung. She is on the second-line oncology waiting list for chemotherapy, and the outcome is not good.*

## Background

In 2020, the latest South African National Cancer Registry showed that breast cancer was the most commonly diagnosed cancer among women, with an age-adjusted incidence rate of

**Box 38.1 The big five in cancer care across sub-Saharan Africa**

- Awareness
- Access
- Standardized treatment guidelines
- Integrated supportive care
- Equitable service delivery

30.14 per 100,000 women and a lifetime risk of 1 in 30 (1). That year, 9259 women were diagnosed with breast cancer, accounting for 23.25% of female cancers in South Africa. 11.6% of these women were under the age of 40 (1). This data is based on people presenting symptomatically to clinics, with a small minority of women engaging in screening programmes. Screening programmes are not legislated in many African countries and this is further hampered by the lack of mammography services (2, 3). Only 33.1% of women with health insurance undergo regular breast screening across Ivory Coast, Burkina Faso, Namibia, and Kenya (3). In many parts of Africa, mammography is not available or, if available, the quality is variable. Access to digital and 3D tomosynthesis and high-risk MRI screening is available to only the few and low-cost alternative options, such as use of handheld screening equipment (iBreast Exam), need to be further explored.

Breast cancer presents as locally advanced breast cancer (LABC) with more palpable disease in most lower-middle-income environments. Teaching breast self-examination and primary healthcare nurse-based clinical assessment training programmes have improved screening and remain useful tools to effectively reduce mortality in limited-resource settings. For South Africa, given the large proportion of women who present with clinically detectable, later-stage cancer, clinical breast examinations conducted in primary health clinics—for all symptomatic women and asymptomatic women over the age of 35—is a low-cost option for population-level screening in the medium term (4).

The understanding of the healthcare cost in the African continent is limited but critical to guide effective delivery strategies. The current per capita health expenditure, PPP (purchasing power parity; current international \$) is reported by the World Bank ([www.worldbank.org](http://www.worldbank.org); 2022). The amount is diminishing from South Africa (1,340), Botswana (1,131), Tunisia (885), Egypt (699), Morocco (552), Kenya (248), Nigeria (245), Mozambique (130), the Central African Republic (109), Ethiopia (78), to Congo Dem Rep (49). In comparison—the US (12,434), the UK (6,371), Brazil (1,696), and India (273).

## Early diagnosis

The international trend of screening based on risk and not age can be effectively trialled in LMICs. The concept of going ‘back to basics’, ensuring breast self-examination (BSE) and primary care access to breast assessment, is also encouraged. This is a cost-effective way of improving breast disease detection that can be taught to women by both public and private healthcare providers (5). Though the US Preventative Task Force and American Academy of

Family Physicians concluded that BSE does not contribute additional benefits to preventing breast cancer mortality where routine mammographic screening is commonplace, BSE may be of value in low-income settings where population-level mammographic screening is not available. Studying models that rely solely on breast examination, be it 'self-examination' or clinical breast examination, provides critical information in terms of patient stage at presentation and outcome, particularly in the young non-screened group below 50 years of age (5).

Examples of this model show that when women practice BSE, they can detect abnormalities and present earlier and with smaller tumours to healthcare facilities. Teaching on BSE usually includes the signs of breast cancer; greater awareness of breast conditions; addressing cancer stigma; and information about where to receive care.

Of interest is the development of mobile apps to engage the public in awareness campaigns about concerns around self-breast examination findings, thus aiding in early diagnostic strategies.

Further, extending awareness campaigns across Southern Africa is critical. Specifically, teaching BSE via nursing education and navigation programmes, as well as integrating breast cancer care into other wellness programmes has improved breast cancer awareness. The expanded use of social media and digital platforms since the SARS-CoV-2 pandemic has also assisted in this. The pandemic also highlighted the lack of access to care. However, a study published out of the Breastcare Centre of Excellence (BCCE) showed no difference in age, stage, or cancer biology at times of diagnosis before or during the pandemic. This infers the lack of screening uptake among South African communities.

Learning how multicultural variables impede acceptance of conventional healthcare systems in Southern Africa is also vital. In today's global village, where information access in first-world settings has resulted in the questioning of conventional medical norms with a rapid move to complementary healthcare, it is important to consider the patient's cultural context. Primary care is often first provided by traditional health practitioners in sub-Saharan Africa, and this provides clinical healthcare providers in these contexts with useful experience and insight into managing non-conventional beliefs.

## Breast ultrasound

In addition to self-examination and clinical breast exams, ultrasound of the breast can be used for exploring the characteristics of palpable and impalpable breast lesions, particularly in environments where access to mammography may not be available. The advent of automated ultrasound and AI interpretation is currently being studied in LMI environments. An ultrasound can also be used to guide core needle breast biopsies for diagnostic purposes. Additionally, ultrasounds can be as good as mammography in detecting invasive cancer, particularly when breast cancer presents as a palpable mass. However, an ultrasound is not a recommended test for early stage population screening due to its lack of sensitivity and specificity in detecting ductal carcinoma *in-situ* (DCIS), operator variability, and resource intensity.

South Africa (SA) is classified as an upper-middle-income country and not a 'very low resource setting'. Technically, South Africa has significant disparities in healthcare access and treatment not unlike many LMI countries. Thus, in certain settings, in sub-Saharan Africa the use of an ultrasound-guided core needle biopsy may be the most effective diagnostic tool,

while in the small percentage of women who have health insurance, screening mammography is important.

## Cultural aspects

Perceptions of breast cancer have changed over the last 30 years, with the realization that it occurs in any race, age, or culture (6). Awareness in South Africa has involved both successful and failed community education projects, mainly introduced via media-directed public health campaigns, and breast cancer advocacy and support groups. Health awareness education and support projects based on American and European models, driven largely through pharmaceutical and cosmetic firms whose corporate-social initiatives provide printed leaflets and posters (primarily in English), have achieved limited success (7). Listening to patient navigators from the community, highlighting the reasons for failure of these projects and redirecting information based on local cultural belief systems resulted in an increase in patient attendance to treatment centres. Initial problems such as the diversity of languages spoken, poor literacy in English, and an inherent suspicion of accepting advice from women of a different cultural background were corrected by involvement of the navigator, through the provision of personalized information and training within their community. This training included understanding preconceptions and beliefs around the cause of cancer—which were barriers to accessing care in symptomatic women.

## Barriers to early diagnosis and treatment

Historically (and currently), access to breast cancer screening and treatment in SA, as also seen in other low and middle-income sub-Saharan countries, is characterized by regional and socioeconomic disparities. These differences often start with relatively low levels of knowledge of the disease in certain geographic areas and within certain communities. Knowledge gaps include how breast cancer presents, with resultant late presentation at health facilities (5). Access to care is further hampered by the still vertical medicinal model between the healthcare worker and patient. In other words, if the patient is advised that their symptom is not a concern by a healthcare provider, they may decide not to seek further care, despite their issue posing a genuine health risk.

Studies across sub-Saharan Africa showed that most patients presented with advanced or late-stage disease (3, 4). Since then, a change in awareness and access to care has doubled the percentage of women presenting with stage 2 cancer or lower to 46% of women. Still, significant disparities and barriers to accessing breast cancer services persist in comparison to the United States, where 82% of women are diagnosed with stage 2 cancer or lower.

Lack of clear direction as to where patients with health concerns should present, as well as apathy if no clear answers are given, results in compounded access delays. Patients waiting for bookings for chemotherapy or radiation accept excuses such as ‘the next available date is in four months’ time’ and ‘we will call you,’ and don’t push back when not receiving calls.

Delays in accessing healthcare services are due to both patient- and provider-factors. This makes understanding barriers to receiving healthcare more complex. Patient (mis)beliefs and cultural factors, including suspicion of the biomedical model, are exacerbated by economic, geographical, psychosocial, cultural, financial, and medical influences that all affect

delays to treatment. Investment in breast cancer research and treatment in LMICs should be a global health priority (4).

Medical influences more commonly understood as ‘provider delays’ (defined as the structural or provider-dependent factors which negatively impact on time from the first presentation to a healthcare practitioner to receiving primary surgical/non-surgical treatment) make a not-insignificant contribution to limitations in accessing healthcare in many LMIC. For example, in South Africa, restrictions to accessing the healthcare system and delays in service delivery mechanisms will most positively affect the patient outcome with regards to diagnosis, management, and ultimately cancer survival. Data suggest that patients presenting with advanced disease, with a delay of more than 60 days from tissue diagnosis to primary treatment, may have an increased risk of mortality. A meta-analysis studying the delay from surgery to adjuvant therapy found that a backlog of more than four weeks to chemotherapy, as well as delays to radiation, adversely affect patient outcomes. These delays are often seen in LMICs. Delays to care in environments where there is a patient-driven advocacy result in forced improvement of services. Delays to care in environments with a historic acceptance of poor service and a fatalistic attitude to cancer compound the problems of poor service delivery. If walk-in access was prioritized at specialist centres, women could also initiate their diagnostic process at the specialist level directly, reducing appointment and, therefore, patient costs. Regardless, a quick, coordinated referral would contribute to reductions in delays to treatment. Regionalizing oncology services would also improve access to care and patient compliance, as time and distance stressors would be avoided. Another low-cost solution would be the use of a colour-coding assessment scale for efficient patient navigation and resource management, as described by Benn et al. in 2020 (8). It can thus be seen that interventions are required at multiple levels to ensure access and availability to affordable breast cancer care in sub-Saharan Africa.

## Service delivery: improving quality of care

Service delivery is a key concept in ensuring reasonable healthcare outcomes. South African models that have been instituted in a few public sector units have undergone fundamental improvements, allowing for better clinical care in some settings over the last 20 years. Service delivery models and how they impact patient outcomes are critical issues. Training of primary care physicians, clinical associates, primary care nurses, and community-based patient navigators is also critical. Community-based patient navigators are those from the community who have experienced breast cancer, either within themselves or with close family member(s) and have an increased understanding of community-specific geographical and cultural logistical challenges to care. Thus, navigation programmes, particularly those using community-based navigators, are important. The introduction of clinic advisory boards could also provide meaningful structure to the partnership between health facilities and the community when conceiving and implementing new, community-specific interventions (4). Additionally, we need to perpetuate a service delivery model whereby trained primary care healthcare workers can immediately refer women with suspicious breast concerns to specialist centres where diagnostic investigations can be performed as needed. More publications about breast cancer services in LMICs are needed.

However, we do know that current service delivery in SA, as with other LMI countries, has progressed considerably in some cosmopolitan urban cities. In these public sector units,

diagnosis of breast cancer now includes the global gold standard: triple assessment (i.e. clinical breast examination, imaging by ultrasound or mammography or both, and biopsy). However, the quality of a facility's radiology and pathology services may be variable, affecting the efficacy and reliability of the triple assessment.

In South Africa, access to diagnostic, treatment, and surgical services is not homogeneous. Late-stage presentation of disease continues to prohibit individual management approaches, such as BCT (breast conserving treatment). A lack of treatment facilities and specialist capability to perform these procedures in the public sector limits access to them for many women. Significant delays to receiving radiation services further hamper the acceptance of BCT in the public sector. The BCT rate in the only American College of Surgeons NAPBC-accredited private breast unit, the Netcare Milpark BCCE, sits at 93%. Currently, private-public partnerships with the BCCE are underway to offer services to improve the surgical care of patients without medical insurance.

## Addressing national strategies

In Kenya, the development of a national strategy for the prevention and control of noncommunicable diseases (NCDs) 2015–2020 provides a roadmap to improve (breast) cancer care and the quality of life of all Kenyans (7). A systematic review of overall African NCD prevention policies and their implementation highlighted that the equity coverage and response for such policies remained poor across African countries (9). Further, only 20 (43.4%) of the 46 World Health Organization (WHO) member states in sub-Saharan Africa have active cancer registries spanning a wide range of completeness and coverage (10).

A national-level policy document on breast cancer screening and treatment has also been drafted and launched in South Africa (4). The policy document addresses options for improving access to breast cancer-related services. It looks at the current environment regarding breast cancer-related care. In all, the South African Breast Cancer Control Policy document hopes to improve patient access; improve communication between regional and central breast units; and ensure more timely access to all treatment modalities. Barriers to the implementation of equitable breast cancer care access—including perceived costs—are discussed, and health delivery models which could help achieve South Africa's goals are suggested. The aim of this policy is to decrease current provider-dependent delays. Additionally, increased availability of multidisciplinary teams at the level of specialist centres should improve access to care and, thus, decrease the number of LABCs. This would likely also produce a knockdown effect, with a resultant decrease in low survival rates.

Interestingly, the SARS-CoV-2 pandemic improved the uptake of online multidisciplinary meetings (MDM). This resulted in more public-sector-based online MDMs. Publications to determine whether this has improved access to care are not yet available.

## Access to care: open-access clinics

Access is a bigger barrier in LMI countries than awareness. An understanding of 'Hostile Hospital' environments needs unpacking—be it from assessing the financial implications of quality care to the logistics of patients accessing care. Patients are often required to first access

a primary healthcare service. This is followed by a referral to tertiary institutions, which is complex and not easy to traverse.

Such a barrier can be circumvented by open-access clinics. Further, regional hospitals need to have simple guidelines for patients presenting with breast problems. This is to ensure efficient, frustration-free patient assessments. Appropriate diagnostic structures must also be in place with systems that facilitate easy referral. Referral from and collaboration with traditional health practitioners or non 'western' health practices needs further study for improved patient access to care and better patient outcomes.

Healthcare models throughout the world offer differing levels of care in terms of funding access, medical intellectual availability, geography, and/or post-treatment qualitative support. Standardized care ensures better quality for all patients. Opportunity exists to create unique partnerships between the public and private sector as well as between academic and regional centres, with horizontal (both learning) and not vertical (we can show you the best way) associations in true 'Mandela' style. This will ensure collaborative best breast healthcare is possible.

## Defining treatment guidelines

The international guidelines that dictate core biopsies for the diagnosis of breast cancer are often not followed in sub-Saharan Africa. Encouraging the correct methodology of cancer diagnoses through radiology services with guided core biopsies and not by surgical biopsies needs to be audited by medical funders.

Answering the question as to why so many surgical biopsies are done is complex for simple handheld core biopsies on palpable masses under ultrasound guidance is a cost-effective diagnostic method. Educating physicians to perform radiological guided diagnostics is critical.

Funders should not be authorizing surgical removal of breast masses without the prerequisite core needle biopsy confirming the diagnosis followed by a documented discussion in an accredited multi-disciplinary meeting with feedback to the patient and funders.

Pivotal to treatment is accurate diagnostic pathology. This requires not only accurate specimen interpretation, but appropriate specimen handling, processing, and accurate receptor analysis. Digital pathology provides a useful aid to the interpretation and quality assurance when used in LMI settings.

Further, the advent of digital multi-disciplinary meetings provides an opportunity to expand access to medical expertise and drive improved patient decision-making with improved outcomes. Exporting National Consortium of Breast Centres (NCBC) programmes, expertise, particularly with regards to patient navigation and quality outcome measures (NQMBC), would aid in ensuring the provision of cancer care that is complete. Complete care considers each patient's risk assessment, diagnosis, oncological management, psychosocial care, reconstruction, and long-term surveillance.

Currently, treatment of breast cancer varies from following best practice to patients undergoing mastectomies without primary oncology care for advanced cancers, while also not receiving radiation or adjuvant oncology care. Multidisciplinary treatment guidelines that are accepted internationally and have been driven locally from the combined units need to be



adopted across the continent. Ensuring that both private and public breast units adhere to internationally recognized guidelines would improve overall patient treatment.

The cost of oncology drugs and immunotherapies is also prohibitive and often not available to many patients. A possible solution is to increase access to drug trials within the setting of verified trial units.

Another big stumbling block to care is the lack of radiation oncology services in sub-Saharan Africa, resulting in a high mastectomy rate due to the misguided belief that a mastectomy decreases the need for radiation. With most cancers in sub-Saharan Africa being diagnosed with node-positive disease or as a LABC, the need for radiation remains. Thus, we need to increase the availability of intraoperative radiation services.

## Supportive care

Survivorship is a relatively new concept in South Africa that is not well offered to patients post-best cancer care. Surveillance for cancer recurrence is often approached in a non-multidisciplinary manner. This is further complicated by cancer survivors having comorbidities such as human immunodeficiency virus (HIV), tuberculosis, and other NCDs. In fact, the high prevalence of HIV infection in South Africa and the nature of HIV mean that breast cancer is commonly diagnosed together with concurrent HIV infection, with these patients often presenting at a younger age than those who have breast cancer but are HIV-negative (4).

Palliative care is also fragmented. Greater focus is needed to ensure prioritization of palliative and supportive care for our patients when considering the estimated increase in cancer mortality from 520,348 in 2020 to about 1 million deaths per year by 2030. The prevalence of breast cancer in sub-Saharan Africa is also predicted to double by 2050 (10) (see Chapter 19).

To end, sub-Saharan African multi-disciplinary breast units in both the public and private sectors exist, though they require corporate-social support so as to facilitate the big five in cancer care across Southern Africa (awareness, access, standardized treatment guidelines, integrated supportive care, and equitable service delivery). Africa grows on the spirit of UBUNTU—togetherness—and this is a principle by which we should work to not only better breast cancer care, but towards achieving Sustainable Development Goal (SDG) 3.4 by 2030.

## Key messages

- Improve education and awareness on breast health, including signs of breast cancer, and BSE.
- African governments must invest in breast cancer care, as no progress is sustainable without political will.
- Embrace digital pathology interpretation of breast specimens for both core biopsies and final pathology.
- Increase the number of breast specialist centres nationwide and ensure that they are staffed with multidisciplinary teams.
- Train primary healthcare nurses on how to perform clinical breast examinations and begin screening of asymptomatic women older than age 35 (in addition to offering to screen for all symptomatic women).



- Strengthen existing referral systems, including through facilitated patient transport systems.
- Increase support for and links to patient advocates and counsellors in communities and within breast specialist centres to ensure comprehensive, full-spectrum care.

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39

## USA

### A value-based breast care perspective

*F. Lee Tucker and Samilia Obeng-Gyasi*



**Figure 39.1** USA

‘Waterfalls between countries, source of energy.’

Visceral landscapes by Pascale Pollier.

Histology Breast cancer cells in carbon dust technique created by © Pascale Pollier MMAA, Registered Medical Illustrator, Artem Medicalis. Rocky Mountains USA background landscape image AI generated and edited in Adobe Photoshop.

## Introduction

The meaning of value in breast care delivery varies with the individual perspectives of care-givers, patients, facilities, and payors. Value has become one of the most urgent topics in healthcare management over the last two decades as a means to improve access and clinical outcomes while reducing the rapid rise in healthcare costs to society as well as individuals.

Care providers typically view value from a perspective of reducing overuse and inefficiency while improving outcomes, while patients are primarily concerned with costs and their subjective care experience. Payers and facilities have a shared concern over rising costs and fiscal sustainability.

The delivery of high-quality breast care in any socioeconomic environment is a complex and costly endeavour. Reliance on clinical guidelines and clinical best practices has contributed to high utilization of costly technologies resulting in improved clinical outcomes such as survival. The healthcare environment has historically been described as volume-driven, wherein more care has been conflated with better care. Unfortunately, uneven care with both over-utilization and underutilization, is commonplace. Providing optimal care is a challenge in resource-limited environments, just as optimal care delivery in high-resource environments can be wasteful. High-income nations have seen healthcare costs, as a per cent of gross domestic product (GDP), rise from a range of 5–8% of GDP in 1980 to 9–17% of GDP in 2019, with no end in sight (1).

The challenge of uneven global healthcare delivery with variable outcomes and rapidly rising costs requires a new approach. An expression of value is needed that divides the cost of delivering care into a quality numerator that includes patient-reported outcomes. Additionally, an evolutionary change from volume-based reimbursement to value-based compensation for care is required. There is general agreement that any value definition must include costs, clinical outcomes, and the patient's subjective experience. Value can be increased by holding costs constant while improving clinical outcomes (including the patient's experience), by maintaining clinical outcomes while reducing costs or, better still, a combination of these strategies. By eliminating or reducing over—and under—treatment, it should be possible to reduce adverse events and improve overall clinical and patient-reported outcomes.

## Seminal value-based proposals

Porter and Teisberg introduced the concept of value-based healthcare (VBHC) in 2006, a method of reigning in healthcare expenditures while maintaining or improving outcomes (2). The principles as originally presented were not specific to breast care processes, however they serve as a valuable introduction. Subsequently, six key steps were introduced as a guide to VBHC implementation (3).

- Re-organize care around patient conditions (or groups of conditions) into integrated practice units (IPUs) covering the full cycle of care
- Measure outcomes and costs for every patient, in the line of care
- Move to value-based reimbursement models, and ultimately bundled payments for conditions
- Integrate and coordinate care across multi-site care delivery systems
- Expand or affiliate across geography to reinforce excellence
- Build an enabling information technology platform

In an independent, parallel initiative, the Institute for Healthcare Improvement (IHI) introduced the 'Triple Aim', a concept statement for improving healthcare performance (4).

1. Improve the experience of care
2. Improve the health of populations
3. Reduce per capita costs of care

The intent of the Triple Aim is to implement the three components across the healthcare landscape in unison.

## Cost of care

The cost of delivering care is the all-important denominator of the value quotient. The complexity of modern healthcare, including breast care services, creates significant challenges to obtaining accurate cost estimates. Depending on the patient's path through the system, the costs to provide procedures, clinical staff, tests, supplies, and facility space such as operating rooms can vary greatly. Individual departmental budgets pose unnecessary impediments to calculating costs for services funded through organizational silos. Care delivered by non-affiliated entities, providers, and economic competitors adds to the challenge of accurate costing.

Traditional methods of estimating costs based upon fixed and variable expenses are time and resource-consuming and lack accuracy. Activity-based costing (ABC), proposed by Cooper and Kaplan in 1988, was found to be a more useful approach by industry than previous methods of cost accounting, but proved difficult and time-intensive in use (5). Kaplan and Anderson revised and simplified the methodology in 2004 and introduced time-driven activity-based costing (TDABC) (6). The TDABC approach is an attempt to streamline the costing process and place it in reach of most healthcare facilities. To date, costing data has not been reported in most published accounts of VBHC implementation. Most literature reports of VBHC implementation in clinical settings either omit costing data completely or do not include fully operationalized TDABC methodology in the reported care cycles. Even though TDABC has not yet achieved widespread acceptance in the healthcare environment, it provides the most accurate, time efficient costing estimates to date; an essential component of the value quotient.

Kaplan and Porter published a detailed implementation roadmap for TDABC in healthcare facilities, based on the VBHC process (7). The seven steps developed by Kaplan and Porter for full deployment include: 1. Select the medical condition, 2. Define the care delivery value chain (CDVC), 3. Develop process maps of each activity in patient care delivery, 4. Obtain time estimates for each process, 5. Estimate the cost of supplying patient care resources, 6. Estimate the capacity of each resource and calculate the capacity cost rate, and 7. Calculate total cost of patient care. Although not specifically designed for breast care, the principles and methods can be directly applicable to breast services.

## Value-based breast care (VBBC)

Interdisciplinary breast programmes or units are ideally suited to develop, implement, and evaluate value—quotient practices since most already function as an IPU. Many of these programmes serve broad populations of patients with breast disease as well as an asymptomatic

### **Box 39.1 The essential elements of a fully operationalized VBBC programme**

- Clinician-executive director
- Interdisciplinary leadership team
- Integrated information technology (IT)
- Data-driven management culture
  - Identification of standardized clinical and service outcomes metrics
  - Identification of relevant adverse events
  - Identification of standardized PROMs
- Cost reporting
- Education
- System—wide coordination of care
  - Affiliations
  - Population health

screened population. Interdisciplinary breast care is entering its fourth decade of development in many locations, and the components of a fully developed interdisciplinary care team are, at least nominally, familiar to most readers.

How does an existing breast programme or service unit implement a VBHC process? An important question in resource-limited environments is, ‘How can a VBBC programme be developed where breast services are needed but not yet organized into a service unit or formal programme?’ Not every clinical site currently has—or can justify—the full complement of staff for a comprehensive IPU. For most care scenarios, the process begins by cultivating the leadership skills of breast-specialized clinicians before scaling programme ambitions to the clinical and financial resources available. Once established, the service unit can affiliate by data and resource-sharing with more established programmes to achieve the benefits of VBHC (see Box 39.1).

The roster of the breast programme (or IPU) leadership team membership may outwardly resemble an existing breast programme advisory board or leadership committee, but the priorities and roles of the various functions must be adapted to the specific tenets of VBBC.

## **Organizational model of the VBBC programme**

### **Leadership—clinician executive**

The executive is both VBBC programme champion and visionary, promoting a culture of value. Physicians can share the management responsibility with a non-clinical administrator (Dyad model) or undergo specialized leadership training to complement a cross-specialty breast care knowledge base. In whatever form the leadership is configured, it must have the full support of the parent organization’s chief operating officer and board of directors or governmental agency, as appropriate. The job description should include

in writing the scope of authority and accountability to access information technology resources, establish and revise programme priorities, and allocate resources within the scope of breast care services. The executive should have authority to create and administer the capital budget and operating budget, subject to senior leadership approval. Since a critical responsibility of the VBBC programme mandate is to improve the breast health of the community served, this oversight should span community mammographic screening of asymptomatic individuals and continue through support, rehabilitation, and end of life. Leaders should be well-versed in all aspects of the VBBC process as it is applied to breast care services. The VBBC leadership reports all aspects of programme performance to the organization's senior leadership team. In particular, costing data and care cycle value quotient results are reported to the chief financial officer (CFO) or other designee for the purpose of eventual reimbursement contract (and future bundled payment) negotiations on behalf of the organization.

## **Interdisciplinary leadership committee**

The leadership committee oversees all aspects of the VBBC. In any but the most basic breast care delivery environments, the complexity of VBBC implementation and management requires efficiency through delegation of specific responsibilities to subcommittees.

### **Quality subcommittee.**

This team defines the care delivery chain and develops process maps to support the TDABC process. The subcommittee determines the frequency of reporting and receives and audits all outcomes data. The subcommittee works towards the use of standardized definitions for metrics to facilitate meaningful local, regional, national, and international comparisons. The subcommittee works collaboratively with the cost subcommittee to ensure alignment between costing data and clinical care cycle process maps.

### **Clinical care cycle outcome metrics.**

Longitudinal care cycles are important to define because they allow for costing over the duration of the patient's breast care. There is no current consensus on the definition of individual breast care cycles, but as programmes gain experience with the VBBC methodology, agreement on definitions will be desirable for value comparisons across markets. A compelling reason to begin VBBC with associated TDABC as soon as possible is the process establishes a value baseline in one's organization and costs become known. Management of the value expression of each care cycle can begin as soon as the data is available for review.

### **Patient-reported outcomes measures (PROMs)**

The International Consortium for Health Outcomes Measurements (ICOHM) initiative reported a standard set of value-based patient-centred outcomes for breast cancer in 2016 (8). The metrics include a few measures obtained clinically or administratively; however, the majority are subjective patient assessments of the care experience and are deemed by the ICOHM to be applicable in most parts of the world. The standardization of PROMs is an important step forward and their adoption is strongly encouraged.

### **Population health subcommittee**

This subcommittee is charged with monitoring screen attendance rates according to established guidelines in the smallest geographic or demographic locale for which data is available (vide infra, breast programme strategies). Based on attendance data, the subcommittee can direct resource allocation to underserved locales with the aim of improving early detection. Depending on the programme's resources, allocated resources might include mammographic screening, educational programmes, volunteerism, or a combination of these offerings. In addition to community screening, identification and risk-stratification of asymptomatic relatives based on risk-assessment at the time of screening offers the opportunity for genetic counselling, testing and the development of customized surveillance protocols for persons who would otherwise not be eligible for routine screening.

### **Cost subcommittee**

Accurate estimation of costs should evolve to time-driven activity-based costing (TDABC) methodology. The cost subcommittee works in concert with the quality subcommittee to obtain process maps for each care cycle to capture costing data for the complete spectrum of breast care, from the screening mammogram to final completion of treatment.

### **Education subcommittee**

The education subcommittee serves as VBBC champions with active and visible support of the process. Placing education in a dedicated subcommittee allows for the efficient prioritization of educational opportunities based on a needs assessment to ensure the entire clinical care team and all levels of management are on board, particularly if VBBC is the first value-based initiative in the facility. IT and finance department staff associated with the VBBC will benefit from a specific clinical orientation into breast disease evaluation and management. Patients and the lay community should receive information to include them in the VBBC process, to recruit submission of PROMs and promote regular mammographic screen attendance.

## **Dedicated information technology**

The IT designee(s) must be carefully selected for commitment to participation in the requisite work of the quality and cost subcommittees. Adequate responsibility should be afforded to the IT staff for data retrieval from patient financial records, medical records, tumour registry, and claims data. Larger programmes have migrated to breast-specific databases. Care must be taken to ensure definitions are uniform and representative of the specific care cycle.

## **Resource allocation, capital, and programme prioritization**

The leadership team is tasked with the evidence-based allocation of resources, capital expenditures, and the operating budget. The leadership team must scrutinize the value quotients derived for individual care cycles to identify value variances in clinical outcomes, PROMs, and associated costs. Cost outliers should lead to investigation of over- and underutilization of procedures, redundant processes, or testing. An example of programme prioritization



would be the development of a population screening initiative with resource allocation to under-screened locales. Once established, care cycle value quotients should be reassessed regularly to inform programmatic revisions and budget considerations. Outcomes, PROMs and costing data must all be collected on an ongoing basis to create a continuous cycle of outcomes analysis, programme improvement, and value enhancement.

## System integration and regionalization

Standardization of the definitions of outcomes metrics is an essential prerequisite for regionalization of breast care value initiatives. Careful attention to both the numerator and denominator is required; inclusive time periods for the measure must be clearly and consistently stated. An agreed set of actionable core measures should be selected based on clinical relevance. These measures can be selected or revised from the facility's historical practice, selected based on known problem areas, created as new metrics or from all of these. Importantly, they should include characteristics of service delivery, professional performance, and clinical outcomes.

Data sharing across an individual health system is commonplace in many locales and can greatly expand the regional reach of a VBBC programme. The addition of costing data to the process allows for comparisons of efficiency and identification of capacity limitations and underutilization. Strategic planning to enhance value through space, equipment, and human resource allocation is greatly facilitated. Health system acquisition and merger activity affords a promising opportunity to expand VBBC across even greater geographies.

## The value quotient—putting it all together

How can a programme calculate a value quotient? Using quantitative outcomes data from the ICOHM standard set of PROMs reported on a quantitative nine-point scale, individual process steps can be reproducibly evaluated by dividing the PROM score for that step by the TDABC-derived cost. More broadly defined numerators (process steps) can be used, but granularity and usefulness may be reduced. Value calculations become more challenging when using clinical outcomes data. How does one divide cost into a complete course of chemotherapy without adverse events? Or one with several adverse events? One method might be to create a standardized numerical scale for each clinical outcome metric that factors in adverse events so that a reproducible numerical result is calculated. The score, ranging from 1 to 10, could then be divided by the TDABC-derived cost to arrive at a value quotient for the care process step. Development of these process-step scales would be a worthwhile next step for programmes implementing VBHC and standardization of the scales would permit meaningful comparison across facilities, regions, and even countries.

## Health equity and value

In the United States, despite significant advancement in the diagnosis and treatment of breast cancer, racial and socioeconomic disparities in breast cancer diagnosis, treatment, and



survival persist (9). For example, individuals residing in resource poor neighbourhoods are more likely to present with advanced stages of breast cancer and have higher mortality rates than those in resource-rich areas (10). Further, living in a neighbourhood with low socioeconomic status has been associated with filing for bankruptcy (11, 12). Similarly, who identify as Black experience more aggressive breast cancer subtypes, face barriers in systemic treatment completion and have worse survival (13). VBBC provides leaders an avenue to identify disparities in diagnosis and management to equitably improve long term outcomes.

## Conclusion

VBBC practices are gaining momentum in the US and Europe. A disciplined approach to their implementation requires definitional standardization of outcomes metrics, identification, and use of standardized adverse event reports and adoption of PROMs as recommended by the ICOHM. The TDABC methodology has advantages over previously used costing methods, but it remains a complex undertaking and requires the collaborative expertise of finance, IT, and clinical staff.

Further work is needed to define discrete breast care cycles to encompass benign and malignant diagnoses and, possibly separate *in-situ* vs. invasive cancer care cycles. A balance must be maintained between an emphasis on outcome measures and costing data. A disproportionate focus on costing can result in cost savings at the expense of clinical outcomes. An emphasis solely on outcomes and PROMs reduces the potential value enhancements from costing which are desperately needed to address the global rise in healthcare expenditures.

## Key messages

1. Breast care is by nature multidisciplinary and complex; the cost to society and individuals is rising.
2. The IHI's 'Triple Aim' and Porter's value-based healthcare initiatives are mutually supportive, compatible strategies for breast health programmes.
3. Breast care IPU's are well positioned to implement all aspects of value-based healthcare, but requires a nuanced approach; adaptation of existing priorities, accountabilities, and responsibilities is required.
4. The TDABC is the most accessible and accurate methodology for estimation of costs, but requires focused expertise of finance, clinical, and IT staff.
5. Standardization of clinical outcomes metrics is currently inadequate; standard definitions are essential for meaningful value comparisons. Breast care leaders, organizations, and agencies with an international perspective should prioritize these efforts.
6. Adoption of ICHOM's standardized set of PROMs is encouraged as an important numerator of the value quotient.

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## Worldwide breast cancer initiatives

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### The WHO Global Breast Cancer Initiative

Breast cancer is the most common cancer worldwide and the leading cause of cancer deaths among women, disproportionately affecting individuals in low- and middle-income countries (LMICs). Breast cancer five-year survival rates in high-income countries exceed 90%, compared with 66% in India and 40% in South Africa. Breast cancer is the most common cancer among women in 86% of countries and is the first or second most common cause of cancer-related deaths among women in 95% of countries. In sub-Saharan Africa, where half of all breast cancer deaths occur in individuals under 50 years of age, 100 deaths from breast cancer at this young age causes 210 children to become maternal orphans. The chronic social disruption and financial harm that come with breast cancer will continue to have an impact on LMICs for generations to come (see Chapter 2).

To provide strategic guidance and coordination aimed at reducing global breast cancer mortality in LMICs, WHO established the Global Breast Cancer Initiative (GBCI) in 2021. The goal of the initiative is to provide evidence-based recommendations for a phased approach to implementing interventions focused on improving early detection, diagnosis, treatment, and supportive services. It was in essence a political global initiative to support government in their global health issues. To improve existing healthcare delivery systems, it is necessary to monitor programmatic inputs, outputs, and outcomes to determine possible gaps in care delivery. The roadmap for achieving this goal is the GBCI framework, which was developed by a coalition of 150 global experts and published by WHO on International Women's Day 2023. Three evidence-based key performance indicators (KPIs) corresponding to the three GBCI Pillars were established to identify system gaps that may exist to reduce breast cancer mortality by 2.5% per year, which over a 20-year period would save 2.5 million lives.

Recent data show that only seven of the most developed countries are meeting, and six additional countries are close to meeting, the GBCI goal. This outlines a possible gap with countries requiring further guidance on a set of essential measures to consider to scale-up action for improve breast cancer care (1).

### The three pillars of the WHO GBCI breast cancer patient-care pathway

The GBCI Implementation Framework (2) (Figure 10.1) provides national programme managers, policymakers, and multisectoral actors the guidance needed to assess, strengthen, and scale-up services for the early detection and management of breast cancer.

- Pillar 1. Health promotion for early detection (prevention and pre-diagnostic interval)
- Pillar 2. Timely breast diagnostics (diagnostic interval)
- Pillar 3. Comprehensive breast cancer management (treatment interval)

## **Pillar 1: health promotion for early detection (prevention and pre-diagnostic interval)**

The KPI benchmark of Pillar 1: at least 60% of invasive breast cancers are stage I or II at diagnosis.

This is based on data showing that every country that has undergone a sustained decline in breast cancer mortality rates of 2% per year or more for at least three consecutive years has achieved this level of early detection (3). On the other hand, no country where late-stage breast cancer detection is below this level has shown a sustained decline in breast cancer mortality (4). These findings urge that governments should focus on the development of functional, resource-appropriate early-detection programmes.

Early-detection programmatic strategies will vary based on health-system readiness at the national and/or subnational levels. In settings where late-stage breast cancer presentation is common, and women present with cancers that are easily felt or seen, stage shifting is required to increase the fraction of patients initially diagnosed with early-stage disease. Early detection begins with breast-health awareness through the establishment of early-diagnosis programmes. These programmes focus on identifying people with signs and symptoms suggesting malignancy and linking them with cancer diagnostic services. Breast cancer screening (an alternate early-detection programmatic strategy in which women in a target age group without recognized signs or symptoms of breast cancer are invited to undergo testing yearly or every other year) may be an aspirational goal once health-system prerequisites have been established. However, organized, population-based screening is not an appropriate or practical initial step in any setting until the required infrastructure and quality control measures are in place and fully functional. Thus, all healthcare systems require the capacity to diagnose symptomatic breast complaints, such as lumps, thickenings, or other clinical detectable abnormalities, regardless of whether they can afford and effectively organize mammographic screening programmes.

## **Pillar 2: timely breast diagnostics (diagnostic interval)**

The KPI benchmark of Pillar 2: breast cancers diagnosed within 60 days (two months) of initial presentation.

This is based on the concept that the clinical detection of breast cancers early in their course will improve breast cancer outcomes only if the pathologic diagnosis and initiation of high-quality treatment are timely. The clinical detection of breast cancers early in their course will improve breast cancer outcomes only if the pathologic diagnosis and initiation of high-quality treatment is timely. Cancers vary in terms of time to progression, depending on their underlying biology. Thus, health systems must be able to distinguish promptly between malignant and benign breast findings. Treatment should start within three months of diagnosis, as studies have identified that delay beyond this period leads to lower rates of breast

cancer survival (5). By securing a definitive diagnosis within two months, the stage is set for initiating treatment within three months.

### **Pillar 3: comprehensive breast cancer management (treatment interval)**

KPI benchmark of Pillar 3: >80% of breast cancer patients complete their recommended treatment.

This is based on the notion that access to, including the affordability of standard breast cancer treatment is a major barrier in most LMICs. One of the most common challenges in LMICs relates to patients who do not complete the treatment initiated or have such significant delays in doing so that the therapeutic benefits are limited (6). Patients might not be able to complete the full course of treatment for a variety of reasons, including inadequate access and unaffordable out-of-pocket expenses. Incomplete treatment leads to poorer patient outcomes, including recurrence and death. Lack of treatment completion also negatively affects quality of life because patients suffer the side-effects of treatment but fail to receive its full clinical benefits.

In summary, by using this GBCI framework all stakeholders can achieve the initiative's goal to assure feasibility and quality by providing evidence-based recommendations for a phased approach to implementing interventions and strengthen health systems towards the attainment of universal health coverage.

There is a clear need to strengthen health systems to be able to respond to the growing burden of breast cancer, using sustainable, cost-effective, and equitable breast cancer early detection and treatment services, particularly in LMICs. To be successful and sustainable, these efforts must be integrated within a community-health framework that engages primary-care facilities, secondary (district) level hospitals, and tertiary care centres. These efforts would not only support health promotion but also empower women to seek and receive healthcare throughout the life cycle.

City Cancer Challenge (C/CAN) is a non-governmental organization (NGO) program-matically launched by the Union for International Cancer Control (UICC) at the 2017 World Economic Forum Annual Meeting in Davos, Switzerland (<https://citycancerchallenge.org/>). Now an independent NGO, C/Can leads a city-based partnership initiative that supports cities around the world as they work to improve access to quality, equitable cancer care. Now in 15 selected cities globally, C/Can seeks to transform the way in which stakeholders from the public and private sectors collectively design, plan, and implement cancer solutions. In 2023, C/CAN established a partnership with WHO to advance the implementation of the WHO GBCI at the city level and identify resource-appropriate strategies for implementing evidence-based approaches to improve breast cancer outcomes guided by the GBCI KPIs linked to the three GBCI Pillars. Cities are focal points for healthcare innovation and service delivery, making them ideal for interventions in cancer care. C/CAN is a multi-sectoral cancer initiative supporting city-led solutions in the design, planning, and implementation of cancer treatment using breast cancer as a flagship disease-specific set of strategies that are similarly relevant to other solid adult cancers. By increasing access to effective care and empowering women, the framework aims to address healthcare inequities that disproportionately affect women.

In 2025, during the fourth high-level meeting of the United Nations General Assembly, the heads of state will together set a vision to prevent and control non-communicable diseases. Through a political declaration decided in the UN General Assembly, a priority will be decided on prevention and control of cancer, including breast cancer as one of the priorities towards 2030 and 2050 (7).

## Lancet Breast Cancer Commission

The Lancet Breast Cancer Commission was published in 2024 and aims to raise the standard of breast cancer care to close the existing equity gap, both between and within countries (8). Breast cancer is an important non-communicable disease to tackle globally because of its high and rising incidence and prevalence. Six themes with goals to achieve are identified alongside proposed measurable indicators of change.

### Theme 1: breast cancer prevention

Two complementary primary prevention approaches are outlined: *population prevention* (minimising risk factor exposure for everyone) and *personalized prevention* (delivery of prevention strategies to those at increased risk). Potentially modifiable risk factors include exogenous hormone use, physical inactivity, little or no breastfeeding, alcohol consumption, post-menopausal overweight, and obesity. Up to 25% of breast cancers in high-income countries could be prevented by addressing these. Non-modifiable risk factors such as increasing age, genetic predisposition, family history, and female sex also play significant roles in breast cancer development.

The success of *population prevention* hinges on sustained behavioural change. Policy interventions, such as taxation on tobacco and alcohol, have been effective in changing behaviours and reducing exposures particularly among disadvantaged groups. However, significant challenges to policy implementation include industry influence, inadequate prioritization, and variations in political systems.

*Personalized prevention* could occur by coordinated systematic risk assessment at a young age, incorporating genetic testing with personalized advice regarding evidence-based interventions for those at higher than average risk of breast cancer. Tools for risk assessment should be validated and adapted to diverse populations, with a focus on integrating assessments into routine healthcare settings. Successful implementation requires overcoming the barriers of clinician education, ensuring access to medications (e.g. tamoxifen), and addressing healthcare anxiety among recipients.

Monitoring progress in breast cancer prevention involves measuring the uptake of personalized risk assessment and preventive interventions, as well as changes in modifiable risk factors. Equitable access to resources and interventions is paramount, alongside research into novel prevention strategies. Addressing breast cancer risk factors is likely to have benefits for other non-communicable diseases, highlighting the importance of comprehensive prevention efforts in health.

## Theme 2: personalizing breast cancer treatment

An aspirational goal of the Commission is for all people with breast cancer to be able to access personalized treatment; the right treatment at the right time, while respecting personal preferences. Various approaches are required to achieve this.

*Precision medicine* is only part of personalized breast cancer treatment. Genomic studies have identified key germline genetic variants such as *BRCA1/2*, and genomic variants in tumours such as amplification of the *HER2* gene and *PIK3CA* mutations. In addition, epigenetics, tumour microenvironment, spatial biology, and single-cell analysis are being explored. These advancements will enhance the prediction of risk of relapse, treatment response, and early detection of metastases. Pan-cancer trials may also enable the investigation of rarer molecular markers within and across tumour types. Living diagnostic tools such as organoids and patient-derived models offer exciting avenues for refining treatment approaches, although these are unlikely to be applied in LMICs soon.

*Evidence-based medicine:* Achieving personalized medicine also involves fostering diversity of patients in *clinical trials* since these provide the evidence for new treatment implementation and guidelines. Future clinical trials must be adaptable and financially feasible, emphasizing risk-adapted strategies to ensure inclusivity beyond pharmaceutical-driven initiatives.

*Optimization* of breast cancer treatment involves tailoring therapies based on individual risk profiles. Patients with early-stage, less aggressive cancers may benefit from optimized management, for example, omitting surgical axillary staging or omitting either endocrine therapy or radiotherapy, reducing unnecessary toxicity, treatment burden, and costs. Additionally, high-risk breast cancers may need escalation of treatment and neoadjuvant systemic therapy is becoming the standard of care in this setting.

*Personalization* of treatment requires a deeper understanding of both individual tumour biology, and the context of cancer presentation in the individual patient and their preferences and choices for treatment. *Technology* will play a pivotal role in facilitating personalized care, improving communication within healthcare systems, and enhancing research through digital tools and AI algorithms. Efforts to bridge the digital divide and address disparities in access to care and research are crucial. Collaboration, education, and innovation to produce digital solutions can empower patients and healthcare providers, ensuring equitable access to personalized breast cancer care worldwide.

*Value-based healthcare* approaches aim to deliver optimal outcomes at lower cost. Implementing such strategies in breast cancer care could enhance treatment decisions and resource allocation, benefiting patients globally.

## Theme 3: optimal and inclusive management of metastatic disease

Many patients with metastatic breast cancer feel abandoned and isolated, and some do not receive appropriate care. In order to tackle this, the Commission identifies four key areas requiring urgent attention:

1. **Data:** The number of people living with metastatic breast cancer worldwide is currently unknown. Globally, cancer registries usually do not record cancer recurrences. Efforts

to establish mandatory recording of metastatic cancer recurrence and overcome data sharing barriers are essential, and the International Agency for Research on Cancer and the ABC Global Alliance are defining the essential data to be collected.

2. **Individualized management with equitable access to evidence-based therapies:** Metastatic breast cancer is a spectrum of disease and therefore management must be individualized. Outcomes in metastatic breast cancer have improved considerably, with the median overall survival now 5 years for two of its three main subtypes. In some subgroups, survival is considerably longer and therefore is now beginning to be cost-effective. Validated tools from ASCO (9) and ESMO (10) can now be used for treatment prioritization. A further therapy optimization approach involves the development and use of biomarkers to identify those who will derive the most benefit. It is also crucial to address the global inequities between and within countries in accessing therapies, clinical trials and supportive care.
3. **Clinical care and the use of evidence-based guidelines:** Multidisciplinary care and guideline use have both been shown to improve outcomes for patients. The generation and utilization of resource-adapted guidelines are key, as well as supportive care from diagnosis.
4. **Stigma:** Stigmatization of individuals with metastatic breast cancer persists, driven by misconceptions and societal attitudes. Addressing stigma requires comprehensive, patient-centred approaches spanning socioeconomic factors, with community-based initiatives playing a pivotal role.

Efforts to improve metastatic breast cancer care can serve as a model for enhancing cancer care across different tumour types. Updating cancer registries, shifting treatment paradigms, and combating stigma are fundamental steps towards achieving more equitable and effective cancer management globally.

## Theme 4: tackling breast cancer gaps and inequities through global collaboration

This is covered in the summary of the WHO Global Breast Cancer Initiative in the first part of this chapter.

## Theme 5: identifying the hidden costs of breast cancer

The hidden burden of serious health-related suffering (SHS) remains unmeasured in global health metrics and is therefore overlooked and undervalued. The impact of breast cancer extends beyond physical symptoms, affecting quality of life, relationships, and financial stability. Patients face distress at diagnosis, through treatment and survivorship, with treatments that often lead to long-term challenges and fears of recurrence. Moreover, caregivers experience social and financial hardships, compounding the burden.

A pilot study, as part of the follow-up work of the Lancet Commission on Palliative Care and Pain Relief (11) and in collaboration with the Lancet Commission on Cancer and Health



Systems (12), examined SHS in breast cancer patients, revealing its presence across all stages of the disease. The study estimated that each patient has approximately 175 days of SHS in their last 12 months of life and that around two-thirds of these days of suffering are probably preventable with improved access to supportive and palliative care.

The Lancet Breast Cancer Commission initiated the Costs and Supportive Care in Breast Cancer (CASCARA) study in the UK. This highlighted income loss, employment changes, and financial strain among patients and caregivers, even in a health system that is free at the point of care. Many struggled to cover additional treatment costs and experienced a decline in their financial situation post-diagnosis.

Addressing these challenges requires global capacity building in supportive care and psychosocial services. Recognizing and quantifying the true costs and suffering associated with breast cancer is crucial, as is integrating them into global health metrics to inform policy and resource allocation.

## **Theme 6: communication and empowerment in breast cancer**

Patient empowerment, defined as being fully informed and supported to participate confidently in health decisions, is crucial. The Commission carried out a comprehensive literature search focused on LMICs to challenge commonly held preconceptions about patient empowerment.

Huge global disparities in the empowerment of breast cancer patients exist, impacting treatment decisions and overall autonomy. While some regions prioritize patient involvement in decisions, others do not. Stark differences occur within countries too, exemplified by US reproductive autonomy rights variations. Communication, empowerment, and choice are interlinked, and various interventions aim to support patient autonomy in breast cancer treatment decisions, including culturally adapted approaches and accessible decision aids. Effective communication improves quality of life, as well as treatment adherence, which can improve survival. Healthcare professionals play an important role in improving this communication. The Commission outlines a framework to help with patient-centred consultations. It is also highlighted that prioritizing autonomy by placing patients at the centre of clinical communication facilitates patients to exercise empowerment in other aspects of their lives. Eight patient-centred approaches in different areas that intersect to form the aspirational advocacy framework were identified (Figure 40.1).

In 2020, an innovative initiative known as ‘London Global Cancer Week’ was launched with the primary goal of enhancing healthcare services for cancer patients in developing nations. This initiative encompasses a comprehensive array of activities, including meetings, webinars, panel discussions, and hands-on workshops, all organized within a designated timeframe of a week.

The topics explored are diverse and vital, covering crucial areas such as public health policymaking, effective data collection methodologies, advancements in cancer care, and groundbreaking cancer research. The events feature sessions presented by organizations in the field, including the WHO, the International Agency for Research on Cancer (IARC), Lancet Oncology, and the International Atomic Energy Agency (IAEA).

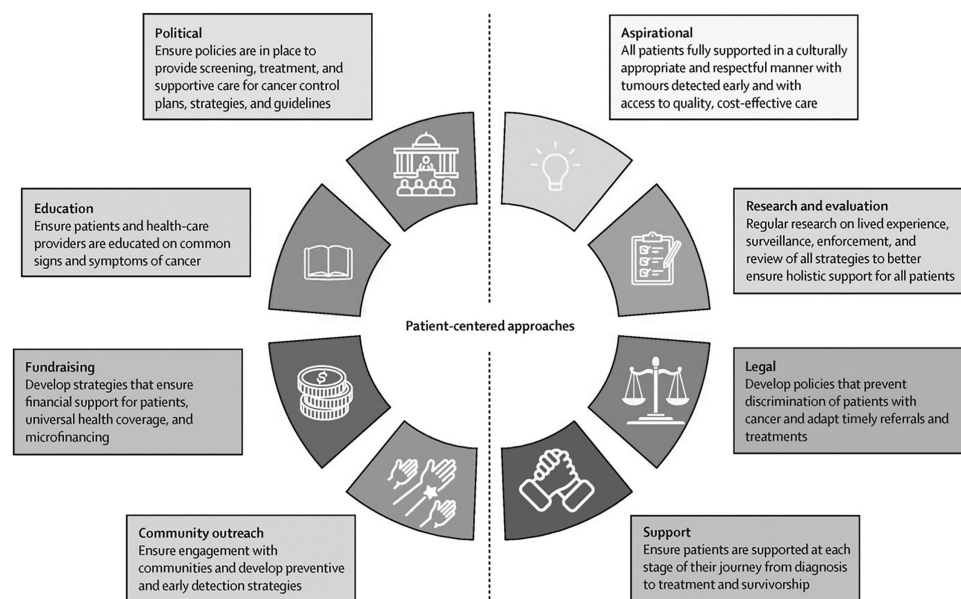


**Figure 40.1** Aspirational advocacy framework.

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The discussions aimed to raise awareness and foster action to bridge the gaps in access to quality cancer treatment, highlighting the need for urgent collaborative efforts to ensure that all cancer patients, regardless of their geographic or socioeconomic status, receive the care they deserve.

## Key messages

- The GBCI identified an implementation framework for policymakers to guide the global management of breast cancer.
- The Lancet Breast Cancer Commission presents an evidence-based roadmap to address global breast cancer challenges that can be adapted to the local context.
- Urgent action is needed to challenge existing practices and promote equity.
- Data-driven targets must be measured to hold stakeholders accountable and advocate for better approaches.
- Global collaboration is key to preventing breast cancer and improving outcomes.

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# Conclusion

*Didier Verhoeven, Cary S. Kaufman, Pankaj G. Roy, and Sabine Siesling*

This work is the result of a worldwide project intended to address a global approach to the quality of breast cancer care, which began in 2010 in Paris. Over the years, a large faculty of experts was formed who interacted with each other to find solutions for better care for women with breast cancer all over the world. After the first edition, the faculty grew further, with the introduction of virtual meetings, participation of the GBCI from WHO, The Lancet Commission on breast cancer and the creation of GRAND ROUNDS eCANCER webinars, strengthening the collaborations.

The authors aspire for a global, coordinated alliance among breast cancer clinicians, advocates, management specialists, policymakers, and others to optimize the quality of breast cancer care and value across diverse socio-economic, political, and geographic environments. The intention is to highlight on the international agenda the sustainable approaches to provide access to high-quality breast care globally.

The authors hope their work will serve as a comprehensive guide to deliver high-quality care around the globe. The aim is to promote strategic planning for breast cancer control with active surveillance of incidence, stage at time of diagnosis and survival through population-based cancer registries. They promote a value-based healthcare model using patient-centric care through which evidence-based, resource-appropriate care pathways define integrated clinical practice. There are recommendations that may conserve resources, defining and avoiding overtreatment, overdiagnosis, reducing inefficiencies. Having the book freely available for all interested people will stimulate discussions and interactions on a wider basis.

Improved clinical outcomes with lower costs requires a transformation of health delivery systems including better organized public health systems with universal coverage and the development of public-private partnerships where appropriate (1).

Improved breast cancer outcome is best achieved through systematic approaches such as prevention, early detection, prompt diagnosis, and effective cancer management, where multidisciplinary teamwork is pivotal. Value-based price threshold can guide the allocation of limited resources to achieve high-quality care. Newer drugs or other treatments, when launched for routine clinical care, are allocated value by assessing the clinical benefit along with comparative cost-effectiveness. Governments must ensure their health system is equitable across the population it serves. It is crucial to take the personal circumstances of the patient, patient's preferences for treatment, process, and outcomes and individual patient needs into account to tailor the care within the resources available. As we like to create a living book, please send your feedback and proposals to the available link: <https://www.azklina.be/form/breastcancer>

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