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Tumor twins in breast cancer: toward hybrid biological-digital models for adaptive precision oncology

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Abstract

Precision oncology in breast cancer has improved patient stratification but remains limited by static biomarkers that fail to capture tumor heterogeneity and therapy-induced evolution. Tumor twins have emerged as patient-specific models designed to mirror tumor behavior and predict treatment response. Two complementary approaches have matured: biological tumor twins, including patient-derived organoids and tumor-on-chip systems, and digital tumor twins integrating clinical, imaging, and multi-omics data into computational models. However, these paradigms have largely evolved independently, and current computational tools often function merely as one-way enabling technologies rather than dynamically coupled systems. In this Review, we synthesize recent advances in both fields and introduce the conceptual framework of genuine hybrid tumor twins. These bidirectionally coupled, closed-loop systems leverage real-time non-destructive biological sensing to continuously calibrate computational simulations, which in turn enable predictive digital models to actively guide experimental and clinical interventions. We address critical biological and operational bottlenecks, including culture-induced experimental bias, validation, data interoperability, and clinical implementation. Finally, we outline a practical three-phase translational roadmap spanning technical platform harmonization, retrospective uncertainty calibration, and adaptive prospective clinical trials. By bridging continuous biological monitoring with dynamic computational forecasting, hybrid tumor twins provide a realistic blueprint to advance adaptive, real-time precision oncology in breast cancer.

Keywords Breast cancer · Hybrid tumor twins · Digital twins · Patient-derived organoids · Tumor-on-chip · Precision oncology · Computational modeling · Translational oncology

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Introduction: from stratified to individualized oncology

Breast cancer (BC) remains the most frequently diagnosed malignancy and a leading cause of cancer-related mortality among women worldwide, despite major advances in early detection and treatment [1]. Precision oncology has improved patient stratification by aligning therapeutic decisions with molecular features such as hormone receptor status, HER2 amplification, and genomic risk signatures. However, current clinical decision-making still relies largely on static, population-based biomarkers that insufficiently capture tumor heterogeneity, microenvironmental influences, and therapy-induced evolutionary dynamics, leading to suboptimal treatment selection and the emergence of resistance [2]. These limitations highlight a critical unmet need for dynamic, patient-specific models capable of forecasting therapeutic response and tumor evolution in real time. Tumor twins have emerged as a promising conceptual framework to address this challenge by generating individualized representations of tumor behavior to guide clinical decision-making (Fig. 1) [3, 4]. In BC, tumor twin technologies have developed along two largely independent trajectories. Biological tumor twins are experimental models derived from patient material, including patient-derived organoids (PDOs), organ-on-chip platforms, and bioprinted tissues,

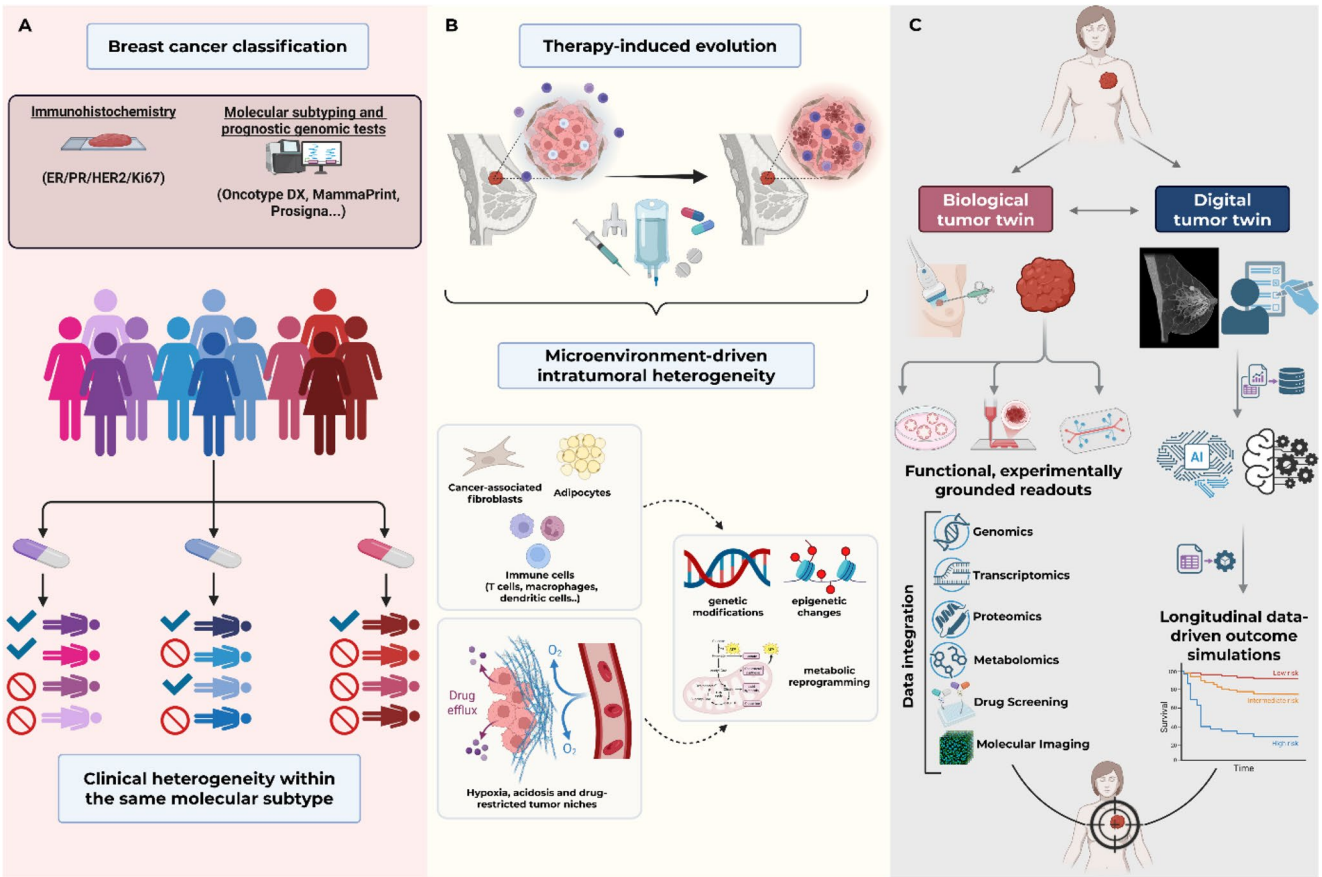


Fig. 1 Conceptual evolution from stratified precision oncology to tumor twins in breast cancer. (**A**) Conventional precision oncology relies on population-based stratification using static biomarkers (e.g. hormone receptor or HER2 status), resulting in heterogeneous clinical outcomes among patients receiving similar treatments. (**B**) Intratumoral heterogeneity, microenvironmental complexity, and drivers of therapy resistance, including subclonal selection, spatial discordance, and receptor conversion, limit the predictive value of baseline biopsies and dictate treatment failure. (**C**) Tumor twins represent patient-specific models designed to capture dynamic tumor behavior over time. A structured flowchart illustrates how biological tumor twins provide functional, experimentally grounded readouts, whereas digital tumor twins integrate longitudinal clinical, imaging, and multi-omics workflows to simulate disease trajectories. Together, these approaches lay the foundation for individualized, adaptive cancer care. Created in BioRender. Corbet, C. (2026) https://BioRender.com/9xv5sr7

which provide functional readouts of drug sensitivity. Digital tumor twins are computational representations that integrate longitudinal clinical, imaging, and multi-omics data to simulate tumor growth, treatment response, and disease evolution over time.

Despite their individual strengths, these biological and digital approaches remain largely disconnected, functioning as static or one-way analytical tools rather than adaptive systems. We argue that neither approach alone is sufficient to guide clinical decision-making, and that their convergence into true hybrid tumor twins, defined as closed-loop, bidirectionally coupled systems where biological measurements continuously calibrate computational models and digital predictions inform adaptive experimental testing, represents a necessary paradigm shift toward dynamic precision oncology. BC provides an ideal framework to explore this integration, given the extensive development of experimental models, high-resolution imaging modalities, and computational frameworks in this disease.

However, translating these concepts into clinical practice faces major hurdles: current BC applications rely predominantly on retrospective, small-cohort, or isolated enabling technologies, and no prospectively validated, closed-loop hybrid twin currently exists in routine oncology. In this Review, we synthesize recent advances in biological and digital platforms, establish a rigorous definition of hybrid tumor twins to distinguish genuine closed-loop systems from one-way artificial intelligence (AI)/organoid tools, critically assess their translational readiness and limitations, and propose a structured roadmap to bridge enabling technologies toward clinical implementation in early and advanced BC.

Biological tumor twins: experimental avatars of breast cancer

Biological twins aim to recapitulate patient-specific BC biology ex vivo while preserving clinically relevant features such as molecular subtype, cellular heterogeneity, and therapeutic sensitivity. Among available platforms, PDOs and tumor-on-chip systems represent highly promising functional modalities, yet delivering actionable readouts within urgent clinical decision windows remains a primary operational barrier [5, 6]. Evaluating the translational readiness of BC biological models therefore requires strictly distinguishing technical feasibility and retrospective concordance from forward-looking validation and proven clinical utility.

Patient-derived organoids: functional relevance and clinical utility

BC organoids have evolved from proof-of-concept systems into large, subtype-spanning biobanks encompassing hormone receptor (HR)-positive, HER2-positive, and triple-negative disease. Advances in tissue processing and culture conditions have improved establishment success, particularly from surgical specimens. In contrast, biopsy-derived organoids remain significantly more challenging due to low tumor cellularity and normal epithelial outgrowth, with post-treatment or metastatic biopsies presenting additional hurdles related to therapy-induced tissue necrosis and reduced cell viability [7–9]. Importantly, compared with conventional two-dimensional cultures, BC organoids better preserve histopathological, mutational landscapes, cell-matrix interactions, and microenvironmental physico-chemical conditions such as heterogeneous oxygen gradients, making them valuable platforms for experimental drug testing [10–12] (Table 1). While retrospective studies have reported observational concordance between ex vivo organoid drug sensitivity and patient response [13, 14], prospective interventional evidence demonstrating that organoid-guided treatment selection improves patient clinical outcomes (e.g. progression-free or overall survival) in metastatic BC remains extremely limited [15]. Similarly, proof-of-concept evidence suggests that diagnostic biopsy-derived organoids can reflect neoadjuvant chemotherapy (NAC) sensitivity [16], yet these findings must be interpreted cautiously. Indeed, in this key feasibility report, matched organoid-patient treatment responses were evaluated in only five patients, with organoids successfully derived in fewer than half of the attempted NAC cases, highlighting substantial barriers to routine clinical implementation. Turnaround time also remains a critical constraint. Integrated patient-derived xenograft and organoid

Table 1 Comparative features of biological, digital, and hybrid tumor twins in breast cancer

Tumor twin type	Study platforms	Primary inputs	Key outputs / applications	Time-to-result	Throughput	Clinical readiness	Study design	Refs
Biological	Patient-derived organoids (PDOs); bioprinted structures; tumor-on-chip systems	Tumor tissue; limited clinical annotation	Functional drug response; resistance profiling; biomarker discovery	Several weeks (PDOs); days (tumor-on-chip)	Low-moderate	Early clinical pilots; limited routine use	Multicentric USA, 2020)	[12]
							Monocentric (USA, 2022)	[17]
							Monocentric (Germany, 2024)	[21]
							Monocentric (The Netherlands, 2022)	[22]
							Monocentric (France, 2024)	[23]
							Monocentric (Spain, 2024)	[24]
Digital (static)	Retrospective ML models; imaging- or omics-based predictors	Baseline clinical, imaging, and/or multi-omic data	Risk stratification; response prediction; subtype classification	Minutes-hours	High	Retrospective validation; limited adaptivity	Multicentric (USA, Sweden, Taiwan, 2021)	[25]
							Multicentric (UK, 2026)	[26]
							Multicentric (USA, 2026)	[27]
Digital (adaptive)	Longitudinal mechanistic or data-driven models	Serial imaging; clinical follow-up; molecular monitoring	Dynamic prediction; therapy rehearsal; disease trajectory simulation	Near real time (data-dependent)	High	Emerging clinical feasibility studies	Monocentric (USA, 2025)	[28]
							Monocentric (USA,2025)	[29]
							Monocentric (France, 2025)	[30]
							Multicentric (UK, 2026)	[31]
Hybrid	AI-integrated organoids; organ-on-chip-digital frameworks	Functional biological data + longitudinal clinical and molecular data	Iterative therapy optimization; uncertainty-aware predictions; trial simulation	Days-weeks (iterative cycles)	Moderate	Conceptual to early translational stage	Not reported	N/A

The overview highlights primary data inputs, typical applications, time-to-result, scalability, and current level of clinical readiness for each approach

N/A: not applicable

(PDX/PDxO) workflows have demonstrated functional utility in individual advanced triple-negative BC (TNBC) cases, but the long timelines required for initial PDX engraftment and subsequent organoid derivation often mean actionable data become available only after first-line treatment failure [17], preventing routine alignment with standard clinical decision-making windows. Furthermore, while organoid-forming efficiency from post-NAC residual tumors correlates with increased recurrence risk and poor clinical outcomes [18], and optical metabolic imaging offers rapid non-destructive readouts to visualize metabolic cell states and predict treatment efficiency [19], these approaches currently serve as complementary research tools rather than validated clinical diagnostics. Additional studies have revealed treatment-induced selection of resistant cell populations and metabolic reprogramming associated with relapse [13, 20].

Culture-induced biases, artifacts, and microenvironmental deficits

Despite these strengths, a fundamental limitation of standard organoid cultures is their missing microenvironmental complexity and the presence of culture-induced biological biases [32, 33]. Conventional cultures lack

vascular structures, stromal components, and infiltrating immune cells, particularly T lymphocytes, which precludes functional evaluation of standard-of-care immune checkpoint inhibitors in BC. Additionally, reliance on non-physiological extracellular matrices (e.g., Matrigel) and synthetic growth factor cocktails can drive subclonal selection, alter cellular proliferation rates, and induce receptor conversion (such as loss or downregulation of estrogen and/or progesterone receptor expression during passage). These culture artifacts may lead to the decoupling of organoid's functional behaviors from the original patient tumor. Crucially, if such biased experimental readouts are subsequently used to calibrate computational models, these systematic experimental errors may be propagated or even amplified within the digital component of a hybrid twin framework. To address these deficits, co-culture systems incorporating cancer-associated fibroblasts, macrophages, adipocytes, and immune cells have revealed microenvironment-driven resistance mechanisms that are not captured by tumor-intrinsic profiling alone [34–36]. Autologous co-culture approaches preserve patient-specific microenvironmental context and demonstrate how stromal and immune interactions reshape tumor phenotypes and therapeutic response [37–41]. However, donor-dependent variability, limited standardization, and incomplete integration of vascular, stromal and immune compartments currently constrain routine clinical deployment.

Organ-on-chip, bioprinting, and advanced 3D culture platforms

Microengineered tumor-on-chip and bioprinting technologies extend biological tumor twins by enabling controlled manipulation of extracellular matrix (ECM) composition, mechanical properties, spatial organization, and perfusion [6, 21–47]. These features are particularly relevant in BC, where ECM remodeling and tissue stiffening critically influence invasion, immune infiltration, drug delivery, and therapeutic resistance [48, 49]. Microfluidic BC-on-chip systems commonly incorporate three-dimensional ECM environments and perfused architectures that support long-term culture and dynamic cell-cell interactions. Embedding PDOs or tumor slices within microfluidic devices has revealed how matrix architecture regulates immune cell infiltration, cytokine gradients, and treatment response, even when ECM composition itself remains fixed [6, 21, 22]. These platforms highlight the importance of physiological matrix organization but remain limited in their ability to systematically vary key biophysical parameters such as stiffness.

Bioprinting technologies address this limitation by enabling precise spatial control over ECM composition and architecture to generate machine-controlled bioprinted structures. Breast tissue-derived decellularized ECM bioinks have been used to generate models incorporating cancer stem cells and stromal fibroblasts, better preserving invasive phenotypes and therapeutic resistance than generic hydrogels [24]. Spatial patterning allows reconstruction of heterogeneous tumor-stroma interfaces, while standardized ECM layers combined with high-speed interferometric imaging enable reproducible, image-driven drug response assessment at single-organoid resolution [42]. Integration with real-time metabolic and multi-analyte sensing further enhances functional readouts [44]. Recent advances have focused on decoupling biochemical composition from bulk mechanical properties. Embedded bioprinting strategies demonstrate that ECM composition can modulate epithelial-mesenchymal transition and invasion independently of stiffness, revealing receptor-mediated signaling effects that are masked in conventional systems [43]. Dynamic ECM models in which cancer-associated fibroblasts drive progressive matrix stiffening recapitulate fibrotic evolution, hypoxia, vascular remodeling, and therapy resistance, including radioprotection mediated by stromal signaling [23]. Gelatin methacryloyl-based hydrogels further enable spatial stiffness gradients and incorporation of tissue-specific ECM components while maintaining experimental control and scalability [50–52].

Advances in organoid generation platforms that control morphological features and mechanical microenvironments have further revealed shape- and mechanic-dependent tumor growth dynamics, expanding the parameter space for digital twin construction [45, 46]. Alongside PDOs, organ-on-chip systems, and bioprinted constructs, a broader spectrum of 3D tumor culture models, including multicellular tumor spheroids, ex vivo tumor slices, scaffold-based and scaffold-free cultures, is increasingly being explored for drug screening and resistance studies [53, 54]. These platforms reproduce selected features of tumor architecture, cell-cell and cell-matrix interactions,

and treatment responses that are incompletely captured by conventional 2D cultures, while offering different levels of experimental complexity and scalability. In particular, tumor slice cultures can preserve native tissue architecture, stromal components, and aspects of the tumor microenvironment, whereas spheroid-based systems are amenable to controlled and higher-throughput drug testing. Depending on the platform, limitations including standardization, vascularization, model-to-model variability, and uncertain concordance between ex vivo drug sensitivity and patient outcomes remain barriers to clinical translation (Table 2). Rather than constituting tumor twins per se, these models may complement PDOs and engineered platforms by expanding the range of experimentally tracTable 3D systems available for functional drug-response assessment. Within this broader spectrum of 3D tumor models, organ-on-chip and bioprinted structures are particularly suited to the development of dynamically tunable biological platforms. By enabling systematic parametrization of ECM composition, stiffness, spatial architecture, and temporal evolution, these platforms generate experimentally grounded inputs that are particularly well suited for integration with digital modeling approaches.

Translational status and clinical applications of biological twins in breast cancer

Clinical translation of tumor twin-related approaches in BC currently spans functional biological models, computational treatment simulations, and image-guided surgical applications (Table 1). Biological platforms have progressed from small feasibility studies using biopsy-derived PDOs to assess NAC response [16] to single-patient proof-of-concept reports in which PDxO/PDX screening informed treatment selection [17]. A retrospective metastatic BC cohort further associated PDO-guided therapy with improved disease control and longer progression-free survival [15], while an additional case report demonstrated the feasibility of PDO-guided drug selection in multidrug-resistant disease [55]. Prospective studies are now evaluating functional precision oncology in more structured clinical settings: TOWARDS-II (NCT05464082) combines PDX, PDO, and PDxO profiling with genomic and circulating tumor DNA (ctDNA) analyses in patients at risk of early recurrence

Table 2 Advantages and disadvantages of biological, digital, and hybrid tumor twin approaches in breast cancer

Tumor twin type	Main advantages	Main disadvantages
Biological	• Provide experimentally grounded, patient-specific drug-response data • Partially preserve tumor heterogeneity • Allow direct testing of therapeutic combinations	• Variable establishment success • Incomplete immune, stromal, and vascular representation • Culture-induced bias • Limited standardization • Turnaround times may exceed clinically actionable windows
Digital (static)	• Rapid and scalable • Integrate high-dimensional clinical, imaging, and multi-omics data • Support risk stratification and response prediction	• Often dependent on retrospective datasets • Susceptible to data bias and limited explainability • Inability to capture treatment-induced evolution or support continuous recalibration
Digital (adaptive)	• Incorporate longitudinal patient data • Enable dynamic prediction, therapy rehearsal, and resistance forecasting • Can be iteratively updated	• Require frequent and standardized longitudinal data • Vulnerable to missing information, uncertainty, and model drift • Substantial validation and regulatory requirements
Hybrid	• Integrate functional biological testing with multimodal computational modeling and prediction • Support longitudinal analysis of dynamic experimental responses • May enable bidirectional validation and iterative model recalibration • May facilitate patient-specific treatment-response prediction and optimization	• Requires complex wet- and dry-lab synchronization • May propagate experimental and culture-induced biases into computational predictions • Demands interoperable data and specialized infrastructure • High cost and regulatory complexity • Limited clinical evidence for closed-loop implementation

The table summarizes the principal strengths, technical disadvantages, and translational limitations of each approach. It highlights the complementary capabilities of these models alongside the operational and regulatory hurdles associated with the clinical deployment of integrated hybrid tumor twins

[56], whereas ORIENTA (NCT06102824) compares PDO-guided therapy with physician-selected treatment in advanced HER2-negative BC [57] (Table 3).

Despite these advances, biological BC applications remain supported predominantly by small, retrospective, or specialized cohorts. Major shortcomings include limited prospective validation, prolonged derivation times, heterogeneous biological workflows, and variable success rates across centers. Ongoing efforts to standardize workflows, accelerate organoid derivation, automate screening, and integrate multi-omics profiling are beginning to address these barriers. In parallel, initiatives aimed at improving access to organoid resources have emerged, including shared biobanks and digital repositories. International efforts such as the Human Cancer Models Initiative and OrganoidDB facilitate dissemination of biological materials and transcriptomic datasets, supporting reproducibility and cross-study comparison. Continued progress in standardization and data sharing will be essential to transition biological avatars from specialized research tools to scalable clinical assets.

Digital tumor twins: data-driven and mechanistic models

Digital tumor twins are computational representations designed to simulate tumor growth, treatment response, and disease evolution at the level of individual patients [58]. Inspired by engineering applications, these models integrate clinical, imaging, and molecular data and are continuously updated as new information becomes available, enabling individualized trajectory forecasting and in silico therapy rehearsal [59, 60]. As patients undergo routine imaging, biopsies, and clinical follow-up, large volumes of longitudinal data are generated. Static models relying on baseline datasets or fixed assumptions are poorly suited to capture therapy-induced tumor evolution and emerging resistance. In contrast, adaptive digital twins assimilate incoming data to recalibrate predictions and refine therapeutic recommendations in near real time [61]. Core digital twin functionalities include longitudinal data integration, multiscale modeling, and prospective evaluation of therapeutic strategies, with applications extending from clinical decision support to trial design and medical education.

Several proof-of-concept implementations across oncology demonstrate how dynamic digital twins function as virtual avatars supporting clinical decision-making. The FarrSight®-Twin platform integrates genomic variants, whole-slide imaging, and time-stamped clinical events to simulate treatment and immunotherapy response in BC [31, 62]. Beyond breast oncology, the Stanford-NCI-DOE lung cancer twin incorporates longitudinal imaging, pathology, and clinical data to continuously update tumor growth trajectories [63], while in glioblastoma, Bayesian MRI-based digital twins assimilate voxel-level imaging features to iteratively recalibrate cellular proliferation, tissue invasion, and radiosensitivity parameters [64]. Together, these paradigms illustrate how dynamic digital frameworks assimilate multiscale data to forecast treatment response. Digital tumor twins encompass a spectrum of modeling strategies, ranging from mechanistic mathematical representations to data-driven AI frameworks and mixed approaches combining both.

Mechanistic models: mathematical representations of tumor behavior

Mechanistic models describe tumor growth, microenvironmental dynamics, and treatment effects using mathematically defined biological rules, offering high interpretability at the cost of simplifying assumptions [65]. Continuum models based on ordinary or partial differential equations simulate population-level dynamics, nutrient diffusion, and drug transport [66, 67], whereas agent-based models capture discrete cellular heterogeneity and local spatial interactions [68]. Multiscale frameworks combining these approaches enable exploration of tumor behavior across biological scales, linking intracellular signaling to tissue-level dynamics [66]. While similar approaches have been demonstrated in cardiology [69] and transplantation [70], digital twins must remain disease-specific. Instead of adopting a one-size-fits-all architecture, oncology digital twins must be tailored to the specific biology of each cancer type. For example, a glioblastoma twin must account for infiltrative tissue dissemination and local radiosensitivity [64], whereas a BC twin emphasizes hormone receptor signaling dynamics,

Table 3 Representative clinical and translational applications relevant to tumor-twin approaches in breast cancer

Approach	Study/reference	BC setting / cohort	Patient-specific model or input	Clinical / translational application	Evidence level / current status
Biological	Shu et al., 2022 [16]	Locally advanced BC receiving NAC $N=17$ patients	Biopsy-derived PDOs	Ex vivo sensitivity testing matched to patient NAC regimens	Retrospective concordance ($n=5/5$ evaluable). Small sample size precludes clinical utility conclusions.
	Guillen et al., 2022 [17]	Stage IIA TNBC with pCR after NAC, subsequent early metastases $N=1$ patient	Matched primary and metastatic PDX and PDxO models (HCI-043/051)	Single-patient ex vivo screening to identify and clinically guide second-line therapy	Single-patient proof-of-concept. PDxO-informed eribulin induced complete hepatic remission (PFS 138 vs. 41 days prior), followed by bone progression. Extended PDX/PDxO timelines exceed first-line decision windows.
	TOWARDS-II (NCT05464082) [49]	High-risk treatment-naive stage I-III TNBC or HR-low/HER2-negative BC $N=80$ patients (planned enrollment)	PDX, PDO and PDxO models + genomic/ctDNA profiling	Recurrence risk prediction and functional drug profiling for post-recurrence selection	Ongoing prospective, non-randomized phase II study. Active recruitment; primary outcomes and utility results pending.
	Lin et al., 2024 [15]	Locally advanced unresectable or metastatic BC $N=45$ patients	PDOs + customized drug screening	PDO-guided personalized treatment selection	Feasibility demonstrated (90.2% establishment success, 46/51 samples); 78.4% predictive accuracy. Prospective interventional validation required.
	Zhang et al., 2025 [48]	Multidrug-resistant metastatic luminal B/HER2- BC $N=1$ patient	Pleural effusion-derived PDOs	Functional screening to identify salvage combinations	Single-patient case report. PDO-guided gemcitabine/cisplatin achieved partial response (RECIST) and ascites reduction. Useful proof-of-concept: lacks generalizable utility evidence.
	ORIENTA NCT06102824 [50]	Pretreated locally advanced or metastatic HER2-negative BC $N=252$ patients (planned enrollment)	PDO-based drug sensitivity testing	Randomizd comparison of organoid-guided vs. physician-selected treatment	Ongoing prospective, multicenter, open-label, randomized phase II trial. Active recruitment (completion estimated for June 2027); no outcome data reported.
Digital	Wu et al., 2025 [71]	TNBC receiving NAC $N=105$ patients	Longitudinal multiparametric MRI + mechanistic biophysical model	pCR prediction and in silico schedule optimization (128 schedules)	Retrospective proof-of-principle study. Predicted pCR with AUC of 0.82; virtual schedules predicted + 21–25% pCR gain. Unvalidated in vivo.
	Christenson et al., 2025 [78]	TNBC receiving NAC $N=50$ patients	Longitudinal MRI + probabilistic digital twin	In silico optimization of chemotherapy dosing and temporal delivery	Retrospective simulation. Predicted 17.6% tumor cell reduction or 12.7% dose reduction without losing efficacy. Unvalidated in patients.
	VISION study (NCT06409221) [79]	Stage II–III TNBC receiving neoadjuvant chemo-immunotherapy $N\leq200$ patients	Clinical variables + genomic/transcriptomic data from diagnostic FFPE biopsies	FarrSight® -Twin-based prediction of pCR upon NAC	Retrospective observational validation ($n=94$ interim analysis). DNA inputs predicted pCR with AUC of 0.77 (negative predictive value of 74% for non-pCR). Predictions did not guide treatment.
Digital / surgical	Timóteo et al., 2026 [81]	Breast-conserving surgery $N=4$ patients	Supine MRI-derived digital twin + 3D surface sensing registration	Extended-reality real-time intraoperative tumor localization	Prospective technical pilot. Demonstrated intraoperative workflow integration (0–5 mm alignment deviation); proves clinical feasibility, no treatment response prediction.
Hybrid biological-digital	No prospectively validated BC implementation identified to date	N/A	Bidirectional coupling of functional biological models and dynamic digital simulations	Closed-loop treatment optimization via iterative feedback	No prospectively validated implementation reported in BC. Biological and computational components have reached clinical testing only as isolated, static modalities.

The table summarizes the current translational status of biological avatars and digital frameworks, detailing the specific clinical setting, patient cohort size, patient-specific model or input, intended application, and primary findings

N/A: not applicable

HER2 status, and chemotherapy sensitivity [71, 72], and lung cancer twins prioritize oncogenic driver mutations such as EGFR or ALK alterations [63].

AI-based, imaging-derived, and mechanistic-AI mixed twins

AI-based digital twins leverage machine learning (ML) to predict clinical outcomes from high-dimensional datasets, including multi-omics profiles, clinical variables, and longitudinal imaging capturing nonlinear relationships beyond explicit mechanistic assumptions [73, 74]. Multi-omics integration is central to this effort, as cancer progression arises from complex interactions across genetic, epigenetic, metabolic, and microenvironmental scales. However, effective oncology digital twins should not rely solely on raw data streams. Their clinical relevance also depends on integrating patient-specific data with clinical expertise, treatment guidelines, and contextual decision criteria. Incorporating domain knowledge such as prognostic factors, comorbidities, and therapeutic constraints ensures that model outputs align with established clinical reasoning. Deep learning frameworks enable fusion of heterogeneous data modalities, including non-invasive liquid biopsy-based platforms, improving diagnosis and treatment prediction while minimizing patient burden [75]. In BC, AI models integrating clinical and biological features have demonstrated predictive performance for survival and treatment benefits across diverse patient populations [30].

Imaging-derived digital twins personalize mechanistic models using non-invasive patient-specific imaging data, overcoming the limitations of generic tumor geometries. MRI-based frameworks enable spatially resolved simulations of intra-tumoral heterogeneity and treatment response, anchoring model parameters directly to patient-specific structural dynamics, as demonstrated in TNBC [28]. To combine interpretability with computational flexibility, mechanistic models are increasingly augmented with data-driven AI [66]. Frameworks such as TumorTwin integrate mechanistic cores with ML-based parameter calibration [76], while physics-informed neural networks (PINNs) embed governing biological equations directly into neural architectures [77]. By embedding physical constraints into data-driven learning, these mechanistic-AI hybrids mitigate the black-box nature of conventional AI models, enabling robust parameter inference even from noisy or sparse clinical data [78].

Translational status and clinical evaluation of digital twins in breast cancer

Clinical evaluation of computational and digital twin frameworks in BC currently spans retrospective risk prediction, imaging-calibrated treatment simulation, and prospective precision trial stratification. Early studies established proof-of-concept feasibility using AI-driven imaging tools to retrospectively identify individuals at elevated future BC risk, supporting personalized screening schedules [25–27] (Tables 1 and 2**)**.

Computational models have also progressed toward dynamic response simulation across distinct clinical scenarios. MRI-calibrated mechanistic frameworks have been used to simulate spatial tumor regression, predict pathological complete response (pCR) to NAC, and virtually optimize drug dosage schedules in TNBC [28, 29]. In retrospective validation studies of virtual cohorts, the VISION trial (NCT06409221) evaluated the FarrSight®-Twin digital platform to predict pCR and survival outcomes in patients with early TNBC treated with standardized chemotherapy regimens [31, 79] (Table 3**)**. In prospective clinical evaluation, the LINUX platform trial utilized AI-driven similarity network fusion subtyping to guide precision therapy selection in patients with HR+, HER2- advanced BC progressing after CDK4/6 inhibitor therapy, achieving significantly improved objective response rates compared with physician's choice therapy across multiple molecular subgroups [80]. Although not a closed-loop digital twin, the LINUX trial demonstrates how data-driven computational stratification can directly inform adaptive clinical decision-making. Beyond systemic therapy, anatomical digital-twin applications incorporating real-time biomechanical tissue modeling have demonstrated technical feasibility for dynamic tumor localization during breast-conserving surgery [81] (Table 3).

Key challenges and hurdles to clinical implementation

Despite these technical advances, digital tumor twins remain largely at a proof-of-concept stage, constrained by major translational hurdles. A primary barrier to clinical adoption is model explainability and transparency. Clinicians require clear, traceable reasoning pathways and are unlikely to rely on black-box algorithms that generate treatment recommendations without biological justification. Furthermore, rigorous uncertainty quantification is mandatory for clinical deployment, allowing oncologists to evaluate model confidence and distinguish robust therapeutic predictions from uncertain projections [66].

From an operational standpoint, generating real-time digital twins is hindered by data silos, non-standardized electronic health record formats, incomplete longitudinal records, and delays in clinical data acquisition. Current digital models are also constrained by limited spatial resolution of routine clinical imaging and infrequent temporal sampling of circulating biomarkers, such as ctDNA or immune cell dynamics [82]. While serial liquid biopsies, advanced quantitative radiomics, and high-frequency monitoring will improve model fidelity, their integration into routine workflows remains unstandardized.

Finally, digital tumor twins are typically initialized from retrospective multimodal cohorts and refined through individual patient data. As individual twins accumulate, they may form virtual cohorts capable of supporting in silico clinical trials and population-level comparative effectiveness research. Establishing standardized technical, data-formatting, and interoperability protocols will be essential to scale digital tumor twins across institutions and enable their closed-loop coupling with biological avatars in hybrid modeling frameworks.

Hybrid twins: merging the biological and the digital

Hybrid tumor twins represent the conceptual pinnacle of twin technology by integrating patient-derived biological models and computational architectures into an iterative, closed-loop, bidirectional framework (Fig. 2). In a true hybrid twin system, experimental readouts from living biological platforms continuously calibrate and update computational simulations, while digital models run high-throughput in silico simulations to actively guide, optimize, and re-program subsequent biological experiments or clinical interventions [83, 84]. This reciprocal feedback loop is designed to dynamically capture therapy-induced tumor evolution, refine predictive precision, and accelerate bench-to-bedside decision cycles.

Conceptual rigor: distinguishing genuine closed-loop twins from enabling technologies

A critical appraisal of current literature reveals that the vast majority of studies claiming "hybrid" or "AI-augmented" modeling are not genuine hybrid twins. Instead, they represent static, one-way enabling technologies. To establish conceptual clarity, enabling technologies must be rigorously distinguished from closed-loop hybrid systems. Computational frameworks analyzing organoid drug screens, such as network-based learning algorithms in colorectal and bladder cancers [85], high-content image analysis evaluating intratumoral drug penetration [86], single-cell RNA sequencing models deriving prognostic indices [87], and deep learning architectures for phenotypic classification [88–92], are one-way analytical tools. Similarly, transformer-based architectures like PharmaFormer [93], supervised ML classifiers [94–96], scalable computer vision platforms [97], and privacy-preserving federated learning classifiers [98, 99] serve as computational enhancers of biological data. They extract patterns, predict sensitivity, or automate readouts, but they do not form a bidirectionally coupled system where digital predictions dynamically steer biological testing or patient management in real time. At present, while individual enabling biological models and computational algorithms have reached high technical sophistication, no prospectively validated, closed-loop hybrid tumor twin currently exists in clinical practice for BC or any other solid malignancy. Current state-of-the-art platforms remain one-way workflows where biological outputs train a static

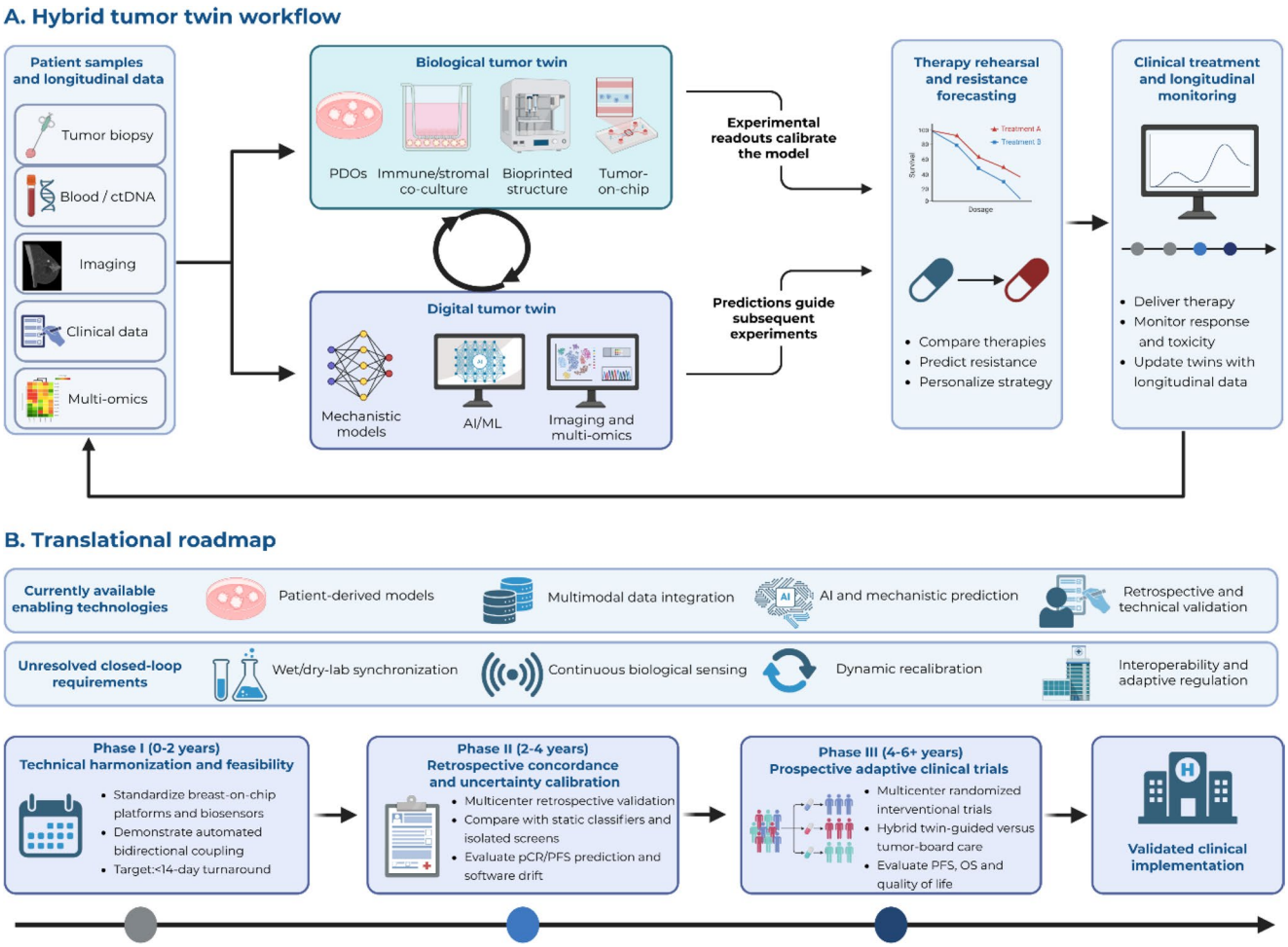


Fig. 2 Hybrid tumor twins as an integrative framework and translational roadmap for functional precision oncology in breast cancer. The flowchart distinguishes current technological achievements from unresolved closed-loop requirements. Biological tumor avatars (e.g. patient-derived organoids, bioprinted structures, tumor-on-chip systems) and static digital models serve as foundational enabling technologies. Genuine hybrid tumor twins merge these approaches through a closed-loop, bidirectional feedback architecture, whereby real-time non invasive/destructive experimental readouts continuously calibrate computational models, and digital predictions actively steer subsequent biological or clinical interventions. The lower panel delineates a dedicated three-phase translational roadmap spanning technical harmonization, retrospective uncertainty calibration, and prospective adaptive clinical trials required to move these platforms from proof-of-concept into routine clinical practice. Created in BioRender. Corbet, C. (2026) https://BioRender.com/8lhoocb

digital model, or computational predictions are tested once in a laboratory setting without continuous reciprocal recalibration.

Operational, biological, and regulatory bottlenecks

Bridging biological and digital platforms into functional hybrid tumor twins requires overcoming technical, operational, and regulatory hurdles distinct from standard genomic AI tools (Table 2). A primary operational barrier to closed-loop hybrid deployment is the temporal mismatch between physical biological assays and computational execution. Standard patient-derived organoid drug assays require four to eight weeks for cellular expansion and testing, whereas computational models execute simulations within seconds or hours. Waiting for end-point biological cell viability assays creates a latency that causes computational predictions to drift out of sync with clinical decision windows. Biological models provide functional, patient-specific drug response data but remain

constrained by scalability, standardization, and turnaround time. Digital twins offer scalability and longitudinal modeling capabilities but depend critically on parameters calibrated by functional inputs. To overcome this bottleneck, physical biological assays must integrate non-destructive, real-time sensing modalities. Technologies such as high-speed interferometric imaging, micro-biosensors, and real-time optical metabolic monitoring generate continuous ex vivo functional data streams [100]. These continuous data allow PINNs and mechanistic differential equations to recalibrate parameter values in near real time, providing dynamic calibration without destroying the biological culture.

A fundamental biological challenge closely tied to these temporal synchronization constraints is the spatial and dynamic mismatch between static biological sampling and patient-level tumor evolution. BC is characterized by profound spatial heterogeneity and dynamic subclonal selection under therapeutic pressure [2]. A biological twin generated from an initial baseline biopsy captures only a localized spatial snapshot of a single tumor lesion. Under the selective pressure of systemic therapies, such as endocrine agents, HER2-targeted drugs, chemotherapy, or antibody-drug conjugates, tumors undergo receptor conversion, histological transformation [71, 72], and subclonal evolution, rendering the initial biological twin progressively unrepresentative of the patient's evolving disease burden [101, 102].

Requiring continuous serial tissue biopsies to update the biological twin is clinically unfeasible due to invasiveness, procedural risks, and sampling bias. To resolve this tension, hybrid twins must operate on an asynchronous temporal scaling framework. In this model, the digital twin is updated continuously using non-invasive, longitudinal patient data streams, including ctDNA kinetics, serial liquid biopsy profiling, quantitative radiomics, and routine clinical imaging [28, 103, 104]. These frequent non-invasive data calibrate the computational twin to track multi-lesion tumor burden and systemic evolutionary trajectories without repeated physical biopsies.

Conversely, biological twin regeneration is structured as an episodic, event-triggered process. Biological resampling and avatar re-establishment are initiated only upon specific clinical or biological inflection points, such as documented disease progression, acquired resistance, loss or gain of targetable receptors, or severe sustained divergence between digital model projections and observed clinical trajectories. By decoupling continuous digital tracking from episodic biological re-anchoring, the hybrid framework reconciles the spatial limitations of single-lesion biological models with the patient-level requirements of dynamic precision oncology.

Data harmonization for hybrid twins extends beyond traditional clinical interoperability standards such as FHIR, OMOP, DICOM, and SNOMED-CT [105–109]. It requires mapping high-dimensional, multi-omics, and live optical imaging outputs directly onto computational spatial meshes. Defining standardized bidirectional data exchange protocols, where computational outputs automatically re-program microfluidic pumps to alter drug dosing sequences in experimental setups, is essential to move from static prediction to closed-loop hybrid execution. Regulatory translation of closed-loop hybrid twins further requires novel oversight paradigms. Standard frameworks designed for fixed, "locked" medical software or static diagnostic kits are ill-suited for continuous, adaptive systems that re-calibrate based on longitudinal patient inputs. In line with recent regulatory developments, such as the European Union AI Act mandates for high-risk clinical software, hybrid twin platforms must incorporate explicit uncertainty quantification, traceable reasoning pathways, and robust risk-management protocols. Because hybrid twins rely on dense, multimodal, longitudinal patient datasets, including raw genomic sequences and high-resolution imaging, data protection and privacy are critical. Privacy-preserving architectures such as federated learning, encryption, audit trails, and differential privacy enable multi-institutional model training and validation without centralizing sensitive patient data [110]. Furthermore, explainability tools, including Shapley additive explanations and attention-based visual mapping, are essential to establish clinician trust, ensure transparent liability attribution among software developers and oncologists, and prevent black-box decision-making [111, 112].

Beyond regulatory hurdles, data accessibility and knowledge aggregation pose substantial challenges. Restricted access to publications, proprietary scripts, and non-open-science resources currently limits the integration of existing biological knowledge. Incomplete publication of raw data and metadata, particularly in omics repositories, further constrains reproducibility and secondary analytical validation. While online scientific libraries

enable increasingly sophisticated literature exploration, they remain largely document-centric rather than providing structured, machine-readable knowledge aggregation. Emerging tools that support natural language querying and AI-assisted synthesis, as well as platforms specifically designed for multi-omics integration and interpretation, are beginning to address these limitations.

Stakeholder analyses indicate strong enthusiasm for digital twin applications in BC, alongside widespread recognition of substantial technical, regulatory, and organizational barriers [113]. Regulatory agencies increasingly view digital twins as strategic research priorities, but routine clinical translation will require robust validation, standardized data pipelines, and clearly defined regulatory approval pathways. Hybrid modeling systems that combine mechanistic simulations with data-driven learning enable therapy rehearsal, uncertainty-aware predictions, and scalable deployment [114, 115]. However, biological variability, limited sample sizes, batch effects, and technical heterogeneity remain significant operational challenges for AI-integrated organoid platforms [116–121]. Harmonized protocols, benchmark datasets, federated learning, and rigorous external validation will be critical to ensure reproducibility and generalizability across institutions [122, 123]. While several commercial entities are actively implementing AI-enhanced organoid platforms for drug discovery and translational research, these efforts often lack comprehensive real-time clinical data integration and prospective validation. Ultimately, regulatory approval of hybrid tumor twins will require transparent reporting, explicit uncertainty quantification, and multicenter randomized trials demonstrating definitive clinical benefit over standard care.

A dedicated three-phase translational roadmap

Transitioning hybrid tumor twins from experimental concepts to validated clinical assets requires a practical, phased translational roadmap tailored specifically to closed-loop biological-digital interaction.

Phase I: Technical harmonization and feasibility (0–2 years) Focuses on standardizing functional biological platforms with real-time non-destructive biosensors. The primary goal is to demonstrate automated, bidirectional coupling between experimental readouts and computational calibration within turnaround timelines compatible with standard clinical decision-making windows prior to treatment initiation.

Phase II Retrospective concordance and uncertainty calibration (2–4 years) Focuses on evaluating hybrid twin architectures against large, multi-center retrospective clinical trial cohorts. Studies must prove that closed-loop hybrid models outperform static genomic classifiers, radiomic algorithms, or isolated organoid screens in predicting pathological complete response and progression-free survival without experiencing software drift.

Phase III Prospective adaptive clinical trials (4–6 + years) Involves multi-center, randomized interventional trials comparing clinical outcomes (such as progression-free survival, overall survival, and quality-of-life metrics) in patients whose treatment selection is guided by closed-loop hybrid twin simulations versus standard multidisciplinary tumor board care.

By integrating continuous biological sensing, dynamic algorithmic recalibration, asynchronous temporal updating, and adaptive regulatory compliance, this roadmap establishes a realistic pathway toward implementing functional hybrid tumor twins in personalized oncology.

Conclusions and future directions

Tumor twins are transforming the conceptual framework of precision oncology, shifting the field from static, biomarker-based patient stratification toward dynamic, patient-specific modeling of cancer evolution. While biological and digital tumor twins have independently advanced our ability to model BC behavior, their full translational impact will remain unrealized as long as they operate in isolation. Biological models provide essential functional drug sensitivity readouts but face inherent constraints in turnaround time, scalability, and microenvironmental complexity. Conversely, computational models offer rapid trajectory simulation and longitudinal scalability but depend entirely on physiologically accurate inputs to avoid computational drift. The convergence of these modalities into closed-loop hybrid tumor twins offers a unique opportunity to bridge experimental biology with predictive computation. By establishing reciprocal feedback loops, where real-time non-destructive biological measurements continuously calibrate computational models and digital simulations dynamically steer subsequent experimental or clinical interventions, hybrid twins enable individualized therapy rehearsal, real-time response forecasting, and early identification of acquired resistance. Furthermore, the aggregation of individual hybrid twins into virtual patient cohorts holds substantial potential to support in silico clinical trials, optimize combination treatment regimens, and accelerate drug development in BC.

Achieving this vision, however, requires moving beyond isolated enabling tools toward prospectively validated, closed-loop systems. As outlined in our translational roadmap, overcoming current barriers will demand coordinated multi-center efforts to establish non-destructive real-time biological sensing, standardize interoperable data architectures, and implement asynchronous temporal scaling frameworks to account for subclonal tumor evolution and spatial heterogeneity. Equally critical will be the establishment of adaptive regulatory and ethical frameworks tailored to continuously learning software, alongside multi-center prospective trials demonstrating that hybrid twin-guided decision-making improves survival outcomes compared with standard multidisciplinary care. Hybrid tumor twins represent a necessary step toward adaptive precision oncology, with the power to fundamentally reshape clinical decision-making in BC. Continued, close interdisciplinary collaboration among oncologists, bioengineers, computational scientists, and regulatory bodies will be essential to translate these concepts into routine practice and deliver meaningful clinical benefits to patients.

Abbreviations

AI	artificial intelligence
BC	breast cancer
ctDNA	circulating tumor DNA
DICOM	digital imaging and communications in medicine
ECM	extracellular matrix
FHIR	fast healthcare interoperability resources
HR	hormone receptor
ML	machine learning
MRI	magnetic resonance imaging
NAC	neoadjuvant chemotherapy
OMOP	observational medical outcomes partnership
pCR	pathological complete response
PDO	patient-derived organoid
PDX	patient-derived xenograft
PINNs	physics-informed neural networks
SNOMED-CT	systematized nomenclature of medicine-clinical terms
TNBC	triple-negative breast cancer

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Declarations

Ethics approval and consent to participate Not applicable.

Consent to publish Not applicable.

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References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A (2024) Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74:229–263
2. Guo L, Kong D, Liu J, Zhan L, Luo L, Zheng W, Zheng Q, Chen C, Sun S (2023) Breast cancer heterogeneity and its implication in personalized precision therapy. Exp Hematol Oncol 12:3
3. Kim SY, van de Wetering M, Clevers H, Sanders K (2025) The future of tumor organoids in precision therapy. Trends Cancer 11:665–675
4. Wang H, Arulraj T, Ippolito A, Popel AS (2024) From virtual patients to digital twins in immuno-oncology: lessons learned from mechanistic quantitative systems pharmacology modeling. NPJ Digit Med 7:189
5. Shi Y, Guan Z, Cai G, Nie Y, Zhang C, Luo W, Liu J (2024) Patient-derived organoids: a promising tool for breast cancer research. Front Oncol 14:1350935
6. Neagu AN, Whitham D, Bruno P, Versaci N, Biggers P, Darie CC (2024) Tumor-on-chip platforms for breast cancer continuum concept modeling. Front Bioeng Biotechnol 12:1436393
7. Schwerd-Kleine P, Wurth R, Cheytan T, Michel L, Thewes V, Gutjahr E, Seker-Cin H, Kazdal D, Neuberth SJ, Thiel V, Schwickert J, Vorberg T, Wischhusen J, Stenzinger A, Zapatka M, Lichter P, Schneeweiss A, Trumpp A, Sprick MR (2025) Biopsy-derived organoids in personalised early breast cancer care: Challenges of tumour purity and normal cell overgrowth cap their practical utility. Int J Cancer 156:2200–2209

8. Sachs N, de Ligt J, Kopper O, Gogola E, Bounova G, Weeber F, Balgobind AV, Wind K, Gracanin A, Begthel H, Korving J, van Boxtel R, Duarte AA, Lelieveld D, van Hoeck A, Ernst RF, Blokzijl F, Nijman IJ, Hoogstraat M, van de Ven M, Egan DA, Zinzalla V, Moll J, Boj SF, Voest EE, Wessels L, van Diest PJ, Rottenberg S, Vries RGJ, Cuppen E, Clevers H (2018) A Living Biobank of Breast Cancer Organoids Captures Disease Heterogeneity. Cell 172:373–386e310
9. Dekkers JF, van Vliet EJ, Sachs N, Rosenbluth JM, Kopper O, Rebel HG, Wehrens EJ, Piani C, Visvader JE, Verissimo CS, Boj SF, Brugge JS, Clevers H, Rios AC (2021) Long-term culture, genetic manipulation and xenotransplantation of human normal and breast cancer organoids. Nat Protoc 16:1936–1965
10. Richiardone E, Van den bossche V, Corbet C (2022) Metabolic studies in organoids: current applications, opportunities and challenges. Organoids 1:85–105
11. Hubert CG, Rivera M, Spangler LC, Wu Q, Mack SC, Prager BC, Couce M, McLendon RE, Sloan AE, Rich JN (2016) A Three-Dimensional Organoid Culture System Derived from Human Glioblastomas Recapitulates the Hypoxic Gradients and Cancer Stem Cell Heterogeneity of Tumors Found In Vivo. Cancer Res 76:2465–2477
12. Rosenbluth JM, Schackmann RCJ, Gray GK, Selfors LM, Li CM, Boedicker M, Kuiken HJ, Richardson A, Brock J, Garber J, Dillon D, Sachs N, Clevers H, Brugge JS (2020) Organoid cultures from normal and cancer-prone human breast tissues preserve complex epithelial lineages. Nat Commun 11:1711
13. Mazzucchelli S, Signati L, Messa L, Franceschini A, Bonizzi A, Castagnoli L, Gasparini P, Consolandi C, Mangano E, Pelucchi P, Cifola I, Camboni T, Severgnini M, Villani L, Tagliaferri B, Carelli S, Pupa SM, Cereda C, Corsi F (2024) Breast cancer patient-derived organoids for the investigation of patient-specific tumour evolution. Cancer Cell Int 24:220
14. Wu H, Wang W, Zhang Y, Chen Y, Shan C, Li J, Jia Y, Li C, Du C, Cai Y, Zhang Y, Zhang S, Wu F (2024) Establishment of patient-derived organoids for guiding personalized therapies in breast cancer patients. Int J Cancer 155:324–338
15. Lin YY, Gao HF, Li H, Hu Q, Du BL, Li S, Xu FP, Cheng MY, Zou JC, Zheng XX, Zhu T, Wang K (2024) Clinical efficacy of tumor organoid-guided cancer therapy for locally advanced unresectable or metastatic breast cancer. Int J Cancer 155:697–709
16. Shu D, Shen M, Li K, Han X, Li H, Tan Z, Wang Y, Peng Y, Tang Z, Qu C, Jin A, Liu S (2022) Organoids from patient biopsy samples can predict the response of BC patients to neoadjuvant chemotherapy. Ann Med 54:2581–2597
17. Guillen KP, Fujita M, Butterfield AJ, Scherer SD, Bailey MH, Chu Z, DeRose YS, Zhao L, Cortes-Sanchez E, Yang CH, Toner J, Wang G, Qiao Y, Huang X, Greenland JA, Vahrenkamp JM, Lum DH, Factor RE, Nelson EW, Matsen CB, Poretta JM, Rosenthal R, Beck AC, Buys SS, Vaklavas C, Ward JH, Jensen RL, Jones KB, Li Z, Oesterreich S, Dobrolecki LE, Pathi SS, Woo XY, Berrett KC, Wadsworth ME, Chuang JH, Lewis MT, Marth GT, Gertz J, Varley KE, Welm BE, Welm AL (2022) A human breast cancer-derived xenograft and organoid platform for drug discovery and precision oncology. Nat Cancer 3:232–250
18. Ye HS, Zhou D, Li H, Lv J, Huang HQ, She JJ, Nie JH, Li TT, Lu MD, Du BL, Yang SQ, Chen PX, Li S, Ye GL, Luo W, Liu J (2024) Organoid forming potential as complementary parameter for accurate evaluation of breast cancer neoadjuvant therapeutic efficacy. Br J Cancer 130:1109–1118
19. Walsh AJ, Cook RS, Sanders ME, Aurisicchio L, Ciliberto G, Arteaga CL, Skala MC (2014) Quantitative optical imaging of primary tumor organoid metabolism predicts drug response in breast cancer. Cancer Res 74:5184–5194
20. Radic Shechter K, Kafkia E, Zirngibl K, Gawrzak S, Alladin A, Machado D, Luchtenborg C, Sevin DC, Brugger B, Patil KR, Jechlinger M (2021) Metabolic memory underlying minimal residual disease in breast cancer. Mol Syst Biol 17:e10141
21. Maulana TI, Teufel C, Cipriano M, Roosz J, Lazarevski L, van den Hil FE, Scheller L, Orlova V, Koch A, Hudecek M, Alb M, Loskill P (2024) Breast cancer-on-chip for patient-specific efficacy and safety testing of CAR-T cells. Cell Stem Cell 31:989–1002e1009
22. Chakrabarty S, Quiros-Solano WF, Kuijten MMP, Haspels B, Mallya S, Lo CSY, Othman A, Silvestri C, van de Stolpe A, Gaio N, Odijk H, van de Ven M, de Ridder CMA, van Weerden WM, Jonkers J, Dekker R, Taneja N, Kanaar R, van Gent DC (2022) A Microfluidic Cancer-on-Chip Platform Predicts Drug Response Using Organotypic Tumor Slice Culture. Cancer Res 82:510–520
23. Desigaux T, Comperat L, Dusserre N, Stachowicz ML, Lea M, Dupuy JW, Vial A, Molinari M, Fricain JC, Paris F (2024) Oliveira, 3D bioprinted breast cancer model reveals stroma-mediated modulation of extracellular matrix and radiosensitivity. Bioact Mater 42:316–327
24. Gonzalez-Callejo P, Garcia-Astrain C, Herrero-Ruiz A, Henriksen-Lacey M, Seras-Franzoso J, Abasolo I (2024) Liz-Marzan, 3D Bioprinted Tumor-Stroma Models of Triple-Negative Breast Cancer Stem Cells for Preclinical Targeted Therapy Evaluation. ACS Appl Mater Interfaces 16:27151–27163
25. Yala A, Mikhael PG, Strand F, Lin G, Smith K, Wan YL, Lamb L, Hughes K, Lehman C, Barzilay R (2021) Toward robust mammography-based models for breast cancer risk. Sci Transl Med, 13
26. Rothwell J, Payne N, Kilburn-Toppin F, Huang Y, Kaggie J, Black R, Hickman S, Kasmai B, Juette A, Gilbert F (2026) Performance of breast cancer risk prediction algorithms across mammography systems in the UK screening programme. NPJ Digit Med, 9
27. Lehman CD, Mercaldo SF, Azam S, Tamimi RM, Carney A, Friedewald SM, Lamb LR (2026) Longitudinal Analysis of Changes in Deep Learning Image-based Breast Cancer Risk Scores over Time, Radiology, 319 e253023

28. Wu C, Lima E, Stowers CE, Xu Z, Yam C, Son JB, Ma J, Rauch GM, Yankeelov TE (2025) MRI-based digital twins to improve treatment response of breast cancer by optimizing neoadjuvant chemotherapy regimens. NPJ Digit Med 8:195
29. Christenson C, Wu C, Hormuth DA 2nd, Ma J, Yam C, Rauch GM, Yankeelov TE (2025) Personalizing neoadjuvant chemotherapy regimens for triple-negative breast cancer using a biology-based digital twin. NPJ Syst Biol Appl 11:53
30. Heudel P, Ahmed M, Renard F, Attye A (2025) Leveraging Digital Twins for Stratification of Patients with Breast Cancer and Treatment Optimization in Geriatric Oncology: Multivariate Clustering Analysis. JMIR Cancer 11:e64000
31. Somaiah N, Kow R, Anbalagan S, Roxanis I, Chauhan R, Kannambath S, Gothard L, Nimalasena S, Noble J, Johns A, Misirlioglu E, Biankin PBA, Babina I, Griffiths M, Asghar US (2026) Abstract PS1-13-06: Personalised Therapy in Triple Negative breast cancer (TNBC), evaluating predictive performance of Bayesian AI Digital Twins. Clin Cancer Res, 32
32. Kozlowski MT, Crook CJ, Ku HT (2021) Towards organoid culture without Matrigel. Commun Biol 4:1387
33. Giolito MV, Feron O, Corbet C (2026) Modeling context-dependent tumor metabolism in 3D systems: implications for functional precision oncology, vol 5. Organoids
34. Wang Q, Yuan F, Zuo X, Li M (2025) Breakthroughs and challenges of organoid models for assessing cancer immunotherapy: a cutting-edge tool for advancing personalised treatments. Cell Death Discov 11:222
35. Magre L, Verstegen MMA, Buschow S, van der Laan LJW, Peppelenbosch M, Desai J (2023) Emerging organoid-immune co-culture models for cancer research: from oncoimmunology to personalized immunotherapies. J Immunother Cancer, 11
36. Polak R, Zhang ET, Kuo CJ (2024) Cancer organoids 2.0: modelling the complexity of the tumour immune microenvironment. Nat Rev Cancer 24:523–539
37. Raffo-Romero A, Ziane-Chaouche L, Salome-Desnoulez S, Hajjaji N, Fournier I, Salzet M, Duhamel M (2024) A co-culture system of macrophages with breast cancer tumoroids to study cell interactions and therapeutic responses. Cell Rep Methods 4:100792
38. Hogstrom JM, Cruz KA, Selfors LM, Ward MN, Mehta TS, Kanarek N, Philips J, Dialani V, Wulf G, Collins LC, Patel JM, Muranen T (2023) Simultaneous isolation of hormone receptor-positive breast cancer organoids and fibroblasts reveals stroma-mediated resistance mechanisms. J Biol Chem 299:105021
39. Shi Y, Cai G, Zhang C, Li H, Nie Y, Yu S, Zhang B, Wu M, Luo W, Liu J, Guan Z (2025) Resveratrol suppresses growth and VCAN expression in a Cancer-associated fibroblast-breast Cancer hybrid organoid. Int Immunopharmacol 153:114451
40. Nguyen HP, An K, Ito Y, Kharbikar BN, Sheng R, Paredes B, Murray E, Pham K, Bruck M, Zhou X, Biellak C, Ushiki A, Nobuhara M, Fong SL, Bernards DA, Lynce F, Dillon DA, Magbanua MJM, Huppert LA, Hammerlindl H, Klein JA, Valdiviez L, Fiehn O, Esserman L, Desai TA, Yee SW, Rosenbluth JM, Ahituv N (2025) Implantation of engineered adipocytes suppresses tumor progression in cancer models. Nat Biotechnol 43:1979–1995
41. Caruso A, Accattatis FM, Giordano C, Gelsomino L, Del Console P, Fiorita MF, Gyorffy B, Bianchi L, Carleo A, De Salvo R, Simoes BM, Clarke RB, Memeo L, Colarossi C, Aiello E, Conforti F, Fuqua SAW, Todaro M, Stassi G, Morelli C, Sisci D, Bonofiglio D, Catalano S, Ando S, Barone I (2025) Adipocyte/Tumor cell crosstalk via IGF-1/TXNIP axis promotes malignancy and endocrine resistance in breast cancer. Cell Commun Signal 23:262
42. Tebon PJ, Wang B, Markowitz AL, Davarifar A, Tsai BL, Krawczuk P, Gonzalez AE, Sartini S, Murray GF, Nguyen HTL, Tavanaie N, Nguyen TL, Boutros PC, Teitell MA, Soragni A (2023) Drug screening at single-organoid resolution via bioprinting and interferometry. Nat Commun 14:3168
43. Shi W, Mirza S, Kuss M, Liu B, Hartin A, Wan S, Kong Y, Mohapatra B, Krishnan M, Band H, Band V, Duan B (2023) Embedded Bioprinting of Breast Tumor Cells and Organoids Using Low-Concentration Collagen-Based Bioinks. Adv Healthc Mater 12:e2300905
44. Dornhof J, Kieninger J, Muralidharan H, Maurer J, Urban GA, Weltin A (2022) Microfluidic organ-on-chip system for multi-analyte monitoring of metabolites in 3D cell cultures. Lab Chip 22:225–239
45. Kheiri S, Yakavets I, Cruickshank J, Ahmadi F, Berman HK, Cescon DW, Young EWK, Kumacheva E (2024) Microfluidic Platform for Generating and Releasing Patient-Derived Cancer Organoids with Diverse Shapes: Insight into Shape-Dependent Tumor Growth. Adv Mater 36:e2410547
46. Fang G, Lu H, Rodriguez L, de la Fuente AMK, Law G, Lin D, Jin D, Gallego-Ortega (2021) Mammary Tumor Organoid Culture in Non-Adhesive Alginate for Luminal Mechanics and High-Throughput Drug Screening. Adv Sci (Weinh) 8:e2102418
47. Zhu J, Ji L, Chen Y, Li H, Huang M, Dai Z, Wang J, Xiang D, Fu G, Lei Z, Chu X (2023) Organoids and organs-on-chips: insights into predicting the efficacy of systemic treatment in colorectal cancer. Cell Death Discov 9:72
48. Sakthivel K, Kotowska A, Fan Z, Portner EJ, Merry C, Nordenfelt P, Simonsen AC, Wright AJ, Swaminathan VS (2026) Integrin-Piezo1 Axis Drives ECM Remodeling and Invasion of 3D Breast Epithelium. Adv Sci (Weinh) 13:e09932
49. Akinpelu A, Akinsipe T, Avila LA, Arnold RD, Mistriotis P (2024) The impact of tumor microenvironment: unraveling the role of physical cues in breast cancer progression. Cancer Metastasis Rev 43:823–844

50. Blanco-Fernandez B, Rey-Vinolas S, Bagci G, Rubi-Sans G, Otero J, Navajas D, Perez-Amodio S, Engel E (2022) Bioprinting Decellularized Breast Tissue for the Development of Three-Dimensional Breast Cancer Models. ACS Appl Mater Interfaces 14:29467–29482
51. Yuan T, Fu X, Hu R, Zheng X, Jiang D, Jing L, Kuang X, Guo Z, Luo X, Liu Y, Zou X, Luker GD, Mi S, Liu C, Sun W (2024) Bioprinted, spatially defined breast tumor microenvironment models of intratumoral heterogeneity and drug resistance. Trends Biotechnol 42:1523–1550
52. Chen Y, Xue D, Huang D, Li X, Duan Y, Chen B (2025) Biofabrication of Tunable 3D Hydrogel for Investigating the Matrix Stiffness Impact on Breast Cancer Chemotherapy Resistance. ACS Biomater Sci Eng 11:1417–1431
53. Peng Z, Lv X, Sun H, Zhao L, Huang S (2025) 3D tumor cultures for drug resistance and screening development in clinical applications. Mol Cancer 24:93
54. Guan X, Huang S (2022) Advances in the application of 3D tumor models in precision oncology and drug screening. Front Bioeng Biotechnol 10:1021966
55. Zhang X, Zhang Z, Chen Y, Xu Y, Sun M (2025) Patient-derived organoid-guided precision therapy for a very young woman with multidrug-resistant metastatic breast cancer: a case report. Front Oncol 15:1630761
56. Espinosa J (2026) Functional Precision Oncology to Predict, Prevent, and Treat Early Metastatic Recurrence of TNBC (TOWARDS-II). ClinicalTrials gov, NCT05464082
57. Wang K, Gao HF (2024) Organoid-based Functional Precision Therapy for Advanced Breast Cancer (ORIENTA), ClinicalTrials.gov, NCT06102824
58. Shen S, Qi W, Liu X, Zeng J, Li S, Zhu X, Dong C, Wang B, Shi Y, Yao J, Wang B, Jing L, Cao S, Liang G (2025) From virtual to reality: innovative practices of digital twins in tumor therapy. J Transl Med 23:348
59. De Domenico M, Allegri L, Caldarelli G, d'Andrea V, Di Camillo B, Rocha LM, Rozum J, Sbarbati R, Zambelli F (2025) Challenges and opportunities for digital twins in precision medicine from a complex systems perspective. NPJ Digit Med 8:37
60. Mollica L, Leli C, Sottotetti FQ, Locati SLD, Marceglia S (2024) Digital twins: a new paradigm in oncology in the era of big data, vol 5. ESMO Real World Data and Digital Oncology
61. Akbarialiabad H, Pasdar A, Murrell DF, Mostafavi M, Shakil F, Safaee E, Leachman SA, Haghighi A, Tarbox M, Bunick CG, Grada A (2025) Enhancing randomized clinical trials with digital twins. NPJ Syst Biol Appl 11:110
62. Cavallo J (2024) Scientists Develop a 'Digital Twin' Model to Predict Cancer Treatment Responses. The ASCO Post
63. Stahlberg EA, Abdel-Rahman M, Aguilar B, Asadpoure A, Beckman RA, Borkon LL, Bryan JN, Cebulla CM, Chang YH, Chatterjee A, Deng J, Dolatshahi S, Gevaert O, Greenspan EJ, Hao W, Hernandez-Boussard T, Jackson PR, Kuijjer M, Lee A, Macklin P, Madhavan S, McCoy MD, Mohammad Mirzaei N, Razzaghi T, Rocha HL, Shahriyari L, Shmulevich I, Stover DG, Sun Y, Syeda-Mahmood T, Wang J, Wang Q, Zervantonakis I (2022) Exploring approaches for predictive cancer patient digital twins: Opportunities for collaboration and innovation. Front Digit Health 4:1007784
64. Chaudhuri A, Pash G, Hormuth DA 2nd, Lorenzo G, Kapteyn M, Wu C, Lima E, Yankeelov TE, Willcox K (2023) Predictive digital twin for optimizing patient-specific radiotherapy regimens under uncertainty in high-grade gliomas. Front Artif Intell 6:1222612
65. Baker RE, Pena JM, Jayamohan J, Jerusalem A (2018) Mechanistic models versus machine learning, a fight worth fighting for the biological community? Biol Lett, 14
66. Lorenzo G, Ahmed SR, Hormuth DA, Vaughn B, Kalpathy-Cramer J, Solorio L, Yankeelov TE, Gomez H (2024) Patient-Specific, Mechanistic Models of Tumor Growth Incorporating Artificial Intelligence and Big Data. Annu Rev Biomed Eng 26:529–560
67. Ochieng FO (2025) Mathematical Modeling of Cancerous Tumor Evolution Incorporating Drug Resistance. Eng Rep 7:e70021
68. Jafari Nivlouei S, Soltani M, Shirani E, Salimpour MR, Travasso R, Carvalho J (2022) A multiscale cell-based model of tumor growth for chemotherapy assessment and tumor-targeted therapy through a 3D computational approach. Cell Prolif 55:e13187
69. Corral-Acero J, Margara F, Marciniak M, Rodero C, Loncaric F, Feng Y, Gilbert A, Fernandes JF, Bukhari HA, Wajdan A, Martinez MV, Santos MS, Shamohammdi M, Luo H, Westphal P, Leeson P, DiAchille P, Gurev V, Mayr M, Geris L, Pathmanathan P, Morrison T, Cornelussen R, Prinzen F, Delhaas T, Doltra A, Sitges M, Vigmond EJ, Zacur E, Grau V, Rodriguez B, Remme EW, Niederer S, Mortier P, McLeod K, Potse M, Pueyo E, Bueno-Orovio A, Lamata P (2020) The 'Digital Twin' to enable the vision of precision cardiology. Eur Heart J 41:4556–4564
70. Raynaud M, Aubert O, Divard G, Reese PP, Kamar N, Yoo D, Chin CS, Bailly E, Buchler M, Ladriere M, Le Quintrec M, Delahousse M, Juric I, Basic-Jukic N, Crespo M, Silva HT Jr., Linhares K, Ribeiro MC, de Castro G, Soler Pujol JP, Empana C, Ulloa E, Akalin G, Bohmig E, Huang MD, Stegall AJ, Bentall RA, Montgomery SC, Jordan R, Oberbauer DL, Segev JJ, Friedewald X, Jouven C, Legendre C, Lefaucheur A, Loupy (2021) Dynamic prediction of renal survival among deeply phenotyped kidney transplant recipients using artificial intelligence: an observational, international, multicohort study. Lancet Digit Health 3:e795–e805

71. Dowling GP, Daly GR, Hehir CM, AlRawasdeh MM, Calpin GG, Almasri S, Toomey S, Young LS, Hennessey BT, Hill ADK (2025) Prognostic significance of receptor conversion following neoadjuvant therapy in breast cancer: a systematic review & meta-analysis. Breast 82:104516
72. Vemuru S, Huang J, Colborn K, Yoon Y, Huynh V, Leonard L, Ahrendt G, Christian N, Afghahi A, McLemore L, Sams S, Tevis S (2023) Clinical implications of receptor conversions in breast cancer patients who have undergone neoadjuvant chemotherapy. Breast Cancer Res Treat 200:247–256
73. Zhang L, Lu L, Wang X, Zhu RM, Bagheri M, Summers RM, Yao J (2020) Spatio-Temporal Convolutional LSTMs for Tumor Growth Prediction by Learning 4D Longitudinal Patient Data. IEEE Trans Med Imaging 39:1114–1126
74. Zhang Y, Bao X, Wang Y, Li L, Liu L, Wu Q (2025) Machine learning-based radiomics model: prognostic prediction and mechanism exploration in patients with endometrial cancer. Biomark Res 13:119
75. Zhang W, Ye B, Song Y, Yang P, Si W, Jing H, Yang F, Yuan D, Wu Z, Lyu J, Peng K, Zhang X, Wang L, Li Y, Liu Y, Wu C, Hao X, Zhang Y, Qi W, Wang J, Dong F, Zhao Z, Jing H, Li Y (2025) Integrating multi-omics features enables non-invasive early diagnosis and treatment response prediction of diffuse large B-cell lymphoma. Clin Transl Med 15:e70174
76. Kapteyn M, Chaudhuri A, Lima EABF, Pash G, Bravo R, Willcox K, Yankeelov TE, Hormuth DA (2025) TumorTwin: A python framework for patient-specific digital twins in oncology, arXiv
77. Raissi M, Perdikaris P, Karniadakis GE (2019) Physics-informed neural networks: A deep learning framework for solving forward and inverse problems involving nonlinear partial differential equations. J Comput Phys 378:686–707
78. Zhang RZ, Ezhov I, Balcerak M, Zhu A, Wiestler B, Menze B, Lowengrub JS (2025) Personalized predictions of Glioblastoma infiltration: Mathematical models, Physics-Informed Neural Networks and multimodal scans. Med Image Anal 101:103423
79. Concr VISION (2024) Triple Negative Breast Cancer Sample and Clinical Data Acquisition Study. ClinicalTrials gov, NCT06409221
80. Fan L, Zhang WJ, Li HP, Zeng XH, Teng YE, Gong Y, Jin X, Zhao S, Sun T, Chen WY, Wang SS, Yang J, Zhuang ZG, Ni SJ, He ZX, Fu DY, Song CG, Lv Z, Liang QN, Yu BH, Shi J, Wang N, Liang XR, Zhang NN, Wang Y, Ji P, Liu XY, Chen L, He M, Liu Y, Sui XY, Ma LX, Zhu XZ, Yang F, Ge LP, Wu SY, Wu J, Yu KD, Liu GY, Hu X, Shen Y, Pang Z, Wang JF, Liang F, Yang WT, Wang ZH, Jiang YZ (2026) Shao, B. investigators, Precision treatment with artificial intelligence assisted subtyping enhances therapeutic efficacy in HR+/HER2- breast cancer: The LINUXtrial. Cancer Cell 44:355–365e353
81. Timoteo R, Laborde A, Vaz B, Loucao N, Forghani Y, Cardoso A, Correia M, Santinha J, Simoes Lopes D, Marques T, Gouveia P (2026) Digital twins for non-invasive tumor localization in breast-conserving surgery: a technical pilot study. Breast 88:104807
82. Susilo ME, Li CC, Gadkar K, Hernandez G, Huw LY, Jin JY, Yin S, Wei MC, Ramanujan S, Hosseini I (2023) Systems-based digital twins to help characterize clinical dose-response and propose predictive biomarkers in a Phase I study of bispecific antibody, mosunetuzumab, in NHL. Clin Transl Sci 16:1134–1148
83. Beghin A, Grenci G, Sahni G, Guo S, Rajendiran H, Delaire T, Mohamad Raffi SB, Blanc D, de Mets R, Ong HT, Galindo X, Monet A, Acharya V, Racine V, Levet F, Galland R, Sibarita JB, Viasnoff V (2022) Automated high-speed 3D imaging of organoid cultures with multi-scale phenotypic quantification. Nat Methods 19:881–892
84. Zhao Y, Li S, Zhu L, Huang M, Xie Y, Song X, Chen Z, Lau HC, Sung JJ, Xu L, Yu J, Li X (2024) Personalized drug screening using patient-derived organoid and its clinical relevance in gastric cancer. Cell Rep Med 5:101627
85. Bai L, Wu Y, Li G, Zhang W, Zhang H, Su J (2024) AI-enabled organoids: Construction, analysis, and application. Bioact Mater 31:525–548
86. Zhu M, Zhuang J, Li Z, Liu Q, Zhao R, Gao Z, Midgley AC, Qi T, Tian J, Zhang Z, Kong D, Tian J, Yan X, Huang X (2023) Machine-learning-assisted single-vessel analysis of nanoparticle permeability in tumour vasculatures. Nat Nanotechnol 18:657–666
87. Xu Y, Li J, Wang J, Deng F (2024) A novel CAF-cancer cell crosstalk-related gene prognostic index based on machine learning: prognostic significance and prediction of therapeutic response in head and neck squamous cell carcinoma. J Transl Med 22:645
88. Deben C, De La Hoz EC, Rodrigues Fortes F, Le Compte M, Seghers S, Vanlanduit S, Vercammen H, Van Den Bogert B, Dusetti N, Lin A, Roeyen G, Peeters M, Prenen H, Lardon F, Smits E (2024) Development and validation of the Normalized Organoid Growth Rate (NOGR) metric in brightfield imaging-based assays. Commun Biol 7:1612
89. Zhang S, Li L, Yu P, Wu C, Wang X, Liu M, Deng S, Guo C, Tan R (2023) A deep learning model for drug screening and evaluation in bladder cancer organoids. Front Oncol 13:1064548
90. Matthews JM, Schuster B, Kashaf SS, Liu P, Ben-Yishay R, Ishay-Ronen D, Izumchenko E, Shen L, Weber CR, Bielski M, Kupfer SS, Bilgic M, Rzhetsky A, Tay S (2022) OrganoID: A versatile deep learning platform for tracking and analysis of single-organoid dynamics. PLoS Comput Biol 18:e1010584
91. Branciforti F, Salvi M, D'Agostino F, Marzola F, Cornacchia S, De Titta MO, Mastronuzzi G, Meloni I, Moschetta M, Porciani N, Sciscenti F, Spertini A, Spilla A, Zagaria I, Deloria AJ, Deng S, Haindl R, Szakacs G, Csiszar A, Liu M, Drexler W, Molinari F, Meiburger KM (2024) Segmentation and Multi-Timepoint Tracking of 3D Cancer Organoids from Optical Coherence Tomography Images Using Deep Neural Networks, Diagnostics (Basel), 14

92. Hasnain Z, Fraser AK, Georgess D, Choi A, Macklin P, Bader JS, Peyton SR, Ewald AJ, Newton PK (2020) OrgDyn: feature- and model-based characterization of spatial and temporal organoid dynamics. Bioinformatics 36:3292–3294
93. Zhou Y, Dai Q, Xu Y, Wu S, Cheng M, Zhao B (2025) PharmaFormer predicts clinical drug responses through transfer learning guided by patient derived organoid. NPJ Precis Oncol 9:282
94. Shi H, Kowalczewski A, Vu D, Liu X, Salekin A, Yang H, Ma Z (2024) Organoid intelligence: Integration of organoid technology and artificial intelligence in the new era of in vitro models. Med Nov Technol Devices, 21
95. Lim MH, Shin S, Park K, Park J, Kim SW, Basurrah MA, Lee S, Kim DH (2023) Deep Learning Model for Predicting Airway Organoid Differentiation. Tissue Eng Regen Med 20:1109–1117
96. Spiller ER, Ung N, Kim S, Patsch K, Lau R, Strelez C, Doshi C, Choung S, Choi B, Juarez EF, Rosales HJ, Lenz N, Matasci SM (2021) Mumenthaler, Imaging-Based Machine Learning Analysis of Patient-Derived Tumor Organoid Drug Response. Front Oncol 11:771173
97. Askr H, Elgeldawi E, Aboul Ella H, Elshaier Y, Gomaa MM, Hassanien AE (2023) Deep learning in drug discovery: an integrative review and future challenges. Artif Intell Rev 56:5975–6037
98. Sheller MJ, Edwards B, Reina GA, Martin J, Pati S, Kotrotsou A, Milchenko M, Xu W, Marcus D, Colen RR, Bakas S (2020) Federated learning in medicine: facilitating multi-institutional collaborations without sharing patient data. Sci Rep 10:12598
99. Cai Z, Boys EL, Noor Z, Aref AT, Xavier D, Lucas N, Williams SG, Koh JMS, Poulos RC, Wu Y, Dausmann M, MacKenzie KL, Aguilar-Mahecha A, Armengol C, Barranco MM, Basik M, Bowman ED, Clifton-Bligh R, Connolly EA, Cooper WA, Dalal B, DeFazio A, Filipits M, Flynn PJ, Graham JD, George J, Gill AJ, Gnant M, Habib R, Harris CC, Harvey K, Horvath LG, Jackson C, Kohonen-Corish MRJ, Lim E, Liu JJ, Long GV, Lord RV, Mann GJ, McCaughan GW, Morgan L, Murphy L, Nagabushan S, Nagrial A, Navines J, Panizza BJ, Samra JS, Scolyer RA, Souglakos J, Swarbrick A, Thomas D, Balleine RL, Hains PG, Robinson PJ, Zhong Q, Reddel RR (2025) Federated Deep Learning Enables Cancer Subtyping by Proteomics. Cancer Discov 15:1803–1818
100. Ling S, Xu C, Jiang Y, Xu F, Jin H, Chen H, Chen S, Ding Z, Sun D (2026) Toward continuous monitoring systems: emerging trends of on-chip sensors in organ-on-a-chip. Microsyst Nanoeng 12:61
101. Asghar US, Chung C (2025) Application of digital twins for personalized oncology. Nat Rev Cancer 25:823–825
102. Manganaro L, De Sario G, Carpino G, Frey LJ, Gaudio E, Syn WK, Alvaro D (2026) V. Cardinale, Digital and Biological Twins in Cholangiocarcinoma: From Translational Research to Precision Medicine—A Narrative Review, Livers, 6
103. Ahmed HM, Al-Hussainy AF, Mustafa WW, Jyothi SR, Nayak PP, Janney JB, Singh G, Sinha A, Sameer HN, Salih RM, Adil M, Salajegheh P (2026) Circulating tumor DNA dynamics predict pathological response and guide therapy personalization in the neoadjuvant setting. Discov Oncol, 17
104. Keller L, Belloum Y, Wikman H, Pantel K (2021) Clinical relevance of blood-based ctDNA analysis: mutation detection and beyond. Br J Cancer 124:345–358
105. Vorisek CN, Lehne M, Klopfenstein SAI, Mayer PJ, Bartschke A, Haese T, Thun S (2022) Fast Healthcare Interoperability Resources (FHIR) for Interoperability in Health Research: Systematic Review. JMIR Med Inf 10:e35724
106. Ianculescu M, Constantin VS, Gusatu AM, Petrache MC, Mihaescu AG, Bica O, Alexandru A (2025) Enhancing Connected Health Ecosystems Through IoT-Enabled Monitoring Technologies: A Case Study of the Monit4Healthy System. Sens (Basel), 25
107. Iancu A, Bauer J, May MS, Prokosch HU, Dorfler A, Uder M, Kapsner LA (2024) Large-Scale Integration of DICOM Metadata into HL7-FHIR for Medical Research. Methods Inf Med 63:77–84
108. Toure V, Krauss P, Gnodtke K, Buchhorn J, Unni D, Horki P, Raisaro JL, Kalt K, Teixeira D, Crameri K, Osterle S (2023) FAIRification health-related data using semantic web Technol Swiss Personalized Health Netw Sci Data 10:127
109. Yang H, Yang M, Chen J, Yao G, Zou Q, Jia L (2024) Multimodal deep learning approaches for precision oncology: a comprehensive review. Brief Bioinform, 26
110. Narayan SM, Kohli N, Martin MM (2025) Addressing contemporary threats in anonymised healthcare data using privacy engineering. NPJ Digit Med 8:145
111. Hasanzadeh F, Josephson CB, Waters G, Adedinsewo D, Azizi Z, White JA (2025) Bias recognition and mitigation strategies in artificial intelligence healthcare applications. NPJ Digit Med 8:154
112. Zhang F, Zhai D, Bai G, Jiang J, Ye Q, Ji X, Liu X (2025) Towards fairness-aware and privacy-preserving enhanced collaborative learning for healthcare. Nat Commun 16:2852
113. Konopik J, Wolf L, Schöffski O (2023) Digital twins for breast cancer treatment – an empirical study on stakeholders' perspectives on potentials and challenges. Health Technol 13:1003–1010
114. Kemkar S, Tao M, Ghosh A, Stamatakos G, Graf N, Poorey K, Balakrishnan U, Trask N, Radhakrishnan R (2024) Towards verifiable cancer digital twins: tissue level modeling protocol for precision medicine. Front Physiol 15:1473125
115. Wang Y, Bergman DR, Trujillo E, Fernald AA, Li L, Pearson AT, Sweis RF, Jackson TL (2024) Agent-Based Modeling of Virtual Tumors Reveals the Critical Influence of Microenvironmental Complexity on Immunotherapy Efficacy. Cancers (Basel), 16
116. Andrews MG, Kriegstein AR (2022) Challenges of Organoid Research. Annu Rev Neurosci 45:23–39

117. Li K, He Y, Jin X, Jin K, Qian J (2025) Reproducible extracellular matrices for tumor organoid culture: challenges and opportunities. J Transl Med 23:497
118. Kolobkov D, Mishra Sharma S, Medvedev A, Lebedev M, Kosaretskiy E, Vakhitov R (2024) Efficacy of federated learning on genomic data: a study on the UK Biobank and the 1000 Genomes Project. Front Big Data 7:1266031
119. Seletkov D, Starck S, Mueller TT, Zhang Y, Steinhelfer L, Rueckert D, Braren R (2025) AI-driven preclinical disease risk assessment using imaging in UK biobank. NPJ Digit Med 8:480
120. Gross M, Dewan A, Macis M, Budd E, Eifler M, Odeniran O, Kahn J, Miller RC, Sanchez W (2025) Decentralized biobanking platform for organoid research networks. Front Blockchain, 8
121. Rieke N, Hancox J, Li W, Milletari F, Roth HR, Albarqouni S, Bakas S, Galtier MN, Landman BA, Maier-Hein K, Ourselin S, Sheller M, Summers RM, Trask A, Xu D, Baust M, Cardoso MJ (2020) The future of digital health with federated learning. NPJ Digit Med 3:119
122. Maramraju S, Kowalczewski A, Kaza A, Liu X, Singaraju JP, Albert MV, Ma Z, Yang H (2024) AI-organoid integrated systems for biomedical studies and applications. Bioeng Transl Med 9:e10641
123. Ahammed B, Kalangi SK (2024) A Decade of Organoid Research: Progress and Challenges in the Field of Organoid Technology. ACS Omega 9:30087–30096

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