

Opinion Paper

Damien Gruson*, Christa Cobbaert, Pradeep Kumar Dabla, Sanja Stankovic, Evgenija Homsak, Kazuhiko Kotani, Ramy Samir Assaad, James H. Nichols and Bernard Gouget

Validation and verification framework and data integration of biosensors and *in vitro* diagnostic devices: a position statement of the IFCC Committee on Mobile Health and Bioengineering in Laboratory Medicine (C-MBHLM) and the IFCC Scientific Division

<https://doi.org/10.1515/cclm-2023-1455>

Received December 17, 2023; accepted January 29, 2024;
published online February 21, 2024

Abstract: Advances in technology have transformed healthcare and laboratory medicine. Biosensors have emerged as a promising technology in healthcare, providing a way to monitor human physiological parameters in a continuous, real-time, and non-intrusive manner and offering value and benefits in a wide range of applications. This position statement aims to present the current situation around biosensors, their perspectives and importantly the need to set the framework for their validation and safe use. The

development of a qualification framework for biosensors should be conceptually adopted and extended to cover digitally measured biomarkers from biosensors for advancing healthcare and achieving more individualized patient management and better patient outcome.

Keywords: biosensors; mobile health; device; data; connectivity; interoperability

Introduction

Advances in technology have transformed healthcare and laboratory medicine, offer great promise for improving

***Corresponding author: Prof. Damien Gruson**, Department of Clinical Biochemistry, Department of Laboratory Medicine, Cliniques Universitaires St-Luc and Université Catholique de Louvain, 10 Avenue Hippocrate, 1200 Brussels, Belgium; Pôle de recherche en Endocrinologie, Diabète et Nutrition, Institut de Recherche Expérimentale et Clinique, Cliniques Universitaires St-Luc and Université Catholique de Louvain, Brussels, Belgium; and Emerging Technologies Division and MBHLM Committee, International Federation Clinical Chemistry and Laboratory Medicine (IFCC), Milan, Italy, Phone: +32 (0)2 7646747, Fax: +32 (0)2 7646930, E-mail: damien.gruson@uclouvain.be
Christa Cobbaert, Department of Clinical Chemistry and Laboratory Medicine, Leiden University Medical Centre (LUMC), Leiden, Netherlands; and International Federation of Clinical Chemistry (IFCC) Scientific Division, Milan, Italy

Pradeep Kumar Dabla, Department of Biochemistry, G.B. Pant Institute of Postgraduate Medical Education & Research, Associated Maulana Azad Medical College, New Delhi, India; and Emerging Technologies Division and MBHLM Committee, International Federation Clinical Chemistry and Laboratory Medicine (IFCC), Milan, Italy

Sanja Stankovic, Center for Medical Biochemistry, University Clinical Center of Serbia, Belgrade, Serbia; Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia; and Emerging Technologies Division and

MBHLM Committee, International Federation Clinical Chemistry and Laboratory Medicine (IFCC), Milan, Italy

Evgenija Homsak, Department for Laboratory Diagnostics, University Clinical Center Maribor, Maribor, Slovenia; and Emerging Technologies Division and MBHLM Committee, International Federation Clinical Chemistry and Laboratory Medicine (IFCC), Milan, Italy

Kazuhiko Kotani, Division of Community and Family Medicine, Jichi Medical University, Shimotsuke-City, Japan; and Emerging Technologies Division and MBHLM Committee, International Federation Clinical Chemistry and Laboratory Medicine (IFCC), Milan, Italy

Ramy Samir Assaad, Medical Research Institute - Alexandria University, Alexandria, Egypt; Egyptian Association of Healthcare Quality and Patient Safety, Alexandria, Egypt; and Emerging Technologies Division and MBHLM Committee, International Federation Clinical Chemistry and Laboratory Medicine (IFCC), Milan, Italy. <https://orcid.org/0000-0003-2340-4246>

James H. Nichols, Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, TN, USA; and Emerging Technologies Division and MBHLM Committee, International Federation Clinical Chemistry and Laboratory Medicine (IFCC), Milan, Italy

Bernard Gouget, Emerging Technologies Division and MBHLM Committee, International Federation Clinical Chemistry and Laboratory Medicine (IFCC), Milan, Italy. <https://orcid.org/0000-0002-8010-1404>

global health and ensuring healthier populations worldwide and enable healthcare providers to monitor and manage patients' health with greater precision and accuracy [1, 2]. The World Health Organization (WHO) recognizes the potential of emerging technologies to transform healthcare and address some of the most pressing health challenges facing people around the world [3, 4].

Biosensors have emerged as a promising technology in the healthcare industry, enabling the continuous, real-time, and non-intrusive monitoring of various human physiological parameters [5]. However, the definition may benefit from clarity regarding the inclusion of both non-invasive and minimally invasive sampling biosensors. A more precise scope is necessary. Additionally, in the subsequent sections of the paper, the mention of continuous glucose monitoring (CGM) – such as an example of a hybrid biomarker positioned between a digital biomarker and the traditional lab biomarker – further emphasizes the evolving landscape of biosensing technologies.

The benefits of biosensor-based diagnostic platforms could also be particularly significant for patients in low- and middle-income countries (LMICs), where “traditional” diagnostic systems can be a significant challenge. Traditional diagnostic methods often require expensive equipment, trained personnel, and specialized facilities, which may not be available in many LMICs. Biosensor-based diagnostic platforms, on the other hand, can be designed to be simple, portable, and user-friendly, making them an ideal solution for LMICs [3, 4]. Overall, biosensor-based diagnostic platforms hold great promise for improving global health and ensuring healthier populations worldwide and could be embedded in emergency services, connected homes, and smart hospitals [6]. However, all sensor-based devices, particularly healthcare devices, require a degree of validation, control, and regulation to ensure that they are clinically relevant, perform analytically and are safe for the end user [7].

This position statement aims to present the current situation around biosensors, their perspectives and importantly the need to set the framework for their validation and safe use.

Sensors and mobile health devices for biological measurement

Biosensors are devices that can detect and measure specific biological, chemical, or physical parameters [8]. There are several modalities for biosensor-based diagnostics, including chemical, magnetic, optical, and nanotechnological

[5, 9]. Biosensors rely on their capacity to transform biological interactions into a type of electric signal that can be detected and quantified [9]. Nano-biosensors result from the integration of nanoparticles during fabrication [9].

Wearable chemical sensors provide a real-time, non-invasive alternative to typical laboratory blood analysis, and are an effective tool for exploring novel biomarkers in alternative body fluids, such as sweat, saliva, tears and interstitial fluid [10]. Another element of definition could be wearable biomarkers which are a particularly exciting area of development in the field of biosensors [5, 6, 10]. These sensors can be worn on the body, such as on the wrist or chest, and can track a wide range of physiological parameters in a non-intrusive manner. Wearable biomarkers have the potential to transform the way we monitor and manage chronic diseases, such as diabetes or heart disease, by providing real-time feedback on a patient's health status.

Value and benefits from sensors and mobile health devices

One of the key advantages of biosensors is their ability to provide real-time monitoring of physiological parameters. Traditional diagnostic tests, such as blood tests or imaging studies, are often time-consuming and can only provide a snapshot of a patient's health at a given moment. Biosensors, on the other hand, can continuously monitor vital signs, such as heart rate, blood pressure, and glucose levels, providing a more complete picture of a patient's health. By providing continuous monitoring of physiological parameters, biosensors can help detect changes in health status before they become severe, potentially reducing the need for hospitalizations and emergency room visits.

Empowerment in diabetes is one of the most significant benefits of sensors and mobile health devices. CGM devices can help patients with diabetes monitor their glucose levels in real-time and adjust their treatment accordingly [11]. CGM sensors have significantly improved the quality of life for diabetic patients. These sensors eliminate the need for frequent finger pricks to measure blood glucose levels, particularly for those on insulin therapy. Current guidelines recommend regular self-monitoring of blood glucose (SMBG) for insulin users, including before meals, after meals, at bedtime, before exercise, and in response to symptoms of hypoglycemia. However, studies have shown that CGM users experience a significant reduction in hypoglycemia compared to traditional glucometer users [12]. Research conducted across multiple European diabetes centers demonstrated that sensor-based glucose monitoring

resulted in a 50–60 % reduction in hypoglycemia time below certain thresholds compared to SMBG with capillary strips [13]. This reduction in hypoglycemia has also been observed in insulin-treated type 2 diabetes patients. Another randomized controlled trial showed a 53–64 % reduction in hypoglycemia time with flash glucose-sensing technology compared to ordinary SMBG [14]. Real-world data analysis of CGM users in different European countries further supported the benefits of frequent glucose monitoring. The study, based on over 63 million sensor scans, revealed that increasing the frequency of daily sensor scans was associated with a proportional reduction in hypoglycemia time [15]. This reduction was evident from the second day of CGM use and was primarily attributed to frequent scanning, patient monitoring, and appropriate self-management without professional intervention. The use of CGM also has positive implications for emergency hospital admissions. Retrospective longitudinal studies have shown a 42 % reduction in all-cause inpatient admission and significantly fewer emergency visits for diabetic ketoacidosis among CGM users compared to SMBG users [16]. Time In Range (TIR) is another important metric provided by CGM, representing the percentage of time spent within the target blood glucose range [17, 18]. Studies have shown that TIR is strongly associated with the risk of microvascular complications. Additionally, CGM can estimate HbA_{1c} levels using a formula derived from average glucose levels measured by CGM, leading to the adoption of the term glucose management indicator (GMI) instead of estimated HbA_{1c} [19, 20].

Biosensors exhibit versatile applications across healthcare domains. Firstly, in cardiovascular health, they could facilitate rapid and precise measurement of cardiac biomarkers. Monitoring of heart failure and natriuretic peptides with major emphasis on biosensing methods is another chronic condition where sensors and mobile health devices can be particularly valuable [21]. BNP is a protein that is released by the heart in response to stress or injury. Monitoring BNP levels can help identify potential heart problems before they become serious, allowing for early intervention and treatment. Biosensing methods can be used to detect BNP levels in real-time, making it possible to monitor patients remotely and detect potential issues before they become serious. Another application in cardiac diseases can concern troponin for diagnosing myocardial infarction [22, 23]. Utilizing chemiluminescence-based immunosensors with sensitive optical readouts and microfluidic setups, these biosensors enable selective cTnI determination within minutes [22, 23]. Other perspectives for biosensors are reported in the field of fertility monitoring, offering

non-invasive tracking of fertility hormones in sweat through wearable devices incorporating nanoelectronics and folded RNA [24]. These innovations allow continuous hormone level monitoring without invasive blood tests. Lastly, biosensors play a crucial role in infectious disease diagnosis, particularly in the early detection of biomarkers such as C-reactive protein (CRP) [25].

Long-distance traveling is another application where sensors and mobile health devices can have a significant impact. For example, devices that monitor vital signs, such as heart rate and blood pressure, can help travelers identify potential health risks before they become serious. This can be particularly important for older travelers, who may have pre-existing health conditions that put them at greater risk. Astronauts also benefit from the use of sensors and mobile health devices [26]. To support the health and performance of astronauts in space, there is an essential need to monitor their status in the space suit. This can be done using a variety of sensors and devices that measure vital signs, body temperature, and other important parameters. This information can then be used to help monitor the health of the astronauts and identify potential issues before they become serious.

Connectivity with digital ecosystem and electronic health records is another benefit of sensors and mobile health devices. By connecting with electronic health records and other digital systems, sensors and mobile health devices can provide valuable information that can be used to improve outcomes for patients. This information can also be used to identify trends and patterns that can help healthcare providers make more informed decisions about treatment.

Early alerts and remote monitoring are two more areas where sensors and mobile health devices can be particularly valuable. Early alerts can help identify potential health risks before they become serious, while remote monitoring can help patients receive care and treatment from the comfort of their own homes. This can be particularly important for patients with chronic conditions or those who live in remote areas.

Finally, data integration is an important benefit of sensors and mobile health devices. By integrating data from a wide range of sources, including sensors and other devices, healthcare providers can get a more comprehensive view of a patient's health. This can be particularly useful for identifying potential health risks and developing more personalized treatment plans. The perspective of data integration through machine learning applications is a reality [27].

The six dimensions to address biosensor safety and fitness-for-purpose

Despite their advantages, the development and implementation of biosensors are not without challenges. Ensuring the accuracy and reliability of biosensors is a critical factor in their adoption and use in clinical settings. Digitally measured biomarkers, derived from biosensors, have not yet gained the same degree of acceptance and recognition in laboratory medicine as conventional laboratory and imaging biomarkers. Various types of health and sickness related data of unknown quality have been gathered. Methodological frameworks are urgently needed to determine whether a certain application is qualifying, ready and appropriate for use. Additionally, there is a need for standardization and interoperability between different biosensors and data management systems to ensure that the collected data is meaningful and actionable. Previously a three-step validation framework, named the V3 validation model has been developed [28]. The V3 framework is illustrated in Figure 1, as applied to digital and conventional laboratory biomarkers. Conventional laboratory biomarkers go through an analytical and clinical validation step as defined in the Biomarkers, Endpoints, and other Tools framework [29]. Digitally measured biomarkers are derived from sensor technology that needs to undergo verification, before the physiological or behavioral measures of interest can be analytically and clinically validated. Whereas laboratory biomarkers go through the validation process based on bench testing, digitally measured biomarkers are highly reliant on human subject testing.

Verification of biosensor technology is an assessment of biosensor accuracy and the objective data that are generated should answer the question: “Is the tool made

right”? Therefore, verification is an *engineering assessment* entirely separate from data collection on human subjects. Verification testing can be completed at the bench, does not demand METC approval, and is the process of ensuring that the sensor works appropriately.

Validation in the V3 framework is the process of ensuring that the digital measurement tool is meeting its intended use and answers the question: “Has the right tool been built”? Validation of biosensors reveals whether the technology is measuring what is intended to measure (clinical validation) and is correct (analytic validation). For proper validation developers should work with researchers to ensure that validation studies are well-designed.

From our perspective, six key elements are critical to consider for the validation of sensors:

- The intended use of the biomarker in the specific care pathway for a specific participant or patient group, as well as scientific validity, and analytical and clinical performance data matching the predefined performance requirements for its intended use
- IVDR 2017/746 compliance
- The interoperability, connectivity, data integration and safety
- The user friendliness
- Affordability and sustainability
- Education and training

Regulatory compliance and specifications assessment

In the case that biosensors fulfill the definition of an IVD as described in the IVDR 2017/746, the IVDR is applicable. It is important to realize that in the European Union, the European Commission has applied the EU IVDR 2017/746 since May 2022 to guarantee safe and effective medical tests.

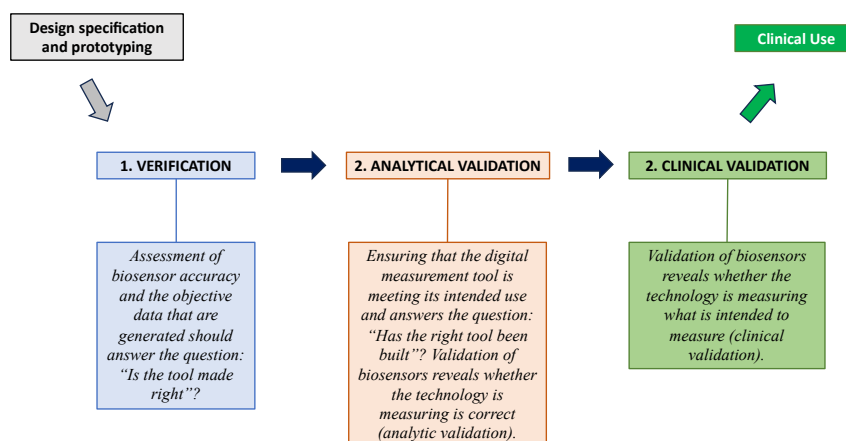


Figure 1: The V3 validation framework (adapted from Ref. [28]).

Depending on the intended use of the test and its risk class, IVD-manufacturers that want to bring their IVDs on the EU-market should, for new medical devices, be compliant to the stringent IVDR requirements. Compared to the former IVDD 98/79/EC, self-declaration is no longer allowed, and all class A nonsterile, B, C and D risk classified tests have to undergo notified body (third party) assessment. Beyond Annex I which describes General Performance and Safety Specifications, the clinical evidence requirement is an essential new feature. This implies that in the technical dossier that is required for notified body assessment, objective data should be presented which underpin the scientific validity, and the analytical and clinical performance of the biosensor. Also, the benefit/harm ratio for patients (in case of sick care) should be addressed. Another new requirement is post-market surveillance which demands that IVD-manufacturers improve their biosensor performance during the entire life cycle of the test.

a. Explicit context of use

- i. Each biosensor device must define its intended use and eventually its role in the clinical care pathway, if applicable (measurement of blood pressure, heart rate, glucose concentration). We can roughly define biosensors for the purpose of use into two main groups: biosensors that are used for medical (monitoring chronic patients) or non-medical purposes (well-being purposes, monitoring the state of individuals during their activities i.e. athletes).
- ii. According to this definition, various necessary instructions for the user should be described in the instructions for use. As an example of medical use, are glucose meters that are intended to monitor the glucose concentration over a longer period, for the purpose of glucose regulation and therapy of diabetics. In the case of medical use, it is necessary to clearly define that their use does not replace but complements/supports the monitoring of their disease, while/next to monitoring other parameters (HbA_{1c}), which are determined in clinical laboratories upon request of the treating medical doctors.
- iii. It is necessary to define acceptable limits of performance of the measured biosensor-derived test result considering the intended use of the test; also, inclusion of warning signs or sounds in case of deviations must be considered.
- iv. Since the biosensors are intended for wider use by untrained individuals, it is also desirable that each software has the possibility of easy display of results (in the form of curves, arrows) and their interpretation in the form of different colors (e.g. green-acceptable; yellow-warning; red-unacceptable, necessary action) or emotions (☺, ☹)

c. Device specification

- i. Each biosensor must have defined dimensions (width, height, depth), device weight. It is necessary to indicate the place on the body where the device is also installed, with clear instructions on how to install it correctly, to ensure adequate measurements.
- ii. It is also important for the manufacturer to state the expected lifetime of the device, within which it guarantees the adequacy of its operation.
- iii. It is important to define possible cases of improper installation/use or to clearly state other restrictions/influences that would prevent improper use or affect the correctness of the measurements.

d. Measured digital biomarker

b. User interface/user experience

- i. Each biosensor must have a defined user interface/software that enables the connection of the device/application with other devices (computers) intended for monitoring and analyzing (follow-up the trend) the measured parameter.
- ii. Instructions for use must be clearly given, which must be adapted according to the different (minimum) previous experiences of the user.
- iii. It is also important for the manufacturer to state the expected lifetime of the device, within which it guarantees the adequacy of its operation.
- iv. It is important to define possible cases of improper installation/use or to clearly state other restrictions/influences that would prevent improper use or affect the correctness of the measurements.
- v. Insofar as the measurand can also be measured in other biological materials (e.g. blood glucose), with other standardized measurement systems (in the laboratory), it is recommended to define the relationship/ratio of concentrations for reasons of data consistency, and support it with evidence (references of the conducted research)
- vi. It is also important to clearly define the measurement system and its possible limitations (interferences,

selectivity, analytical sensitivity, clinical sensitivity and specificity, special conditions for appropriate use)

e. Technical data

- i. For appropriate use, biosensor performance and interpretation of measured values/obtained results, it is important to know the technical data of the measuring system and the determination method.
- ii. It is necessary to clearly define the site of collection (location on a specific part of the body, skin, under the skin, on the muscle), the required (minimum or required) volume of the sample, if it is a collection.
- iii. The manufacturer must provide information on the measurement time; how long does it take to get the result and what is the maximum time range for monitoring the parameter on the device (data storage size) or is it necessary to transfer the data to another computer, for which the exact data must be specified for the necessary connection/transfer.
- iv. It is necessary to define and specify the analytical performance characteristics of the biosensor device (detection limit, linearity, measurement range) which enable appropriate use and interpretation of the results. It is also important to note that post market surveillance is demanded during the entire life cycle of an IVD type of biosensor.

Analytical and clinical performances

Accuracy

Biosensors and wearable devices monitor biometric data, like blood pressure, heart rate and physical activity, as well as analytes such as glucose and electrolytes. They are factory calibrated by the manufacturer and the user cannot change the calibration. These sensors test body fluids other than blood. So, metrological traceability to a blood-based standard may not apply to fluid matrices, and a fluid-based standard has not been established for these devices. For example, continuous glucose monitors (CGM) measure glucose in interstitial fluid, while glucose meters measure capillary blood collected from fingersticks. Blood gas glucose sensors utilize arterial or venous samples, while central laboratory instrumentation requires venous plasma or serum for glucose testing. Laboratory glucose methods are metrologically traceable to a plasma-based standard with glucose analyzed by mass spectrometry. Whole blood

measured by blood gas glucose sensors can be linked to the same plasma standard by comparison to traceable laboratory glucose methods using the same sample set (whole blood analyzed by the blood gas instrument, centrifuged to separate plasma and analyzing plasma by the traceable laboratory method). However, CGM measures interstitial fluid and collecting sufficient interstitial fluid for laboratory analysis is not feasible. Hence, a head-to-head comparison using a matrix derived from the same specimens is not possible. CGM traceability is also challenged by the delay in equilibrium between glucose in the vascular system and interstitial spaces after a meal.

The US Food and Drug Administration recommends comparison of a venous sample analyzed by a traceable laboratory method to establish CGM accuracy [30]. However, the ease of capillary fingerstick collections and rapid analysis by glucose meters has also been utilized since CGM is a clinical replacement for glucose meters and current diabetes treatment protocols have been established using glucose meters. Alternatively whole blood analyzed by a YSI 2300 or YSI 2900 analyzer that has metrological traceability is also an option for establishing CGM accuracy. So, establishing traceability and accuracy of mobile health devices can be challenging. In the EU and in the IVDR metrological traceability of biosensor test results to higher order reference materials, methods and systems is demanded, if available. Calibration hierarchies that describe how to enable metrological traceability are described in ISO 17511:2020. Note that the metrology approach in the EU is different from the USA FDA approach where comparison to predicate devices is the norm.

Measurement uncertainty

A separate issue is defining allowable measurement uncertainty, according to ISO 17511. For conventional biomarkers, the Milan hierarchy describes how to deduce analytical performance specifications [31]. For CGM, until recently, minimum accuracy requirements have not been defined [32]. Allowable error limits have not been established for many mobile devices, and total allowable error limits may be different for biosensors compared to laboratory methods. Sensors not only generate data at a single point in time, but they also make frequent measurements, every several minutes, and can provide continuous data trends such as rate of change (rise or fall) over time. This allows for the ability to predict future events and alarm the wearer before the event occurs. CGM, for example, can warn the wearer of impending hypoglycemia and alarm before the patient

experiences a hypoglycemic event. This allows for intervention preventing potential harm. This ability of mobile devices to trend and alarm the wearer may allow a greater tolerance for bias compared to laboratory methods. Total allowable error limits for accuracy of biosensors will have to consider these factors for clinical outcome.

Precision

There are two considerations for defining precision of mobile devices and wearable sensors – within sensor variability (on the same individual) over the life of the sensor and between sensor variability (between 2 different sensors worn by an individual) over time. These two sensors may come from the same manufacturing lot or different lots and present with different precision. Variability can be measured by wearing two sensors (one on each arm for example) and determining the difference between the sensors over time. Because the sensors average results over time, some of the variability (and bias as well) may be smoothed as the device software calculates data trends. Comparison of biosensor results with a comparative method, like CGM to a glucose meter, can be confounding by variability in both methods. So, establishing true device variability is challenging and the wearer may be better defining how the results will be used in clinical decision-making to change treatment or lifestyle factors rather than comparing bias or variability to laboratory methods.

Quality control and EQA

Since biosensors are wearable devices, analyzing a control sample or testing a proficiency material is not possible by the end-user. Quality control and traceability of sensors is more the responsibility of the manufacturer and challenging to establish by the wearer of the device.

Interoperability, connectivity, data integration and safety

Data interpretation, transfer, security, and privacy

Sensors involves physical, network, and application layers [33]. Implementing biosensors in health systems requires understanding complex security challenges [6]. Data obtained by the sensors and devices can only be transferred to health records with patient's consent. In the data-transfer, the application programming interface (API), which makes the parts of software and application available to the outsiders and can share the data with the other software

and application developed by third parties [34, 35]. Under the security of systems and protection of patient's privacy, the data can be shared among such record systems (i.e., electronic health records [EHR] and personal health records [PHR]). The data should be easily interpretable and useful for health/medical care in the individual patient, facility, community and global situation. For the data-sharing systems, there are currently standardized formats such as DICOM (images) and HL7 FHIR (for instance, it is used in laboratory information systems) [34, 35]. The data for the sharing systems require assurance of compatibility and exchangeability among the measured data.

Validation of the sensor data collection system

In modern healthcare systems, sensor technologies can prove to be an integral part of processes such as improving efficacy and lowering the cost. For clinics and patients' day-to-day experiences, emerging biosensors can help prove to be potential help resulting in major improvements in care delivery system. In general, the appropriateness of using a particular product, can be measured by a term "validation" (e.g., validation of wristwatch measuring heart rate and temperature). Further, "GxP" is a generalized abbreviation for "good practice" and includes compliance to a set of codified quality guidelines, regulations, quality management systems, controls which have been developed into the various specializations for stakeholders such as manufacturers, industries, clinical trials (e.g., clinical trialists, manufacturers, laboratories). Validation is evaluating analytical and clinical performance claims mentioned in the Instructions for Use based on raw and derived measurement data of the sensor and algorithms.

The V3 qualification framework encompasses the following three steps of connected sensor technology: verification of the sensor technology, and validation of the analytical & clinical performance and the *fitness-for-clinical-purpose* of the biosensor. This three-stage process of verification, analytical and clinical validation (V3) proposed by Goldsack, Coravos, Bakker et al. accounts for the unique hardware, software, and algorithmic properties of connected biometric monitoring technologies (BioMeTs). However, it is always challenging to evaluate a connected sensor technology's data supply chain, the data flow and data provenance for information generated from hardware, sensors, software, and algorithms (31, 32).

Connectivity (wifi, bluetooth, NFC...)

Wireless technologies have made significant progress, and they are now being integrated into many mainstream

applications and medical devices. In particular, Bluetooth technology has now been utilised in a variety of medical applications ranging from home-healthcare devices to room equipment. Bluetooth well suited role for cable replacement and mobile connectivity. It is a relatively low-cost technology which also provides excellent security and reliability and coexists well with other wireless technologies. It also uses virtually no power and, because it doesn't travel far, are theoretically more secure than wireless networks. The first mobile device that incorporated both communication and computing features was the Blackberry, which was introduced in 2002. Subsequently, Apple and other smartphones based on the Google Android operating system were introduced for better functioning and desired outcome. Many developers, solution providers and government agencies utilised Bluetooth technology especially during COVID19 era to implement innovative solutions that helped managing the spread, accelerate reopening efforts, with safer treatment of patients during the disease outbreaks. Bluetooth enabled proximity warnings through phone app based technology to remind citizens and visitors to maintain safe distances has helped managing to reduce the risk of viral transmission. Thus, flexibility of Bluetooth technology and easy availability in our phones and devices is helped us to minimize the spread and enabled safe reopening [36, 37].

Interoperability

Recently, BLE (Bluetooth Low Energy) such as iBeacons or Beacons has become a recent alternative for Wi-Fi, especially in IoT devices. BLE are used to send data over short distances and found more suitable for transmitting small amounts of data at 1 Mbps, like sensor readings of temperature, acceleration details, GPS coordinates. However, BLE is not suited for sending data in real-time to a server. LE signals can be picked up by any Bluetooth 4.0 enabled devices. For Android devices, Version 4.3 or later would be perfect, while for Apple devices, the technology runs on Version 4S or later. Wi-Fi works on WLAN 802.11 a/b/g/n/ac devices. For Android devices, Version 4.0 or later is the preferred choice for Wi-Fi connectivity. Bluetooth devices have lower power consumption, but Wi-Fi devices consume more power, and for that reason broadcast range of both technologies is different. Both the technologies emit a signal with a frequency of 2.4 GHz. The iBeacon signals travels for about 30 feet, however Wi-Fi signals can travel over 10 times more distance. Thus, Wi-Fi requires 10 times more power than BLE, even if performing a similar task. Wi-Fi devices need considerable power, about 500 μ W for ten messages per day, while BLE consumes only 50 μ W [38–40] (Tables 1 and 2).

Security – cybersecurity

The user authentication is the process to keep a user's personal information confidential in digital devices. The management systems by identity are classified as the one-factor authentication (user knows), two-factor authentication (user must be) using one-time passwords (tokens), and three-factor authentication (user status) using biometrics such as iris scanners and voice recognition [34, 35]. There are currently several ways to guarantee data security. First, a single sign-on allows using the multiple systems with a single user authentication. It streamlines the access to EHR and other applications by eliminating the need to repeatedly enter the user's names and passwords manually [34, 35]. Second, a gateway security is a specialized device and/or software that protects the systems in a network from unauthorized intrusion, viruses, and other threats [34, 35]. Third, a firewall, which allows or denies the network communications, includes the basic style of 'packet filtering firewall' that can restrict access to specific Internet Protocol addresses (IP addresses) within an organization as well as the more protective style of 'stateful inspection firewall' that can check the complex correlations between internal and external IP address connections [35, 41–43]. Forth, a blockchain uses cryptography (e.g., digital signatures) to control data in a decentralized manner. The data are distributed among participants in blockchain, and since many participants keep a copy of everyone's transaction history, it is impossible to tamper with (even the service provider cannot tamper with or erase the data). Furthermore, there is the advantage that, even if some computers go down, the entire system does not go down.

User friendliness

Several aspects need to be considered [44–47].

Sensor design (small-size, lightweight, wearable, non-/light-invasive)

The Internet of Things (IoT) is an information carrier based on the Internet, traditional telecommunications networks. The information interaction between people and things is the core of the IoT. Radio frequency identification (RFID) is a significant and widespread application scheme for IoT systems. RFID is not only a communication for two-way between two objects, but also has a unique identifier and can be equipped with various sensing functions. The near-field communication (NFC) is developed based on RFID technology combined with wireless interconnection

Table 1: Bluetooth interface.

Features	Classic bluetooth	BLE
Power	Run time on AAA batteries is for days only	Run time is months on coin cell battery
Throughput	700 kbps-2.1 Mbps	100–800 kbps
Version	1.0 and beyond	4.0 and beyond
Frequency	2.40–2.485 GHz	2.40–2.485 GHz
Interface	FHSS, AFH, error detection, forward error correction, data retransmission	FHSS, AFH, error detection, data retransmission
Encryption	SAFER+ 128-bit	AES 128-bit
Network devices	8	Thousands
Output power	20 dBm	10 dBm

BLE, bluetooth low energy.

Table 2: Wireless communication and interface protocols in medical applications (as per IEEE – institute of electrical and electronics engineers).

Features	Bluetooth low energy (BLE)	Thread	Zigbee	WiFi
Frequency	2.4 GHz	2.4 GHz	2.4 GHz	2.4 GHz
Internet protocol version 6 (IPv6)	No	Yes	No	Yes
Bandwidth	1 MHz	2 MHz	2 MHz	22 MHz
Encryption	AES	AES	AES	WPA
Mesh networks	Yes	Yes	Yes	Yes

technology. It is also considered as a subset of RFID. NFC uses the 13.56 MHz frequency band for fast communication of short-distance devices.

Sensors are classified into location, physiological, image, inertial, environmental, binary and tags. Indoor location sensors include wearable and ambient sensors. Parylene-C has been widely used as a surface coating for various materials due to its excellent physical and chemical properties, such as superior flexibility, high transparency, easy preparation. It can be used as new wearable materials due to their ultra-thin, highly flexible, and easy-to-peel properties. A conductive polymer is an additional type of wearable material, which has been widely used in wearable sensors. Conductive polymers are different from conventional organic polymers, as they have high electrical conductivity, electron affinity and redox activity. A hydrogel is another type of wearable material. Like ionic liquids, hydrogels are typically conducted through ionic motion in a hydrated polymer matrix. The modulus of hydrogels may closely match human skin.

User engagement (convenient, stable, non-training, clearly aimed, easily interpreted data, secure, inexpensive)

User engagement means the strength of relationship between a user and a service as sensor and device

systems [35, 41–43]. As an example, the user engagement with a smartphone application is suggested as a user's emotional, cognitive, and behavioral experience. The engagement might be associated with clearly aimed, less trained, convenient, stable, easily interpreted, secure, and inexpensive characteristics of sensor and device systems.

Communication (data-sharing, interactive)

The wearable devices with wireless communication data transmission provide new capabilities for real-time monitoring and dynamic responses. Wireless communication technologies, such as RFID, NFC and Bluetooth, have been widely used for information transmission in wearable electronic devices. Peer-to-peer (P2P) communication is possible between NFC tags and smartphones. Wireless communication technology is required to seamlessly stream important information to the users.

Ultra-high-frequency RFID (UHF RFID) has a long transmission range, but the readers are very expensive (USD 1000–2000). UHF RFID is also more susceptible to environmental impacts, leading to losses.

Low-frequency RFID (LF RFID) has been commercially available for a long time with wide range of applications. The wireless communication of Bluetooth (3–200 m) has a greater read range and requires less power than NFC.

NFC are the better protocols for use in transmitting data from wearable sensors due to their low cost, low power consumption and portability. Thus, the goal of wireless communication technology is to transmit relevant and appropriate information data to the user or clinician in cost effective manners with no data loss.

Medical safety (alarming function, direction of emergency, attentive watch)

Sensor and device systems available to health/medical care should guarantee the user's medical safety. For instance, the systems with some functions of an alarm for adverse phenomena, a direction of emergency and an attentive monitoring seems to be applicable to the medical safety.

Sustainability and affordability

It is crucial to adopt technology contributing to sustainable healthcare and laboratory medicine [48, 49]. Sensors in healthcare have both positive and negative environmental impacts [50, 51]. On the one hand, they help healthcare professionals to monitor patients remotely and provide timely interventions, which can reduce the need for hospitalizations and travel, thereby reducing carbon emissions. On the other hand, the manufacturing and disposal of sensors can have negative environmental impacts due to the use of non-renewable resources and hazardous materials. Moreover, the energy consumption associated with sensor data storage and processing can contribute to greenhouse gas emissions. To address these issues, healthcare systems need to adopt sustainable practices that minimize the environmental impact of sensor use, such as using renewable energy sources, reducing waste generation, and adopting circular economy principles. Additionally, healthcare providers must implement sustainable procurement practices by considering the lifecycle of the products they purchase, including the environmental impact of sensors. By doing so, healthcare can reduce its negative impact on the environment and contribute to a sustainable future.

Finally, regional differences in the use and adoption of biosensors can create challenges for healthcare providers and developers. Different regions and countries may have different attitudes towards biosensors and may face different regulatory and legal hurdles. This can make it difficult to create a standardized approach to biosensors and may limit their overall adoption and impact.

Skills, competences, and education

Sensor's technologies are a major driver for productivity, competitiveness, and innovative capacity. Health, formerly reserved for the medical community, is becoming accessible to the public thanks to digital technology. It becomes possible to easily share the medical data. Access to health information via the Internet contributes to the construction of a form of empowerment and autonomy. Digital tools and connected objects with biosensors allow reactivity, participation, involvement, interactivity. They complement traditional media and can perform strategic functions in the service of the patient. Accessing, understanding, evaluating, and applying health information available on "virtual" media requires many skills.

While information and communication technologies have undeniable advantages for health, they also highlight digital divides, particularly in terms of access and use. The first is access and equipment, the second is usage. More and more people are going online to find answers to their questions. However, this requires the implementation of certain skills related to literacy in general but also specific to the use of this medium: reading, writing, navigating on a website, judiciously using a search engine, judging the reliability of information, sorting out the numerous pieces of information. Health literacy represents the knowledge, motivation, and skills to access, understand, evaluate, and apply health information; and then make judgments and decide about health care, prevention, and health promotion, with the aim of maintaining and promoting one's quality of life throughout one's existence" [52].

Digital literacy integrates the ability to locate, classify, understand, evaluate, and generate information, from the Internet, digital tools and information technologies. Digital health literacy is therefore at the crossroads of several literacies. It brings together under a single term the technological and intellectual skills and ethical behaviors that enable individuals to be autonomous and responsible in their professional and personal uses.

Facilitating access to digital media is not enough to increase the level of digital health literacy of users. It is important to think not only about technical accessibility but also about the content and presentation modes of health information. Populations with low levels of health literacy are also the most likely to seek information in this way, particularly by using a smartphone. Developing digital literacy involves strengthening critical thinking. Social networks and co-learning are essential for critical health literacy, based on qualitative evidence [53]. Social networks can support the development of this health literacy if

	Main issues/ Actions to be made	
Scientific validity	 - collect available peer reviewed literature/studies related to BS/BMD - for clinical use	
The intended use	 - for general health population and clinical use (healthcare devices) - monitor human physiological parameters in a continuous, real-time - monitor and manage chronic diseases - additional tool to “traditional” LM diagnostic systems (examination/tests/analysis)	
Benefits of biosensor-based diagnostic	 - simple, portable, and user-friendly (no need for trained personnel and specialized facilities) - cheaper equipment, - accessible, (receive diagnosis and treatment at the point of care) - providing real-time feedback on a patient's health status - continuously monitor vital signs (heart rate, blood pressure, and glucose levels) - reducing the need for hospitalizations - improved the quality of life/lowering complication/mortality/health risk (astronauts/ older travellers/chronic patients) - connectivity with digital ecosystem and electronic health records - early alerts and remote monitoring - data integration (from different sources)→ personalized risk/treatment	
The six dimensions to address the sensor qualification / critical for validation process	 The intended use in the care pathway, and evaluation of scientific validity, analytical and clinical performance claims - lack of comprehensive studies that demonstrate their long-term benefits IVDR 2017/746 compliance in case of medical biosensors Interoperability, connectivity, data integration and safety - lack of communication with/between different BS and associated devices - lack of communication across different healthcare systems User friendliness Affordability and sustainability - regional differences in the use and adoption - difficult to create a standardized approach Education and training	
Check-list for the six dimensions validation framework	1. Assessing regulatory compliance and specifications of BS/BMD - Valid/actual regulation (IVDR) - Explicit context of use - User interface / User experience - Device specification - Measurand 2. Analytical and clinical performance - Accuracy - Measurement uncertainty - Precision - Quality control and EQA 4. User friendliness - Sensor design - User engagement - Communication - Medical safety	3. Interoperability, connectivity, data integration and safety - Data interpretation, transfer, security and privacy - Validation of the sensor data collection system - Connectivity (wifi, Bluetooth, NFC) - Interoperability - Security- Cybersecurity 5. Affordability and sustainability - Minimize environment impact - Use of renewable and non-hazardous resources/materials - Lifecycle of the products 6. Education and training needs - Skills - Competences - Continue education
Legal aspects, liability and equity	- comply with data protection regulations (safeguard patient information) - liability (accuracy and reliability of the sensor-generated data) - autonomy and informed consent - equity and justice (data misuse, ensure that patients' rights and safety)	
Skills, competences and education	- accessing, understanding, evaluating and applying health information available on "virtual" media - digital health literacy of users (technological and intellectual skills and ethical behaviours) - importance of social networks - awareness: risk of fake information on the internet	

Figure 2: Methodological approach of validation/verification and data integration of biosensors (BS)/*in vitro* diagnostic devices (IVD): main issues and actions.

users master community tools. The concept of digital health literacy is part of the field of health promotion, which itself includes that of prevention, health education and therapeutic patient education [52].

The Figure 2 summarizes the main issues and actions for validation of biosensor technology for use in healthcare.

Ethical considerations

The use of sensors in healthcare has raised various legal and ethical issues that confront society. One of the major concerns is privacy and security. Sensor-generated data is personal and sensitive, and if mishandled or accessed by unauthorized persons, it could result in significant harm to patients. Therefore, healthcare providers must ensure that they comply with data protection regulations and implement adequate security measures to safeguard patient information [54].

Another legal issue is liability. Healthcare providers must be accountable for the accuracy and reliability of the sensor-generated data and the decisions made based on that data. In the case of medical malpractice, providers must be able to demonstrate that they have followed the standard of care and have taken reasonable precautions to prevent errors or negligence [55, 56].

From an ethical standpoint, the use of sensors in healthcare raises issues of autonomy and informed consent. Patients must be fully informed about the use of sensors, the data collected, and how it will be used to ensure that they have control over their own health information [57]. Additionally, the potential for data misuse or discrimination based on sensor-generated data raises ethical concerns related to equity and justice.

Furthermore, the use of sensors in healthcare also raises questions about the impact on the doctor-patient relationship. Sensors can provide a wealth of information that could potentially replace face-to-face interactions between patients and healthcare professionals. This shift in care delivery raises ethical concerns about the quality of care and patient-centeredness.

The use of sensors in healthcare requires careful consideration of legal and ethical issues to ensure that patients' rights and safety are protected while taking advantage of the benefits of this technology.

Conclusions

In conclusion, the development of a qualification framework for biosensors should be conceptually adopted

and extended to cover digitally measured biomarkers from biosensors for advancing healthcare and achieving more individualized patient management and better patient outcome. Experience from conventional laboratory biomarkers should be leveraged to enable appropriate comparison with conventional standards to understand data behavior and limitations. Likely performance criteria from conventional laboratory tests cannot be translated directly to biosensor-derived physiological and behavioral measures. However, as more digitally measured biomarkers are validated according to the V3 framework, we will be able to draw lessons to harmonize their performance criteria. It is also essential that biosensor developers transparently disclose, with sufficient level of detail, how raw data are acquired, processed, and digital results are calculated to determine if a biosensor is fit-for-clinical purpose. Although these sensors have great value and benefits, there are currently several open challenges that must be addressed before they can be widely adopted in clinical settings. These challenges include beyond verifying their analytical and clinical performances, ensuring efficient and secure connectivity, and meeting user needs and interface requirements.

Scientific societies, such as the IFCC, have a crucial role to play in developing a methodological framework that meets these challenges. By bringing together experts from a range of fields, these societies can ensure that the biosensor evaluation framework is comprehensive and effective. They can also promote collaboration between researchers, clinicians, and industry partners, which will be essential for advancing the field and accelerating the adoption of these sensors in clinical practice.

Ultimately, a qualification framework for biosensors will enable clinicians to make better informed decisions, improve patient outcomes, and reduce healthcare costs. By investing in this emerging biosensor field, laboratory specialists can pave the way for a future in which these sensors are widely available and integrated into routine clinical care.

Research ethics: Not applicable.

Informed consent: Not applicable.

Author contributions: The authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: The authors state no conflict of interest.

Research funding: None declared.

Data availability: Not applicable.

References

- Greaves RF, Kricka L, Gruson D, Martin H, Ferrari M, Bernardini S. Emerging technology: a definition for laboratory medicine. *Clin Chem Lab Med* 2022;61:33–6.
- Greaves RF, Bernardini S, Ferrari M, Fortina P, Gouget B, Gruson D, et al. Key questions about the future of laboratory medicine in the next decade of the 21st century: a report from the IFCC-emerging technologies division. *Clin Chim Acta* 2019;495:570–89.
- WHO. Low-cost sensors, 2019. Available from: <https://www.who.int/teams/environment-climate-change-and-health/air-quality-and-health/videos/mosaic/air-quality-management/low-cost-sensors>.
- WHO, merging trends and technologies: a horizon scan for global public health; 2022. Available from: <https://www.who.int/publications/i/item/9789240044173>.
- Haleem A, Javaid M, Singh RP, Suman R, Rab S. Biosensors applications in medical field: a brief review. *Sensors Int* 2021;2:100100.
- Mamdiwar SD, Akshith R, Shakruwala Z, Chadha U, Srinivasan K, Chang CY. Recent advances on IoT-assisted wearable sensor systems for healthcare monitoring. *Biosensors* 2021;11:372.
- McGrath MJ, Scanail CN. Regulations and standards: considerations for sensor technologies. In: *Sensor technologies*. Berkeley, CA: Apress; 2013. https://doi.org/10.1007/978-1-4302-6014-1_6.
- Seshadri DR, Li RT, Voos JE, Rowbottom JR, Alfes CM, Zorman CA, et al. Wearable sensors for monitoring the physiological and biochemical profile of the athlete. *Npj Digit Med* 2019;2:1–16.
- Ramesh M, Janani R, Deepa C, Rajeshkumar L. Nanotechnology-enabled biosensors: a review of fundamentals, design principles, materials, and applications. *Biosensors* 2023;13:40.
- Sempionatto JR, Lasalde-Ramírez JA, Mahato K, Wang J, Gao W. Wearable chemical sensors for biomarker discovery in the omics era. *Nat Rev Chem* 2022;6:899–915.
- Holzer R, Bloch W, Brinkmann C. Continuous glucose monitoring in healthy adults—possible applications in health care, wellness, and sports. *Sensors* 2022;22:2030.
- Elsayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. Summary of revisions: standards of care in diabetes—2023. *Diabetes Care* 2023;46:S5–9.
- Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. *Lancet* 2016;388:2254–63.
- Haak T, Hanaire E, Ajjan R, Hermanns N, Riveline JP, Rayman G. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicenter, open-label randomized controlled trial. *Diabetes Therapy* 2017;8:55–73.
- Dunn TC, Xu Y, Hayter G, Ajjan RA. Real-world flash glucose monitoring patterns and associations between self-monitoring frequency and glycaemic measures: a European analysis of over 60 million glucose tests. *Diabetes Res Clin Pract* 2018;137:37–46.
- Parkin CG, Graham C, Smolskis J. Continuous glucose monitoring use in type 1 diabetes: longitudinal analysis demonstrates meaningful improvements in HbA1c and reductions in health care utilization. *J Diabetes Sci Technol* 2017;11:522–8.
- Grunberger G, Sherr J, Allende M, Blevins T, Bode B, Handelsman Y, et al. American association of clinical endocrinology clinical practice guideline: the use of advanced technology in the management of persons with diabetes mellitus. *Endocrine Practice* 2021;27:505–37.
- Battellino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care* 2019;42:1593–603.
- Beck RW, Connor CG, Mullen DM, Wesley DM, Bergenstal RM. The fallacy of average: how using HbA1c alone to assess glycemic control can be misleading. *Diabetes Care* 2017;40:994–9.
- Heinemann L, Freckmann G, Ehrmann D, Faber-Heinemann G, Guerra S, Waldenmaier D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. *Lancet* 2018;391:1367–77.
- Dahiya T, Yadav S, Yadav N, Mann A, Sharma M, Rana JS. Monitoring of BNP cardiac biomarker with major emphasis on biosensing methods: a review. *Sensors Int* 2021;2:100103.
- hui H, Gopinath SCB, Ismail ZH, Chen Y, Pandian K, Velusamy P. Cardiovascular biomarker troponin I biosensor: aptamer-gold-antibody hybrid on a metal oxide surface. *Biotechnol Appl Biochem* 2023;70:581–91.
- Tannenberg R, Paul M, Röder B, Gande SL, Sreeramulu S, Saxena K, et al. Chemiluminescence biosensor for the determination of cardiac troponin I (cTnI). *Biosensors* 2023;13:1–20.
- Khanmiri HH, Yazdanfar F, Mobed A, Reza Mohammadi F, Rahmani M, Haghighi T. Biosensors; noninvasive method in detection of C-reactive protein (CRP). *Biomed Microdevices* 2023;25:1–10.
- Heidt A. Wearable biosensor measures fertility hormones in sweat. *Nature* 2023. <https://doi.org/10.1038/d41586-023-03812-x>.
- Rafiq A. Space crew health monitoring. In: *Wireless sensor and mobile ad-hoc networks vehicular and space applications*. Austria: Springer; 2015:149–60 pp.
- Sabry F, Eltaras T, Labda W, Alzoubi K, Malluhi Q. Machine learning for healthcare wearable devices: the big picture. *J Healthc Eng* 2022;2022.
- Goldsack JC, Coravos A, Bakker JP, Bent B, Dowling AV, Fitzer-Attas C, et al. Verification, analytical validation, and clinical validation (V3): the foundation of determining fit-for-purpose for biometric monitoring technologies (BioMeTs). *Npj Digit Med* 2020;3:1–15.
- FDA. Silver spring (MD): food and drug administration (US); Bethesda, MD: National Institutes of Health (US). BEST (Biomarkers, Endpoints, and other Tools) Resource. BEST (Biomarkers, Endpoints, and other Tools); 2016. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK326791/>.
- Federal register. Medical devices; clinical chemistry and clinical toxicology devices; classification of the integrated continuous glucose monitoring system; 2022. Available from: <https://www.federalregister.gov/documents/2022/02/18/2022-03504/medical-devices-clinical-chemistry-and-clinical-toxicology-devices-classification-of-the-integrated>.
- Braga F, Panteghini M. Performance specifications for measurement uncertainty of common biochemical measurands according to Milan models. *Clin Chem Lab Med* 2021;59:1362–8.
- Freckmann G, Pleus S, Grady M, Setford S, Levy B. Measures of accuracy for continuous glucose monitoring and blood glucose monitoring devices. *J Diabetes Sci Technol* 2019;13:575–83.
- Aivaliotis V, Tsantikidou K, Sklavos N. IoT-based multi-sensor healthcare architectures and a lightweight-based privacy scheme. *Sensors* 2022;22:4269.

34. Gordon WJ, Patel V, Thornhill W, Bates DW, Landman A. Characteristics of patients using patient-facing application programming interface technology at a US health care system. *JAMA Netw Open* 2020;3:e2022408.
35. Margheri A, Masi M, Miladi A, Sassone V, Rosenzweig J. Decentralised provenance for healthcare data. *Int J Med Inform* 2020;141:104197.
36. Kirthika B, Prabhu S, Visalakshi S. Android operating system: a review; 2015. Available from: https://www.researchgate.net/publication/327387842_ANDROID_OPERATING_SYSTEM_A_REVIEW.
37. Laricchia F. Global connected wearable devices 2016–2022; 2023. Statista. Available from: <https://www.statista.com/statistics/487291/global-connected-wearable-devices/>.
38. Rupareliya K. Bluetooth and bluetooth low energy: definitions, use cases, benefits – business of apps; 2021. Available from: <https://www.businessofapps.com/insights/bluetooth-and-bluetooth-low-energy-definitions-use-cases-benefits/>.
39. Jeon KE, She J, Soonsawad P, Ng PC. BLE beacons for internet of things applications: survey, challenges, and opportunities. *IEEE Internet Things J* 2018;5:811–28.
40. Techopedia. What is a wireless local area network (WLAN)? – Definition from techopedia; 2023. Available from: <https://www.techopedia.com/definition/5107/wireless-local-area-network-wlan>.
41. Thomas PA, Mathew KP. A broad review on non-intrusive active user authentication in biometrics. *J Ambient Intell Humaniz Comput* 2023;14:339–60.
42. Gellert GA, Ramirez R, Jacobs WJ, Maciaz G. Electronic health record workstation single sign-on: a quantification of time liberated for nurses to care for patients. *J Nurs Adm* 2020;50:462–7.
43. Kruse CS, Smith B, Vanderlinden H, Nealand A. Security techniques for the electronic health records. *J Med Syst* 2017;41:1–9.
44. Kamišalić A, Fister I, Turkanović M, Karakatić S. Sensors and functionalities of non-invasive wrist-wearable devices: a review. *Sensors* 2018;18:1714.
45. Yu D, Fan K, Zhang H, Monteiro D, Xu W, Liang HN. PizzaText: text entry for virtual reality systems using dual thumbsticks. *IEEE Trans Vis Comput Graph* 2018;24:2927–35.
46. Yoon H, Park SH. A non-touchscreen tactile wearable interface as an alternative to touchscreen-based wearable devices. *Sensors* 2020;20:1275.
47. Spaulding EM, Marvel FA, Piasecki RJ, Martin SS, Allen JK. User engagement with smartphone apps and cardiovascular disease risk factor outcomes: systematic review. *JMIR Cardio* 2021;5:e18834.
48. Molero A, Calabrò M, Vignes M, Gouget B, Gruson D. Sustainability in healthcare: perspectives and reflections regarding laboratory medicine. *Ann Lab Med* 2021;41:139–44.
49. Eflm Task Force Green & Sustainable Laboratories; 2023. Available from: <https://greenlabs.eflm.eu>.
50. Haghi M, Danyali S, Ayasseh S, Wang J, Aazami R, Deserno TM. Wearable devices in health monitoring from the environmental towards multiple domains: a survey. *Sensors* 2021;21:1–24.
51. Bansal S, Singh K, Sarkar S, Pandey PC, Verma J, Yadav M, et al. Environmental impact of sensing devices. In: *Smart nanostructure materials and sensor technology*. Austria: Springer; 2022:113–37 pp.
52. Sørensen K, Van Den Broucke S, Fullam J, Doyle G, Pelikan J, Slonska Z, et al. Health literacy and public health: a systematic review and integration of definitions and models. *BMC Public Health* 2012;12:1–13.
53. Levin-Zamir D, Bertschi I. Media health literacy, eHealth literacy, and the role of the social environment in context. *Int J Environ Res Public Health* 2018;15:1643.
54. Dhirani LL, Mukhtiar N, Chowdhry BS, Newe T. Ethical dilemmas and privacy issues in emerging technologies: a review. *Sensors* 2023;23:1151.
55. European Commission – Expert Group on Liability and New Technologies – New Technologies Formation. Liability for artificial intelligence report from the expert group on liability and new technologies-new technologies formation; 2019. Available from: https://www.europarl.europa.eu/meetdocs/2014_2019/plmrep/COMMITTEES/JURI/DV/2020/01-09/AI-report_EN.pdf.
56. Janiszewska-Kiewra E, Podlesny J, Soller H. Ethical data usage in an era of digital technology and regulation. McKinsey & Company; 2020. Available from: <https://www.mckinsey.com/capabilities/mckinsey-digital/our-insights/tech-forward/ethical-data-usage-in-an-era-of-digital-technology-and-regulation>.
57. Gruson D. La notion de « Garantie Humaine » de l'IA renforcée dans le projet de loi de bioéthique après le passage au Sénat; 2020. Available from: <https://managersante.com/2020/02/24/pourquoi-fallait-il-renforcer-la-garantie-humaine-de-lia-dans-le-projet-de-loi-bioethique-au-senat-reponses-de-david-gruson-et-judith-meh/>.