Transforming Healthcare Technologies with Wearable, Implantable, and Ingestible Biosensors and Digital Health

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Abstract

Remote monitoring and ubiquitous digital health systems are becoming pervasive among patients and healthcare practitioners. With the explosion of the amount of digital data from such systems, and the ability to analyze and glean insights at large scales, there is substantial demand for innovative sensor technology that would be unobtrusive, highly precise, and easy to use. Digital health systems can provide vital information to healthcare professionals when critical clinical events occur. Accurate and high signal-to-noise ratio measurements are indispensable in this regard. As a secondary yet essential attribute, ease of use is necessary for such systems, especially for unskilled or elderly patients. Ultimately, whether critical or chronic monitoring, the intended clinical application will drive the requirement for different sensor technologies and biosensors' embodiments in medical devices. Wearable, implantable, or ingestible biosensors accordingly serve applications requiring different combinations of a trade-off between accurate and timely monitoring and long-term ease of use. This chapter describes the diseases that have the most critical need for innovation in biosensor systems, the essential components required for such systems, and how they are integrated into healthcare service delivery. It will further describe the types of considerations

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needed as we transition from designing wearable to ingestible and finally implantable biosensors in the order of their potential risk of harm to the patient. Finally, it explains the intricacies of an end-to-end solution that includes devices, data integration, and analytical capabilities needed to transform healthcare technology.

Keywords

Wearables · Ingestibles · Wireless electronics · Biosensors · Healthcare

8.1 Introduction

Digital health was first described by Seth Frank (Frank 2000). At the time, it was perceived as an internet-connected group of applications and media that could connect patients with commerce. However, recently both the WHO (WHO 2019) and the FDA (FDA 2020) have evolved the definition of digital health to include several healthcare aspects, including telemedicine, genomics, artificial intelligence, wearable medical devices, and mobile applications. eHealth (electronic Health) and mHealth (mobile Health) have been topics of extensive research over the past two decades. The inclusion of these technologies in digital health by both the WHO and FDA marks a transition to clinical adoption of these technologies and the vital role that digital health will play in the future of healthcare.

8.1.1 Digitization of Patient Data

8.1.1.1 The Electronic Health Record (her) and Electronic Medical Record (EMR)

Before the emergence of EHR and EMRs, the accumulation of longitudinal data required for causal inference in epidemiological research was demanding in time and resources. EHRs now allow collation of information across different modalities, including unstructured text data, claims information from payors, and quantitative results inclusive of vital statistics and lab results for each patient over the entire continuum of care (Casey et al. 2016). Recent studies show that EHR adoption continues to grow in the United States (Adler-Milstein et al. 2017).

Decision support tools are an essential part of EHR systems. They have been proven to reduce the likelihood of errors with drug allergies, drug–drug interactions, and drug dosing errors (Atasoy et al. 2019). EHRs are also set up through interoperability standards to accept data from additional sources like mHealth devices, capturing time series longitudinal data. These independent and significant data sources are ideally suited for the development of novel decision support tools leveraging the latest advances in machine learning (ML) and artificial intelligence (AI), such as natural language processing (NLP), AI-based classification, and image segmentation algorithms used in radiology.

8.1.1.2 Smart Devices, Social Networks, Wearables, and Internet Applications

In 2016 alone, global smartphone sales reached close to 1.5 billion, one for every fifth person on earth (Carton et al. 2018). An additional source of digital health data is personal devices, patient interactions on social media, and internet applications. Social support, self-care, and psychological health are known to produce better outcomes for patients. It can be a critical addition to the standard of care (Lin and Kishore 2021). There are several consumer devices by companies like Apple Inc., Fitbit (currently owned by Google Inc.), and Samsung in the market with form factors like wrist-worn, ring, and necklace-style, which can collect physiological data like heart rate and photoplethysmography. Data from the Apple Watch device have been used to detect atrial fibrillation (Perez et al. 2019). However, they must be used with care as recommended by Seshadri et al. (2020).

The evolution of biosensor technology coupled with the pervasive use of digital records in US hospitals has created the opportunity for novel analytics that could provide more specific and sensitive clinical decision support for clinicians. Therefore, there is a critical need for devices that are noninferior and on par with traditional medical devices used in hospital settings.

8.1.2 Common Diseases in Need of Novel Biosensor Systems

Over the past decades, researchers have proposed several novel devices and systems for the diagnostics therapeutics and theranostics of diseases such as cardiovascular diseases (CVDs), cancer, Alzheimer's disease (AD), and multiple sclerosis (MS). Biosensors can play a crucial role in improving the timeliness and efficiency of clinical management of these diseases and improving the overall quality of life for patients.

8.1.2.1 Cardiovascular Diseases (CVD)

Globally, the leading causes of mortality and disability are ischemic heart disease and stroke (Roth et al. 2020). The prevalence and mortality of CVDs have increased from 271 million to 523 million and 12.1 million to 18.6 million, respectively, from 1990 to 2019. In the United States, a conservative projection by Pearson-Stuttard et al. (2016) estimated that the total coronary and stroke deaths by 2030 will increase by ≈18% and 50%, respectively. Total costs (direct and indirect costs) of CVD were estimated to be $555 billion in 2015. These costs are expected to double to $1.1 trillion by 2035.

Acute coronary syndrome (ACS) is a class of CVD that includes myocardial infarction (MI) and unstable angina. MI is further divided into ST-segment elevated MI (STEMI) and non-ST elevated MI (N-STEMI). STEMI indicates complete blockage of the coronary artery, whereas N-STEMI indicates partial blockage. Both STEMI and N-STEMI result in heart muscle damage, which in turn produces biomarkers that can be detected. Unstable angina means that clots are formed but not large enough to cause blockages, so heart muscle damage may not occur (Ouyang

et al. 2021). CVDs are the most prevalent cause of mortality. They have received the most attention in terms of the development of novel devices. Examples of these devices are described in Sect. 1.3.

8.1.2.2 Cancer

Cancer is the abnormal growth of groups of cells. It can start in any organ and spread to any part of the body. It is benign if it does not spread and metastasized if it has begun to spread. There are several subtypes of cancer classified based on which organ system is affected or where it originates. Globally, cancer is the second leading cause of death, with 9.6 million deaths as of 2018. In terms of mortality, the leading types of cancer are lung, colorectal, stomach, and breast (Collaboration GBoDC 2019). In 2017, the cost burden of cancer was $177 billion in the United States.

The progression of cancer is stratified into stages, and the treatment plans are formulated depending on the stage of cancer. Biomarkers for cancer play an essential role in the potential for early detection and formulation of prognosis for cancer. Early diagnosis of cancer before it manifests clinically can significantly improve survival rates. The estimated cost savings among the leading cancer subtypes by incidence, breast, lung, prostate, and colorectal cancers, and melanoma could be as high as $67 billion (Kakushadze et al. 2017).

8.1.2.3 Alzheimer's Disease

AD is a neurodegenerative disorder that manifests as the gradual loss of memory and mental function, also known as dementia. Globally, AD is the leading cause of dementia (DeTure and Dickson 2019). Over the past decades, researchers have gathered evidence to show that the leading causes for AD are the accumulation of extracellular formation of beta-amyloid plaques or amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles of hyperphosphorylated tau protein in the brain. There are no known cures for AD. There is a critical need for an early diagnostic tool for managing AD and providing the best quality of life for patients (Carneiro et al. 2020).

8.1.2.4 Multiple Sclerosis

MS is a chronic neurological disease that falls under the category of autoimmune diseases in which the myelin sheath that insulates individual nerves is gradually depleted by the patient's own immune response. MS is predominantly diagnosed in patients 20–40 years of age. The economic burden of this disease has high indirect costs as the progression of the disease in young populations results in fatigue, pain, paralysis, double vision, and inability to perform studies and work (García-Domínguez et al. 2019). Several advancements have been made in treating MS, and early diagnosis is vital to the long-term management of this disease.

8.1.2.5 Viral Infections

Over the last few decades, several viruses have emerged and spread to the scale of epidemics or pandemics. Some examples are human immunodeficiency virus (HIV), avian influenza (AIV), Zika, human papillomavirus (HPV), Chikungunya virus

(CHIKV), rabies virus (RABV), Japanese encephalitis, and human norovirus. Historically, the mortality associated with viral infections has been low compared to other noncommunicable diseases. However, rare occurrences can lead to substantial mortality and infection rates, such as the severe acute respiratory syndrome caused by the novel coronavirus SARs-CoV-2 in 2019. Public policy decisions on containment and management of outbreaks of this nature require accurate infection rates and assessments of populations affected. There is a dire need for advancements in biosensor systems with high accuracy, low complexity, fast response, and low cost to address such crises promptly (Saylan et al. 2019).

8.2 Biosensor Systems

Biosensor systems have several embodiments depending on the application. The broad categories are point-of-care (POC), wearable, implantable, and ingestible devices. Biosensor devices consist of a biorecognition element and a transducer, which can be used to detect the presence of a biomarker for the diagnosis of specific disease conditions.

8.2.1 Biosensor System as a Medical Device

Biosensor systems can be categorized as invasive and noninvasive types. Invasive includes point-of-care technology (POCT) devices that require any incision or blood draw to extract a sample, as well as implantable and ingestible devices. Noninvasive includes POC devices that use any external body fluids and wearables. Figure 8.1 illustrates the categorization of biosensors.

8.2.1.1 Point-of-Care

POC diagnostics has emerged as a fast, portable, and cost-effective method for the early detection and diagnosis of several debilitating diseases. POC devices consist of three components—a biorecognition element, a transducer, and an amplifier or output conditioner that presents the measurement, qualitative or quantitative. POC devices detect biomarkers of four types: genomic, transcriptomic, proteomic, and metabolomic. Researchers over the past several decades have developed several transduction techniques. Electrochemical transduction remains the most commonly used. One of the most successful uses of electrochemical-based biosensors is in POC glucose monitoring. Mahato et al. provide a comprehensive history of the evolution and current state-of-the-art electrochemical biosensors (ECBs) (Mahato and Wang 2021).

Table 8.1 summarizes some of the recent advances in POC biosensor technology for the common diseases described in Sect. 1.2. An exhaustive list of biomarkers for multiple conditions is beyond the scope of this chapter, so a summary is provided. A substantial body of work in detecting viral infections is based on ECBs (Goud et al. 2021; Khan et al. 2020).

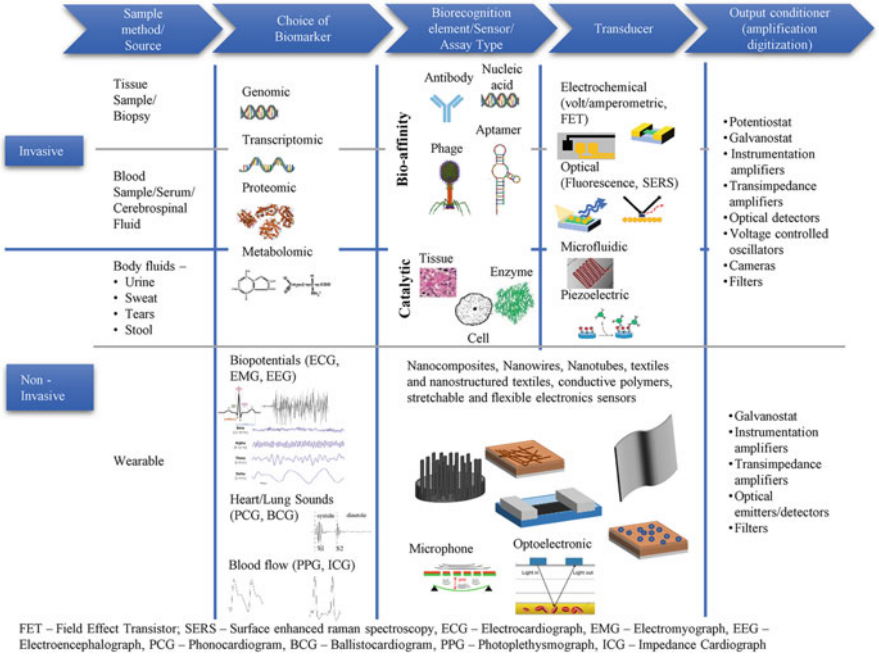

Fig. 8.1 Types of biosensor systems and their subcomponents

An emerging mechanism in the operation of ECB is direct electron transfer (DET). DET-based ECB is gaining attention because it does not require leachable mediators, and they are active in the same redox potential window as the biorecognition elements (Goud et al. 2021).

8.2.1.2 Implantable Devices

Implantable devices are widely used in the treatment of cardiac diseases. Pacemakers, implantable cardioverter defibrillators (ICDs), cardiac resynchronization therapy—biventricular pacemaker (CRT-P), and cardiac resynchronization Therapy—defibrillator (CRT-D) devices are the most prevalent types. They are used to assess and treat different cardiac diseases ranging from arrhythmia to heart failure with a high risk of sudden cardiac death. In heart failure patients, ambulatory pressure measurement at the pulmonary artery using an implantable wireless pressure sensor has been proven to improve clinical management by reducing the risk of re-hospitalization (Desai et al. 2017).

Several promising implantable technologies are under development and have reached the stage of bench validation on animal models. Researchers using pulse transit time directly measured blood pressure on an artery, and Fiala et al. validated this on animal models (Fiala et al. 2013). Vennemann et al. recently described blood flow sensors with the ability to gather data on a patient's smartphone (Vennemann et al. 2020). Marlan et al. described real-time monitoring of lung tumor hypoxia

Table 8.1 Common diseases and the biomarkers associated with diagnostic, prognostic, or therapeutics

Disease	Disease subtype	Diagnostic/ prognostic/ therapeutic	Embodiment of device	Required biosample	Biomarker	Detection mechanisms/operating principle and biomarker
Cancer	Breast cancer (Sharifi et al. 2020; Ranjan et al. 2020; Falkowski et al. 2021)	Diagnostic	POCT	*Tumor* BRCA1/BRCA2, HER-2, EGFR, KRAS *Blood* BRCA1/BRCA2, KRAS, miR-21, miR-155, miR-222 *Serum* HER-2, CA, CEA, PR, ER, p53 *Urine* ER, PR, CEA	CEA, BRCA1/BRCA2, EGFR, KRAS, HER-2, CA, miR-21, miR-155, miR-222	*Surface plasmon resonance (SPR)* CEA, miR-122, PSA, CA125, HER-2, 5LOX, collagen IV *Differential pulse voltammetry (DPV)* miR-155, HER-1, HER-2, CA 15–3, CA125, miR- 21, CEA, CA242, BRCA1, H1047R, VEGFR2 *Microfluidic* EGFR2, glypican-1, CA15–3, CA125, CEA, ErbB2, PTK7, HER-2, PSA, IgG, AFP *Electrochemical impedance spectroscopy (EIS)* HER-1, CA125, miR34a, miR-155, p53 *Cyclic voltammetry (CV)* HER-1, HER-2, HER-3 *Square wave voltammetry (SWV) and linear sweep voltammetry (LSV)* CA242, CA125, p53, miR-21, miR-155, HER-2, IL6, CA15–3 *Amperometry* CA242, CA125, miR, TP53, CD9, CD24, CD44, CD54, CD63, CD81, CD326, CD340, p53 *Capacitive* HER-4, CA19–9 *Electrochemiluminescence* CA15–3, MUCIN-1, CA19–9 *Field effect transistor (FET)* miR-155, HER-1, HER-2, CA125 *Chronocoulometric* miR-21, CA15–3, p53, HER-2, BRCA1 *Fluorescence* CYPIA-1, miR-21, mRi-1246, p53
		Prognostic	POCT		HER-2, BRCA1/BRCA2, ER, PR, Ki67, p53, HSP, GIPC-1, c-myc, c-myb, cyclin D1, cyclin B1, RS/ DJ-1, oncotype DX RS, CK, miR-148, miR-210, miR-21, miR-221, and miR-652.	
		Therapeutic	POCT		HER-2, BRCA1/BRCA2, ER, PR, CA, Ki67, miR-21, and CTC	

(continued)

Table 8.1 (continued)

Disease	Disease subtype	Diagnostic/ prognostic/ therapeutic	Embodiment of device	Required biosample	Biomarker	Detection mechanisms/operating principle and biomarker
	Lung cancer (Yang et al. 2019)	Diagnostic	POCT	*Tumor* EGFR *Serum* CA125, NSE, CYFRA21-1, TPA	NSE, SCCA, TPA	*Electrochemical* NSE, CYFRA21-1, SCCA, CA 125, TPA, VEGF *Optical* NSE, CYFRA21-1, CEA, SCCA, CA 125 *FET* CA 125
		Prognostic	POCT		CYFRA21-1, CEA	
		Therapeutic	POCT		VEGF, EGFR	
	Colorectal cancer (Zhang et al. 2021; Falkowski et al. 2021; Shirafkan et al. 2018)	Diagnostic	POCT	*Tumor* EGFR, IL-6 *Blood* MUC1 *Serum* CEA, CA199, IL-6, p53, miR-92a/miR-29a, let-7 g/miR-21/ miR-31/miR-92a / miR-181b/miR-203 *Urine* P53 *Stool* miR-451, miR-223/miR-92a	CEA, CA199	*Electrochemical* CEA, CA199, MUC1, IL-6, p53, KRAS *Surface plasmon resonance (SPR)* CEA
		Prognostic	POCT		CA199, IL-6, p53, KRAS	
		Therapeutic	POCT		MUC1, p53, miR-143, miR-145	
Alzheimer's disease (Carneiro et al. 2020)	–	Diagnostic	POCT/assay	*Serum* Aβ42, tau protein, ApoE, ApoE4 *Plasma* Tau protein, ApoE *Buffer*	Aβ42, tau protein, ApoE, ApoE4	*Electrical conductance* Aβ42 *Differential pulse voltammetry (DPV)* Aβ42 *Electrochemical impedance spectroscopy (EIS)*

				Aβ42, tau protein, ApoE, ApoE4 *Cerebrospinal fluid (CSF)* Aβ42 *Brain tissue sample* Aβ42		Aβ42, tau protein *Square wave voltammetry* Aβ42, Aβ42/Aβ40 *Surface plasmon resonance (SPR) and localized SPR* Tau protein, Aβ42/Aβ40/tau protein *Linear sweep voltammetry (LSV)* Aβ42/Aβ40
Multiple sclerosis (MS) (Can Demirdöğen 2021)	–	Diagnostic/ prognostic	POCT	*Serum* MS-specific antibodies, miR-145, miR-422/miR-223/ miR-126/miR-23a, anti-myelin basic protein (MBP) autoantibody *Cerebrospinal fluid (CSF)* Anti-myelin basic protein (MBP) autoantibody	Interleukin-12 (IL-12), MBP, MS-specific autoantibodies, miR-145, miR-17, miR-422, miR-223, miR-126, miR-23a	*EIS* IL-12, matrix metalloproteinase-9 (MMP-9) *AC impedance measurement* Myelin basic protein *Cyclic (CV) and square wave voltammetry (SWV)* MS-specific autoantibodies, anti-MBP autoantibody *SPR and localized SPR* MS-specific autoantibodies, miR-422/ miR-223/miR-126/miR-23a *Fluorescence spectrophotometer* miR-145
Cardiovascular diseases (Ouyang et al. 2021)	Risk of CVD	Prognostic	POCT	*Serum/plasma*	cTnI, BNP, TNF-α, SAA, IL-6, fibrinogen	*Field effect transistor (FET)*
	Acute myocardial infarction (AMI)	Diagnostic	POCT	*Serum*	cTnI/Myo/CK-MB, cTnI/h-FABP/copeptin	*Surface-enhanced raman spectroscopy (SERS)* cTnI/Myo/CK-MB *Chemiluminescence* cTnI/h-FABP/copeptin
	Cardiorenal syndrome (CRS)	Diagnostic	POCT	*Plasma*	cTnI/NT-proBNP/NGAL	*SPR and localized SPR*
	Myocardial infarction (MI)	Diagnostic	POCT	*Diluted serum*	cTnI/CK-MB	*Near-infrared enhanced fluorescence*

(continued)

Table 8.1 (continued)

Disease	Disease subtype	Diagnostic/ prognostic/ therapeutic	Embodiment of device	Required biosample	Biomarker	Detection mechanisms/operating principle and biomarker
	Heart failure (HF)	Diagnostic	POCT	*Diluted serum*	BNP/ST2	*Fluorescence*
Viral infections (Goud et al. 2021; Khan et al. 2020)	HPV	Diagnostic	POCT	*Serum/blood* Anti HPV-16-L1: anti-HPV complex, DNA, PT DNA	Anti-HPV-16-L1:anti-HPV complex, DNA	*SWV* Anti-HPV-16-L1:anti-HPV complex, DNA
	HBV	Diagnostic	POCT	*Serum/blood* HBsAb, peptide aptamers, RNA aptamer, DNA	HBsAb, peptide aptamers, RNA aptamer, DNA	*DPV* RNA aptamer, DNA *EIS* *Peptide aptamers*
	HIV-1	Diagnostic	POCT	*Serum/blood* RNA aptamer, HIV-1 p24 capsid protein	RNA aptamer, HIV-1 p24 capsid protein	*FET* RNA aptamer, HIV-1 p24 capsid protein *EIS* Antibody *DPV* RNA aptamer
	Zika	Diagnostic	POCT	*Serum/blood* ZIKV-specific envelop protein antibody, ZIKV-NS1 antibody, antigen ZIKV-derived proteins, aptamer	ZIKV-specific envelop protein antibody, ZIKV-NS1 antibody, aptamer, antigen ZIKV-derived proteins	*EIS* Aptamer, ZIKV-NS1 antibody, antigen ZIKV-derived proteins *SWV* Antigen ZIKV-derived proteins *DPV* Aptamer
	Avian influenza virus	Diagnostic	POCT	*Serum/blood* Antibody horseradish peroxidase–streptavidin conjugate, DNA aptamer (H5N1)	Antibody horseradish peroxidase–streptavidin conjugate	*DPV* DNA aptamer (H5N1)

	COVID	Diagnostic	POCT	*Serum* S-RBD protein, IgG, nucleocapsid phosphoprotein of SARS-CoV-2 *Nasal secretion and saliva* S-RBD protein *Blood/saliva* Viral antigen nucleocapsid protein/IgM/IgG/ C-reactive protein *Saliva* Nucleocapsid protein, (nCovid-19Ab)/SPE, SARS COVID antibody	S-RBD protein, IgG, nucleocapsid phosphoprotein of SARS-CoV-2, IgM, C-reactive protein, SARS COVID antibody	*Chronoamperometry* S-RBD protein, viral antigen nucleocapsid protein/IgM/IgG/C-reactive protein, SARS COVID antibody *EIS* S-RBD protein, IgG *Voltammetry/CV* SARS COVID antibody

using a microfabricated oxygen sensor (Marland et al. 2020). Researchers have also described implantable sensors for multifunctional multianalyte sensing and delivery of drugs or chemicals (Wang et al. 2020). Implantable glucose sensors have reached a commercial stage, and clinical validation is ongoing (Kropff et al. 2017).

Pressure measurements in different organs and blood vessels such as the brain, eye, pulmonary artery, bladders, and orthopedic implants would be valuable for the assessment of several diseases and conditions. The assessment and care for traumatic brain injury, hypertension, heart failure, glaucoma, hydrocephalus, and orthopedic implant effectiveness can be improved by offering greater insight to clinicians. Traditional implantable devices require surgery to implant and then are removed after the desired monitoring period has elapsed. Bioresorbable devices are an emerging technology that could obviate the need for removal. These devices are constructed using materials that biofluids can consume over a pre-defined duration of time. Shin et al. have demonstrated a bioresorbable pressure sensor intended for monitoring healing and chronic diseases (Shin et al. 2019). They used a thermally grown SiO_2 layer to encase the sensor. Si and SiO_2 materials have a slow dissolution rate dependent on the thickness of the layer, temperature, and pH. A Si nanomembrane is used as a piezoelectric sensing element in most pressure sensing applications (Mohankumar et al. 2021). Yang et al. recently described a wax encased pressure sensor using a Si-nanomembrane for sensing intracranial pressure (Yang et al. 2020).

8.2.1.3 Wearable Devices

Wearable devices described in the literature fall under two categories: *clothing and accessory wearables*—sensors integrated into clothing or other accessories such as gloves, watches, armbands, rings, chest straps, headbands, or helmets, or jewelry such as necklaces, and *skin integrated wearables*—sensors integrated into adhesive patches or tattoo-based printable embodiments. The wearables that belong to the first category most often measure heart rate, galvanic skin response, electrocardiogram (ECG) and photoplethysmograph (PPG), blood pressure based on pulse transit time, and actigraphy. Actigraphy includes step counts and calories burned. The second category of wearables most often measures analytes present in sweat, tears, saliva, interstitial fluids, and wound fluids (Mohankumar et al. 2021).

Pertinent to clothing and accessory wearables, several wearable devices have reached a commercial stage and are undergoing various clinical validation studies. Zio Patch, NUVANT MCT, Apple Watch, and Masimo Personal Health are examples of cardiovascular health monitoring devices (Sana et al. 2020). The Cyrcadia breast cancer monitor uses temperature sensors incorporated in wearable adhesive patches and AI methods for diagnostics (S et al. 2020).

Pertinent to skin integrated wearables, saliva is an information-rich body fluid with several valuable biomarkers for disease diagnosis and monitoring. Some examples of biomarkers are CVDs (cardiac troponin I (cnTl), cholesterol), heart failure (tumor necrosis factor-α), stress levels (cortisol, α-amylase), and neurodegenerative diseases (glutamate). Recent trends in research are towards the

implementation of sampling of saliva and embedding biosensors in pacifiers for babies and dentures or mouthguards for adults (Mani et al. 2021).

Sweat-based sensors are convenient because they are noninvasive, and sweat can be sampled from several sites on the body, which offers design flexibility. Sweat can be secreted through exertion or through electrical (iontophoresis) or chemical stimulation. Sweat-based sensors have been demonstrated for several analytes such as lactate, pH, alcohol, sodium, glucose, urea, chloride in a tattoo form factor (Bandodkar et al. 2015), and wrist-band or patch made of textiles or flexible polymers (Mohan et al. 2020). Moon et al. have recently demonstrated touch-based sweat measurement for tracking pharmacokinetic profiles of levodopa which is used in the symptomatic management of Parkinson's disease (Moon et al. 2021).

Tears are rich in protein biomarkers and contain the third-highest concentration of proteins among biofluids, blood being the richest, followed by interstitial fluid (ISF). Several biomarkers in tears have been correlated with ocular diseases (trachoma, glaucoma, keratoconus, and dry eye syndrome) and systemic diseases (diabetes, cystic fibrosis, multiple sclerosis, and Parkinson's disease) (Bandodkar and Wang 2014). The challenges with biofouling and sampling of tears have been a topic of research for several years. A capillary-based sampling of tears at the corner of the eye has emerged as a viable method. Successful integration of tear-based sensors has been demonstrated in contact lens form (Iguchi et al. 2007). Glucose and lactate sensing from tears is the most mature among analytes in the literature thus far.

ISF biosensing is an emerging area of research. ISF is a rich source of protein biomarkers that is similar in proteomic concentration to plasma and serum. ISF is sampled through the skin using minimally- or non-invasive microneedles (Samant and Prausnitz 2018). Lactate and glucose sensing has been demonstrated thus far with microneedle sampling (Bollella et al. 2019). ISF analysis on the microneedle tip is another recent research area that could obviate the need for on-chip analysis or off-chip instrumentation (Teymourian et al. 2021).

The analysis of fluids secreted at wound sites is vital to both the assessment of healing and the development of a closed-loop system for therapeutic management. The wound site should be monitored for changes in blood pressure, oxygen, temperature, pH, microbial activity, and interleukin-6 (IL-6), among other analytes (Brown et al. 2018). Individual physical measures and biomarkers have several candidate biosensor systems proposed in the literature. However, there is still a critical need for a fully integrated wound management solution incorporating all the required biosensors and closed-loop therapeutics.

8.2.2 Biosensor Systems in Pharmaceutics

8.2.2.1 Ingestible Sensors for Monitoring and Diagnosis

The measurement of medication compliance for patients who need to take prescribed medication regularly and the monitoring of the progression of ulcers among patients are two areas where biosensors incorporated in a pill have proven effective. Medication compliance products have received approval from FDA recently and are being

used in the field. Proteus and etectRx (ID-Cap System (FDA 2019)) are recent products with applications in patient compliance. The pills or ingestible event markers, once ingested, transmit signals to a wearable lanyard or patch, which in turn communicates with a mobile app on a smartphone and makes the compliance information like time of pill ingestion available to the patient and physician. These technologies are the most recent advances to reach commercialization following the more mature technology of capsule endoscopy, which facilitates imaging of the upper gastrointestinal tract, small bowels, and colon for diagnosis and prognosis of small bowel bleeding and tumors, Crohn's disease, celiac disease, ulcerative colitis, and colorectal neoplasia (Melson et al. 2021).

8.2.2.2 Closed Loop Continuous Drug Monitoring (CL-CDM) and Therapeutics

Monitoring of physiological status and compliance is an essential part of standard clinical care. However, ultimately, the insights gleaned from monitoring data should drive decisions on how to intervene therapeutically so that the patients may benefit in a timely fashion. Research efforts seek to address two types of challenges in CL-CDM: *first*, to gain a deeper understanding of the variations in pharmacokinetic profiles of drugs along with its inter- and intrasubject variability, and this will lead to the ultimate goal of personalized medicine where drugs and dosages can be prescribed with high specificity for each patient; *second*, improving the ability to quickly and automatically, i.e., without any intervention from the patient or clinicians, adjusting dosages of drugs in response to physiological changes, drug concentration, or a specific analyte reflecting physiological status, measured continuously. The most prominent clinical application for CL-CDM is glucose monitoring and insulin infusion devices (Scholten and Meng 2018).

In typical implementations of CL-CDM, the device includes (a) a continuous real-time implantable biosensor, (b) an external control system device that measures and then computes the necessary dosage of the drug, and (c) a mechanical device, usually an infusion pump, that provides the calculated dosage.

A Continuous Real-Time Implantable Biosensor

Continuous real-time biosensors can consist of bioaffinity sensors or enzymatic sensors and a transduction mechanism that is usually electrical or optical. The most common and mature form of the sensor for glucose monitoring is enzymatic and amperometric. The reason is that enzymatic amperometric sensors have a fast response that is required for a real-time sensor. However, enzymatic sensors require the formulation of specific enzymes that are cumbersome to synthesize for arbitrary analytes (Li et al. 2020a). On the other hand, the advantage of bioaffinity sensors is the availability of several types of biorecognition mechanisms (e.g., DNA, RNA, and aptamers). Several bioaffinity sensors are being developed and, coupled with advances in miniaturization, can lead to multianalyte continuous monitoring systems in the future.

Two recent studies in rat models have demonstrated highly precise feedback-controlled delivery of vancomycin (Dauphin-Ducharme et al. 2019) and tobramycin

(Arroyo-Currás et al. 2018). Electrochemical aptamer-based implantable biosensors were used in these studies. Furthermore, these sensors can be incorporated in flexible and stretchable form factors leading to wearable noninvasive or implantable devices (Zhao et al. 2019).

A Control System Device

The control mechanism's role is to maintain the signal level or, in this context, the analyte of interest. The controller's essential goal is to use the current measurement from the biosensor to predict the dosage of the drug required to maintain the analyte concentration at the desired level. Commercially mature controllers in devices like artificial pancreas may use blood glucose levels or additional parameters and implement proportional integral derivative (PID) controllers or model-predictive control (MPC) designs. In 2016, the OpenAPS (Open Artificial Pancreas System) community used a Do-It-Yourself system to improve the overall percentage time in the normal glucose range and reduce A1C from 7.3% to 6.79% (Wu et al. 2020b). Artificial intelligence (AI)-based approaches to control algorithms may potentially achieve greater accuracy of control but have not yet proven to outperform PID or MPC controllers. As the amount of data available for training AI systems increases, they may become desirable for controller implementations in the future.

An Actuator

One of the essential parts of a CL-CDM is a precise and titrable mechanism to administer the drug. Mechanisms for drug delivery have progressed from requiring invasive cannulae in the early insulin pumps to minimally invasive and pain-free microneedles. Emerging transdermal drug delivery systems use electroporation, where an electric field is applied to increase cell permeability, or iontophoresis, where a voltage gradient is used to deliver drugs. Recently, combinations of microneedles and iontophoresis have been demonstrated (Donnelly et al. 2014), and wearable systems that use iontophoretic methods have also been developed (Wu et al. 2020a).

Materials' advances primarily in nanomaterials and polymers have provided the impetus for improved biocompatibility, specificity, and lower power requirements for these systems. Electroactive biomaterials are an example of such an emerging class of materials based on conductive polymers. These materials are capable of transducing electrical signals into physicochemical signals and vice versa. They can be activated electrically to drive redox reactions and also result in cyclical volumetric expansion and contraction. These physiochemical responses could be used for controlled drug release (Olvera and Monaghan 2020).

8.3 Need, Risk, and Regulation of Medical Devices and Drugs

The regulatory pathways for medical devices and drugs begin with establishing two attributes of the medical device or drug under consideration, namely, intended use and risk and type of harm to the patient. The Food and Drug Administration (FDA)

classifies devices as Class I, II, and III. Regulatory oversight increases from I to III. The FDA provides clearance to market products that fall under Class II, known as a 510(k) clearance, and approval to market for Class III devices, known as premarket approval (PMA). Class III devices have the following definition according to the FDA guidance: "(devices) that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury." In the European Union (EU), the Medical Device Regulation (MDR) classifies devices with more granularity (Class I nonsterile and sterile, Class IIa, Class IIb, and Class III). MDR has a separate directive for in vitro diagnostic devices. Similarly, regulatory oversight increases with class.

Regulatory frameworks embody best practices for manufacturers to follow to create devices and drugs proven to be safe and effective and ultimately improve the quality of life for patients and help clinicians care for their patients. In this sense, the following steps can be treated as a harmonization of the regulatory framework's requirements with the caveat that the requirements will change based on the specific use intended for the device or drug and the reason or indication for when it should be used.

- **User Needs:** The process of uncovering user needs entails market research and technological comparisons of the proposed device or drug and the current standard of care. It is vital to establish why this device or drug is necessary and how it is likely to benefit patients or healthcare in general. This process will reveal requirements both technological and market-related for the proposed device.
- **Risk Management:** The overall risk management procedure is detailed in ISO 14971: Medical Device—Application of risk management to medical devices. The risk management process is active for the entire life cycle of the device or drug and should be periodically evaluated and updated to account for any new information that is uncovered regarding the device or drug throughout its use by clinicians and patients. The process consists of four main steps.
  - **Risk Analysis:** This is the process of uncovering risks by systematically evaluating all foreseeable harm to patients from device-related failures, user-related failures, or unintended use-related failures. For internet-connected devices and drugs, cybersecurity, HIPAA, and GDPR considerations must be included.
  - **Risk Assessment:** This is the process of evaluating each identified risk item and assigning a risk score that would stratify the item as requiring mitigation, justification of how the benefits outweigh the risks, or no mitigation required.
  - **Risk Control:** This is the process of identifying methods and mechanisms that could be used to mitigate the potential harm to patients resulting from the foreseeable harm to patients. Following risk control measure implementation, the risks are reevaluated.
  - **Residual Risk Analysis:** After the implementation of the risk control measures, the risks should be reevaluated, and the residual risk should be determined. If the residual risks are acceptable, then the design and

development process can move forward. This is the final step in the design and development phase.

- **Analytical Validation:** This is the process of verifying and validating that the device or drug performs the functions or interacts with the patient in the manner that was laid out through the process of user needs and risk management. Each requirement is verified against predefined acceptance criteria. In addition, depending on the type of device or drug, there are international standards published by organizations such as the American Association of Medical Instrumentation (AAMI), International Standards Organization (ISO), and International Electrotechnical Commission (IEC) that establish performance and safety-related criteria that the proposed device or drug should satisfy. Compliance with such standards follows best practices. Some are recognized by the FDA and required for obtaining CE mark in the EU. Analytical validation may also be referred to as nonclinical bench testing because it does not involve human subjects or clinical trials.
- **Clinical Validation:** In cases where the device or drug is considered high-risk or requires evidence for claims of efficacy, clinical validation is required. Clinical validation involves the enrollment of human subjects belonging to the intended population of patients who will use the device or drug. Clinical trials should be done following Good Clinical Practices guidelines and conform with the regional regulatory laws (Drago et al. 2018; Richmond and Tatavarty 2018).
- **Commercialization and Clinical Implementation:** This is the final step in the development lifecycle for any medical product. In a general sense, this step will involve establishing good manufacturing practices (GMP), complete traceability and documentation of quality-related operations, and an ability to continuously monitor and react to new findings of safety or effectiveness with corrective or preventive actions. These activities need to be in tandem with clinical adoption and implementation. This step involves patient and clinician education, proving effectiveness so that payors, either private or governmental, will reimburse the cost of use of the product. Higher-risk products will likely require continuous post-market surveillance involving continued clinical studies.

Specifically, pertinent to in vitro diagnostics devices or POC devices, the FDA has additional guidelines and requirements based on whether it is classified as a high-complexity device. In the case of high-complexity, Clinical Laboratory Improvement Amendment (CLIA) will apply, and the testing laboratory must meet the CLIA quality system standard.

An overview of the process from lab-scale proof of concept to commercial deployment and reimbursement was described in this section. Figure 8.2 illustrates some example activities in each of the steps that were outlined.

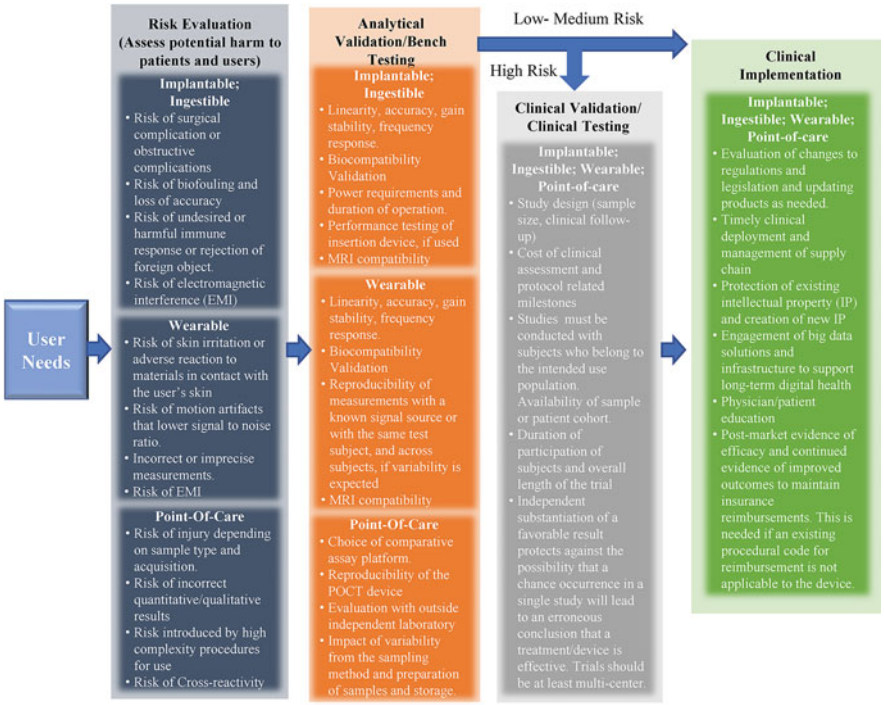

Fig. 8.2 Examples of typical considerations while navigating the path to regulatory clearance for biosensor systems

8.4 System-Level Architectures for Biosensors

As described in the introduction, digitization of patient data is an emerging trend that has great promise in transforming healthcare. A generic system-level architecture is one that involves the following layers:

1. *The sensor layer* consists of the sensing device, which may be wearable, ingestible, and implantable, POCT device, or a smart device.
2. *The network layer* consists of a method to transfer data from the sensing device and digitize the data if needed. The network layer also offers the means for internet connectivity, which may be through a smart device or directly to a mobile network through a gateway.
3. *The data layer* consists of cloud computing and storage resources. These resources generally include the ability to process, transform, and store the data from several devices while maintaining the security of data and Health Insurance Portability and Accountability Act (HIPAA) compliance due to the presence of Personal Health Information (PHI).

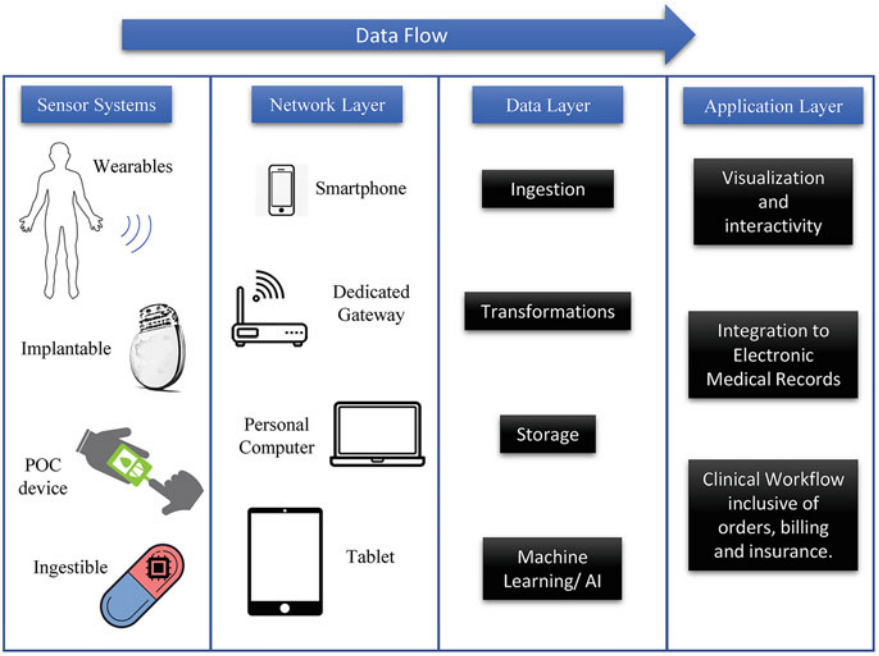

Fig. 8.3 Illustrating the layers of the data flow architecture

4. *The application layer* consists of a cloud-based client or user-facing applications. These applications, in addition to the previously stated HIPAA compliance, will include software implementations that support access, visualization, and integration of healthcare data across different devices and the hospital's information system. The application layers could implement or integrate into an existing medical coding and billing system that is used for medical claims and insurance reimbursements (Fig. 8.3).

8.4.1 Data Flow Architectures

8.4.1.1 Smart Devices as Sensors and Transducers—Local Processing

Smartphones are equipped with a wide range of sensors that are used for various consumer applications. A subset of these sensors can be used as biosensors. Cameras, microphones, light sensors, and force sensors have been demonstrated as viable biosensors for several applications. Chandrashekar et al. have shown that blood pressure can be estimated using the front-facing camera and force sensor. The user presses their index finger against the sensor. A custom application displays the photoplethysmography (PPG) and the estimated blood pressure (Chandrasekhar et al. 2018). Nemcova et al. demonstrated the use of a smartphone's camera and microphone to monitor heart rate, blood oxygen, and blood pressure (Nemcova et al.

2020). Oculocare's Alleye uses smartphone cameras to assess vision and progression of conditions like macular degeneration, which is a debilitating complication from aging and diabetes that can result in blindness (Faes et al. 2021).

The availability of high-quality cameras even in mid-range smartphones has made smartphones a viable tool to replace microscopes and spectroscopy in point of care applications. Several applications of smartphones in sensing and processing data acquired by POCT devices that use optical transduction have been demonstrated (Chen et al. 2021).

8.4.1.2 Medical Device as a Smart Device Accessory

Medical devices can be designed as accessories that connect to a smart device either wirelessly through near-field wireless communication or Bluetooth, coupled through the microphone or a wired connector interface available on the smart device. The data acquired by the medical device can be processed locally on the smart device or sent to the cloud for processing. The result of the processing can be presented on the smart device again or available through a client application that can be accessed from any internet device.

Several smartphone applications that use the in-built camera with an attachment, such as Molescope, SkinVision, and UMSkinCheck, have been commercialized. They use the attachment-enhanced camera to image and algorithmically classify skin lesions as benign or malignant. The accuracy of these classifiers is low and still an area of research, but coupled with the latest advancements in AI-assisted classifications and improvements in the optical components of the accessories; these applications can improve in the future (Davis et al. 2019). Smartphone-based fundus imaging for monitoring and diagnosing diabetic retinopathy has shown great promise as a tool that is both accurate and economical in middle- and low-income countries (Wintergerst et al. 2020). Several researchers have demonstrated microscopy using a smartphone over the past decade. Different microscopy types, including bright field, darkfield, phase, fluorescence, and reflectance confocal microscopy, have been demonstrated (Zhu et al. 2020). Researchers have demonstrated several smartphone-based microfluidic devices for POC applications (Hasanzadeh 2021) and flow cytometry (Li et al. 2020b).

The microphone in smartphones has been used by several researchers to demonstrate monitoring of pulmonary health. Thap et al. used a smartphone to perform lung function tests to determine its effectiveness in a 26 subject cohort with 13 healthy and 13 chronic obstructive pulmonary disease (COPD) patients. The authors concluded that a ratio of forced expiration volume in 1 s to forced vital capacity could be estimated with a high clinical correlation (Thap et al. 2016). Zhou et al. have demonstrated a precise spirometer comparable to a laboratory spirometer by designing a handheld flow head with Bluetooth connectivity. The flow head communicates the flow data to the smartphone, and the smartphone has an app that displays the results (Zhou et al. 2019).

Purohit et al. describe recent advances in smartphones as an optical, electrochemical, and wearable sensing interface (Purohit et al. 2020).

8.4.1.3 Direct Cloud Connectivity—Medical Internet of Things

The data collected in these medical device embodiments are transferred directly to the cloud for processing and analytics. In many cases, a smartphone application may accompany the device only to serve a user interface for data entry-related tasks or only available to clinicians who may use them to access the data from the cloud. Several commercialized devices fall within this category of Medical IoT with direct cloud connectivity. Some examples are Zio Patch by iRhythm Technologies (Yenikomshian et al. 2019), EarlySense (Breteler et al. 2020), and VitalPatch by Vitalconnect (VitalConnect). Although there are several commercialized devices, concerns regarding the security of information, privacy, and data use are ongoing areas of debate and research (Ray et al. 2020).

Remote patient monitoring with implantable device data interrogation at the patient's home has been commercially available from Boston Scientific, known as the Latitude system (Scientific), and Medtronic is known as MyCarelink (Medtronic) (Medtronic MyCareLink 2021; Scientific n.d.; Vinitha Sree et al. 2020; VitalConnect VitalPatch 2021).

8.5 Human Factors and Usability Engineering (HF/UE) Considerations

The risk of harm to the patient due to device failure or incorrect use is a possible outcome of user errors. It behooves the medical device designer or manufacturer to ensure that user errors are either wholly avoided or, if they occur, the consequences should be minor. Human factors engineering is a multidisciplinary field that combines expertise in human behavioral analysis with engineering principles for device-user interface design and strategies to mitigate the potential for harm to a patient due to behavioral patterns. HF/UE is a risk management activity that deals with the analysis and design of the interactivity between the intended user and the device (Borsci and David 2020).

8.5.1 Device Users, Environment, and Interface

A user's interaction with a device typically involves iterative cycles of the following steps: (a) users perceive information about the state of the device; (b) users cognitively accept and process the information and make a decision on what they would like to accomplish; (c) users translate that goal into a sequence of inputs that are compatible with the device's user interface, for example, changing the settings navigating to a different function; (d) the device accepts the user's input and processes it internally to change the state of the system; and (e) the device presents feedback to the user that reflects the change that was performed (Redmill and Rajan 1996). Within this interaction cycle, there are three attributes to consider: (a) the user's characteristics are reflective of their knowledge, education, and cognition; (b) the usage environment considers the circumstances under which the user must

perform these tasks, for example, at home, in a hospital, special environments that may limit their ability to interact with the device; and (c) complexity and type of user interface, for example, does the interface include alarms, displays, buttons, and specific sequence of inputs to function correctly?

8.5.2 User Flow and Task Analysis

During the design and development of a medical device, every step in the flow of interactions with a medical device must be documented. This flow will help identify the specific tasks that the intended end-user must perform. The list of tasks is then analyzed to reveal tasks, if performed incorrectly, that could lead to serious harm to the patient or compromised medical care. These tasks are known as critical tasks. If critical tasks were identified, then mitigation of harm due to failure of these tasks is required. Additionally, usability validation testing must be performed to validate that there are no critical tasks remaining after mitigation. Typically, the risk assessment may be performed using methods like failure mode effects analysis (FMEA) or fault tree analysis (FTA).

Task analysis may be performed analytically with heuristic analysis or expert analysis. Empirical task analysis could be performed by involving a representative group of the intended end user known as focus group. The type of exercise performed with the subjects may include contextual inquiry where the users interact with an existing device that is marketed, interviews to determine the user behavior in hypothetical use scenarios and their attitudes, beliefs, and perceptions, a cognitive walkthrough, or simulated tests with mock devices that may only implement the device user interface.

8.5.3 Mitigation of Use-Related Risk

Risk mitigation can be of three types: (a) inherent safe design, (b) protective measures, and (c) information for safety. Inherent safe design renders the risk highly improbable. Examples include using a connector mechanism that will allow only one orientation for a connection and hiding features that can be mistakenly chosen on the user interface. Protective measures may include warning signs to draw the user's attention if they follow a path that seems incorrect, using alerts or physical safety mechanisms that force the user to deliberate more before choosing a course of interaction with the device. Finally, information for safety involves all risk control measures that are the last resort if inherent safe design and protective measures are infeasible. It includes additional safety training for the user or written warnings and caution statements.

8.6 Challenges and Future Trends

Biosensor development is a rapidly growing area of research driven by the demand for a patient-centric personalized healthcare system. The need for this paradigm shift has been reinforced by the challenges posed by the recent COVID-19 pandemic. Healthcare service delivery needs to shift from hospitals to the patient's home and everyday life. Several challenges and opportunities for continued research and development exist among the biosensor systems described in this chapter.

Challenge I: Biocompatibility: This challenge applies specifically to implantable and wearable devices that require either implantation or direct contact with the skin for prolonged durations of time. The foreign body response is triggered by the body's immune system as soon as an external object comes into contact with the body. There exists a steep trade-off between biocompatibility and selectivity, and sensitivity of biosensors. Future materials innovation may hold the answer to maintain sensor performance while maintaining biocompatibility. *Challenge II: Sample separation:* Biosensor readings may be confounded by the presence of interfering cross-reactive species. Methodologies like microfluidic separation of analytes need to be developed further to improve the separation of the analyte of interest from other biofluid products. In wearables, measurands may be confounded by movement and other artifacts that manifest in the same frequency range as the signal. Better signal and noise separation techniques are needed to overcome this source of incorrect measurements. *Challenge III: Biosensor performance:* Currently, there are no FDA-cleared biosensors for the biomarkers described in this chapter. Biosensors are not yet on par with clinical laboratories in terms of selectivity and sensitivity. Although selectivity may be achieved with bioaffinity-based sensors, sensitivity requires more material innovation. Nanomaterials may hold the solution to this problem. *Challenge IV: Biofouling*: Biosensors rely on surface interaction of the recognition elements and the analyte. Biofouling is the mechanism by which a film of unwanted cells or organisms may accumulate on the surface containing the biorecognition elements. More research is needed to discover antifouling strategies, which may involve material innovation or mechanisms using existing materials. *Challenge V: Intermediate Sample Storage:* Biological samples are highly perishable, so the time duration between extraction and application to the biosensor system should be as short as possible. This may be mitigated by parallel multianalyte testing with biosensors. However, more research is needed to evaluate such multianalyte systems under real use-case scenarios. *Challenge VI: Digital Data:* Data privacy, security, and storage are a significant cause for concern as the digital health era emerges. Cybersecurity is an ongoing effort that must take place in parallel with any new sensor system development. Even mature technologies may face new threats from cybersecurity, so it is important to have constant surveillance, detection of any breaches, and timely responses with patches and updates.

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