1 Sensor-Assisted Next-Generation Diagnostics: Emerging Concepts, Biomarkers, Technologies, and Challenges

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Abstract

The evolution of medical diagnosis has continued to broaden our understanding of diseases. The development of various omics technologies and the continuous advancement of medical sensor technology are pushing medical diagnosis to a more accurate and sensitive next-generation diagnosis (NGD). In this chapter, we begin with the emerging concept of next-generation diagnostics and give concise summaries concerning the construction and application of the hardware and novel technology relied on the next-generation medical diagnosis, including in-vitro diagnosis technologies (liquid biopsy, gas biopsy, etc.), in-vivo diagnosis technologies (sensor implantation, MEMS technologies, etc.) and other health monitoring technologies (wearable or ingestible electronics, Internet of things (IoT), Health Cloud, etc.), and decision-making assistants (information fusion, artificial intelligence (AI), data-mining, etc.). In the end, we briefly introduce the

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new challenges faced by the next generation medical diagnosis on the following aspects: device performance reliability, miniaturization and system integration, ethics-related issues, and expense and patient compliance.

Keywords

Next-generation diagnostics · Biomarkers · Healthcare · Miniaturization

1.1 Emerging Concepts and Connotations of Next-Generation Diagnostics

Early detection and diagnosis of diseases are vital to the lives of patients. However, the previous medical diagnosis is subject to the limited clinical data and the experience of the attending physician, which is prone to misdiagnosis. Emerging sensing detection equipment and information technology provide a wealth of diagnostic tools, making medical diagnosis in the direction of precision, intelligence, and personalized development; thus, the next generation of diagnosis is also considered as a manifestation of precision medicine (Council 2011). Specifically, as shown in Fig. 1.1, while traditional in vitro testing devices can detect pathological markers in body fluids, some emerging wearable and implantable sensors can cover a much wider range of indicators, including nucleic acids, proteins, microorganisms, and even images. In-vitro detection equipment is also constantly updated in iterations, and powerful biochips can achieve high-throughput, real-time detection and point-of-care applications (Azizipour et al. 2020). The multidimensional data collected by these sensors, together with electronic medical records, capture many of the physical health characteristics of the patient and, aided by appropriate algorithms, provide more reliable decision-making. These sensing devices and information processing technologies are closely linked to the diagnosis, prognosis, and treatment of diseases and together map the blueprint for the next generation of diagnostics.

Based on the concept mentioned above, new ideas and technologies would be included to further conclude the kernels and the pursuits of the next-generation diagnosis:

1. **Personalized/precision diagnosis.** It is necessary for the next-generation medical diagnosis to scrutinize the genetic background and disease characteristics of the patients and apply precision medicine to the individual cases, striving to serve the personalized diagnosis and treatment.
2. **Integrated patient records for evidence-based medicine.** The next-generation diagnosis will comprehensively integrate the patient information with genetic information, imaging, patient record, biochemical examination, physical examination, auxiliary examination, etc. These inclusive data underpin the next-generation diagnosis by providing more evidence-based medicine indicators, assisting physicians' decision-making.

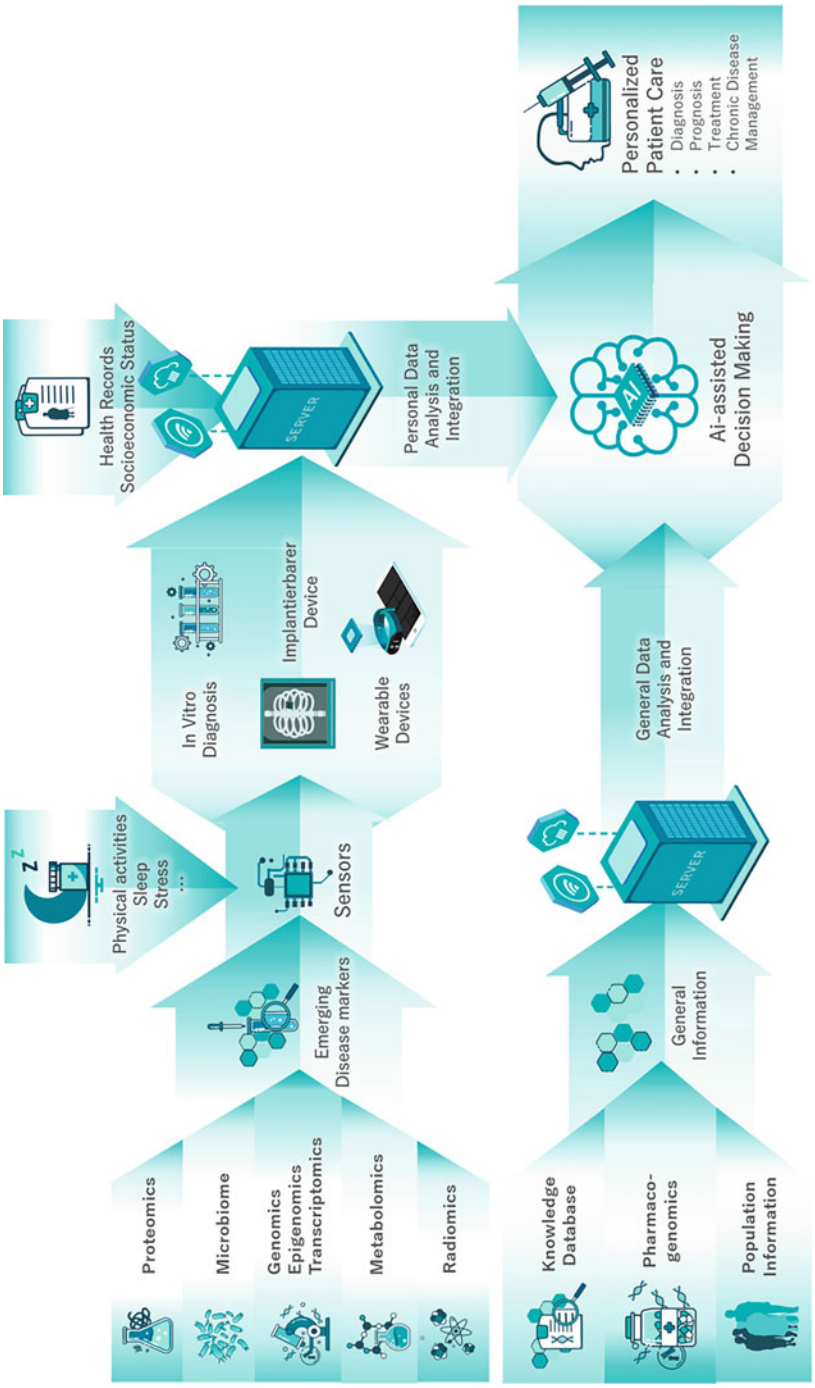

Fig. 1.1 Connotations and compositions of the next-generation diagnosis

3. **Emerging of disease markers and pathogen characteristics.** In order to discover more disease markers, the next-generation diagnosis needs both the underpinning supports of metabolomics, genomics, epigenetics, transcriptomics, radiomics, and proteomics and the technological support of novel advanced sensors. This exploration will consequentially be beneficial for the realization of the high-precision, low-cost in vitro/vivo diagnosis.
4. **Early intervention in the occurrence and development of the disease.** The next-generation diagnosis will incorporate chronic disease management and thus can discover risk factors at an early stage. The sequent intervention will prevent the occurrence or the escalation of the disease.

Several proof-of-concept studies have been conducted and applied to precise/personalized diagnostics, disease risk monitoring, and chronic disease management, demonstrating the superiority of next-generation diagnostics (Guzik et al. 2020). Taking a multimodal fusion technology as an example, multimodal image fusion technology (such as radiological image + ultrasonic image) can overcome the deficiency of single-mode information, which has become a research hotspot in recent years (Antropova et al. 2017). Data mining methods can also extract semantics from previous examination reports and obtain valuable disease information (Kirshners et al. 2012; Mahmoodi et al. 2016).

However, cutting-edge and effective ideas such as precision medicine, personalization, and information fusion have yet to take hold among more doctors, largely because of the unforeseen complexity of next-generation diagnostic technologies. In the case of polygenic and complex diseases such as mental illness and diabetes (Jaffee and Price 2007; Nassief Beshay et al. 2018), the occurrence of diseases is the result of a combination of genetics and environment. Therefore, precision medicine for complex diseases requires comprehensive consideration of multiple levels of information such as protein, metabolite, or epigenetics, so as to make more accurate judgment and assessment of the result of environment–gene interaction and then effectively guide the prevention, diagnosis, and treatment of diseases. Therefore, metabolomics, genomics, epigenetics, transcriptomics, radiomics, and proteomics are expected to be applied in multimodal diagnosis, thus covering early, long-term, and real-time monitoring of the disease. For this initiative, it is necessary to systematically review the emerging biomarkers, detection technologies, and information technologies to assist diagnostic decision-making in order to accelerate the implementation of the next generation of diagnostics.

1.2 Emerging Biomarkers

To discover and utilize more disease markers, the next-generation diagnosis needs both the underpinning supports of metabolomics, genomics, epigenetics, transcriptomics, radiomics, and proteomics and the technological support of advanced sensors. This section focuses on emerging biomarkers associated with disease. According to the report of the World Health Organization (WHO), four

main kinds of noncommunicable chronic diseases are cancers, chronic respiratory diseases, cardiovascular diseases, and diabetes mellitus (World Health Organization 2020). Additionally, acute diseases such as contagion, septicemia, organ failure, etc. are also included in this section. We dissected potential detectable biomarkers for these diseases from the perspective of omics, which will be considered for inclusion in the next-generation of diagnostic criteria.

1.2.1 Biomarkers for Cancer

With the advent of the omics era, a wealth of biomarkers has been discovered with high-throughput analysis. From classic enzymes and antibodies to noncoding RNA, the types of biomarkers have increased while their combinations have also become increasingly diverse. As shown in Fig. 1.2, the genomics, epigenomics, transcriptomics, proteomics, metabolomics, and even fluxomics are rapidly developing, which produce multiple emerging biomarkers; among them, DNA methylation, circRNA, miRNA, and CTCs are famous representatives.

1.2.1.1 DNA Methylation

DNA methylation may take an active role in malignant progression by promoting the expression of oncogenes, suppressing tumor suppressor genes (TSGs), or changing the stability of chromosomes. At the same time, DNA is more stable than other biological molecules, such as protein or RNA, making it more conducive to detection (Li et al. 2012). DNA methylation plays an important role in cancer detection, such as gastric cancer (Tahara and Arisawa 2015), lung cancer (Kneip et al. 2011), and prostate cancer (Litovkin et al. 2014). For the detection of lung cancer, methylation has satisfactory sensitivity (60%) and high selectivity (90%) using blood plasma samples. An even higher sensitivity was achieved when detecting squamous cell carcinoma (SCC) and small cell lung cancer (SCLC) with a sensitivity of 80 and 63%, respectively (Kneip et al. 2011; Pan et al. 2018). The use of DNA methylation as a tumor marker in detection faces concerns such as lack of standard and reproducible detection schemes and difficulties in the DNA purification methods.

1.2.1.2 circRNA

CircRNA, which exists in most cells and plays an important role in the promotion and progression of cancer, is a novel kind of noncoding RNA having covalently closed loop structures. Existing evidence has shown that some circRNA will be enriched in exosomes, which bring new ideas for circRNA detection (Wang et al. 2019b; Li et al. 2021b). Exosomes are also called important mediators of intercellular communication by regulating a variety of biological processes (Zhang et al. 2019b). As shown in Fig. 1.3, previous studies have shown the role of exosomal circRNA in the proliferation of cancer (Zhang et al. 2019a), cancer metastasis (Li et al. 2020), and mediating drug resistance in a variety of cancers (Luo and Gui 2020). Zhang et al. reported the role of circular RNA ciRS-7 (CDR1as) in non-small cell lung cancer (NSCLC) (Zhang et al. 2018). The mechanism is through

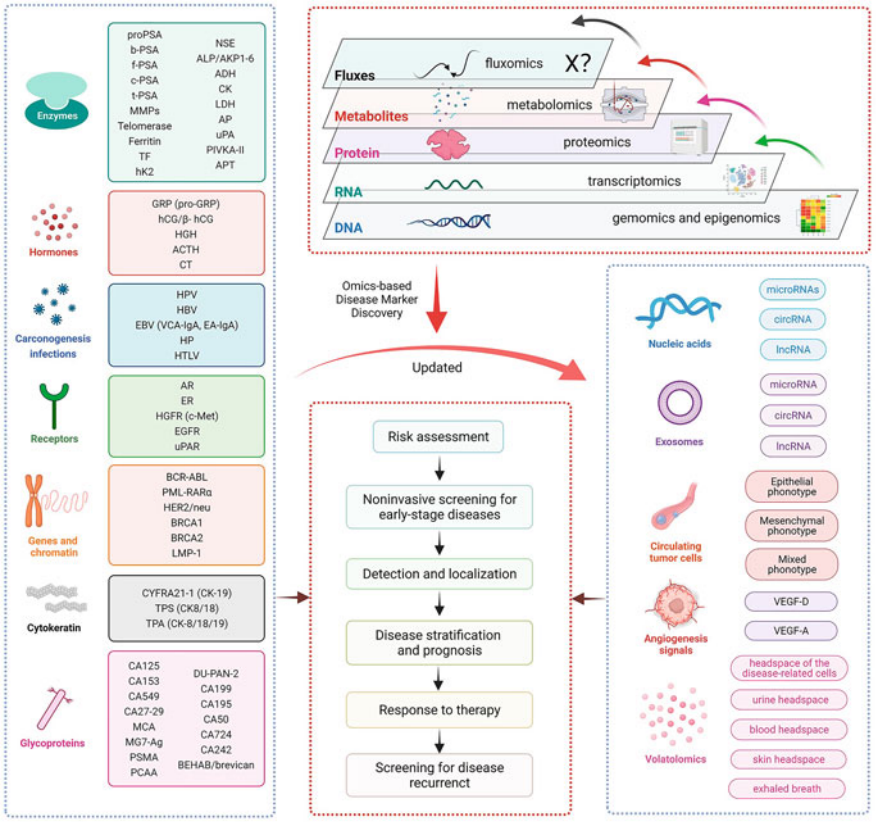

Fig. 1.2 The evolution of disease biomarkers (cancer) (Created with Biorender.com)

downregulation of tumor suppresser miR-7 to upregulation target gene of miR-7, including proto-oncogenes like Ki-67, EGFR, CCNE1, and PIK3CD.15 (Sun et al. 2016). As shown in Fig. 1.3, circRNAs are closely related to the hallmarks of cancer. For example, CDR1as and circHIPK3 can regulate the EGFR, thus activating cell proliferation, and circ-ITCH, circ-ZFR, etc. could intervene the expression or the activation of tumor suppressor genes (TSGs) (such as PTEN and CDK) and, in this way, assist cancer cells in evading antigrowth signals (Su et al. 2019). Meanwhile, cellular apoptosis or autophagy can be resisted by cancerous cells with the help of Hsa_circ_0007534 (Su et al. 2019). Moreover, Has-circ-0020397, CircRNA-MYLK, and Dirc-10,720 could regulate the TERT, VEGF, and the EMT process, respectively, thus influencing the proliferation potential, angiogenesis, and tumor metastasis (Su et al. 2019).

However, there are still some problems in the clinical application of these tests. First, some RNA tests require living tissue. In addition, due to the wide variety of circRNA and the relatively complex functions, its reliability in detection needs to be further confirmed (Meng et al. 2017).

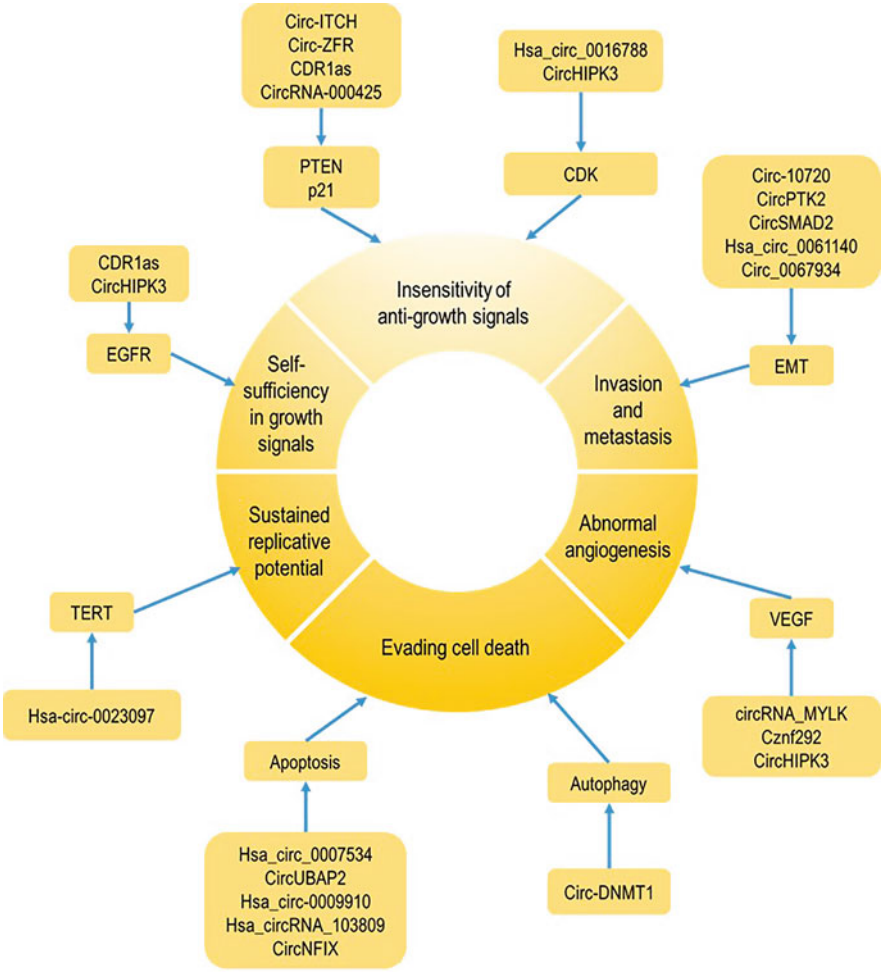

Fig. 1.3 CircRNAs with the hallmarks of cancer. Reprinted from Su et al. (2019)

1.2.1.3 miRNA

miRNA is involved in almost every cellular process, which is essential for organisms' development and homeostasis. Many diseases are related to dysregulation of miRNA, especially cancer, for mature miRNA can combine with some proteins to form RNA-induced silencing complex (RISC), which further regulates gene expression (Calin et al. 2004). Some of them can be used as a site for diagnosis or prognosis or therapeutics target.

1.2.1.4 Circulating Tumor Cells (CTCs)

CTC has an important role in early cancer diagnosis and prognosis. It provides a less invasive means to detect the molecular and genetic profile of metastatic cells and

give a prediction of tumor metastasis before clinically detectable metastasis occurs (Bankó et al. 2019). Because of the heterogeneity of cancer in different regions, the CTC can provide a more comprehensive result than tissue biopsy in several sites (Sundaresan et al. 2016). However, several limits remain, such as insufficient proof grounded in clinical utility (Alix-Panabières and Pantel 2016).

In addition to CTC, some molecular markers such as cell-free DNA (cfDNA) can be detected (Zhang et al. 2017). When apoptosis or necrosis happens, CfDNA can be released from cells as important signals of inflammation and malignant cell activity. Tumor cells can also actively get into or passively be pushed into the bloodstream by external forces ranging from tumor growth kinetics or mechanical forces during surgical operations, and these tumor cells can be shielded by platelets. Moreover, circulating exosomes can be generated by many cell types, including tumor cells, normal cells, and blood cells (even platelets), which provide another way to analyze the tumor burden, thus evaluating the treatment effect and predicting the patient prognosis.

1.2.2 Chronic Respiratory Diseases

Chronic respiratory diseases are a group of diseases including lung cancer, chronic obstructive pulmonary disease (COPD), and asthma, which are serious health issues worldwide (Chen and Wang 2012). Many biomarkers have been discovered, such as serum microRNA (Pattarayan et al. 2018), circulatory cell epigenetics, genome (Gruzieva et al. 2014; Saco et al. 2018), and exhaled breath molecules (Kharitonov and Barnes 2002; Bregy et al. 2018).

1.2.2.1 Exhaled Breath Molecules

Both volatile molecules and nonvolatile molecules, including nucleic acids, proteins, lipids, etc., can exit in exhaled breath. These molecules contain a lot of information about diseases, which makes them potential biomarkers. Compared with traditional imaging, endoscopy, immunology, and other technologies, the detection of exhaled gas is rapid, noninvasive, and relatively simple (Karnon et al. 2007; Broza et al. 2018). At present, the detection method of exhaled gas markers is mainly mass spectrometry based (Bregy et al. 2018; Gaugg 2018). The current development of nanotechnology provides a potential low-cost and rapid detection method for the biomarker detection of exhaled breath (Broza et al. 2018). However, some challenges remain: lack of sensitivity due to the interference of other chemical compounds in exhaled breath, sometimes use of toxic chemicals, and lack of standardization (Khan and Hegde 2020).

1.2.2.2 MicroRNA

Extracellular microRNA is an important biomarker for respiratory diseases. Some existing studies have shown its role in acute lung injury (Guo et al. 2014; Yang et al. 2015b), idiopathic pulmonary fibrosis (Li et al. 2014; Yang et al. 2015a), chronic obstructive pulmonary disease (COPD) (Van Pottelberge et al. 2011; Ellis et al.

2013), and asthma (Liu et al. 2012; Panganiban et al. 2012). For example, research showed that several miRNAs including miR-223, miR-1274a, miR-18a, miR-106a, and miR-146 have been involved in biological pathways that may be relevant to the progress of COPD, including the transforming growth factor β and wnt signal pathways (Ezzie et al. 2012; Salimian et al. 2018).

1.2.3 Cerebrovascular Diseases

1.2.3.1 Trimethylamine-N-Oxide (TMAO)

TMAO produced by gut microbes can be a potential biomarker for cerebrovascular disease. Research has demonstrated the positive dose-dependent association between serum TMAO level and increased cardiovascular risk and mortality (Schiattarella et al. 2017). There may be multiple mechanisms that cause this adverse effect: first, it can promote macrophage foam cell formation in the artery wall (Wang et al. 2011); second, it is related to the reduction of "reverse cholesterol transport" together with general defection of cholesterol metabolic pathway. Exiting methods available for the detection of TMAO include mass spectrometry, ultra-performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS), and nuclear magnetic resonance (Garcia et al. 2017), and other new pathways are shown in Fig. 1.4.

1.2.3.2 Urine Biomarkers

Protein or peptide markers in urine also have broad clinical prospects (Röthlisberger and Pedroza-Diaz 2017). Urine sample is an ultrafiltrate of blood, so it will reduce interference from nonspecific proteins such as albumins, which were originally present with a large amount in the blood. At the same time, the sample can be

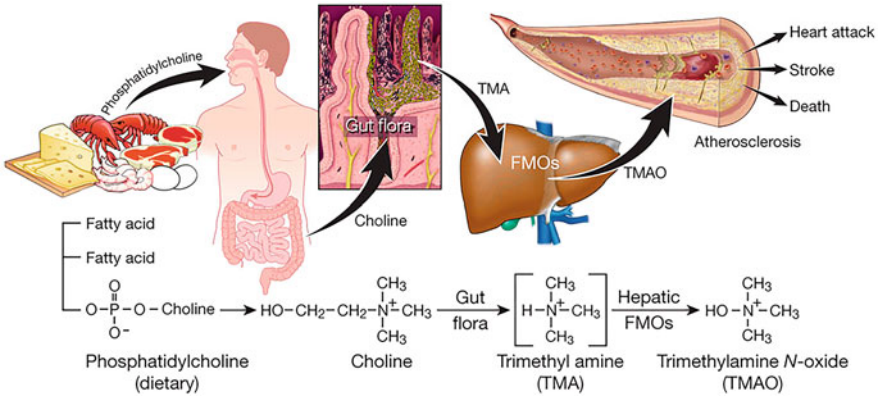

Fig. 1.4 Recently reported pathway for gut-flora-mediated generation of the pro-atherosclerotic metabolite from dietary PC. Reprinted from Wang et al. (2011)

obtained noninvasively, and less pressure is given on the patient. Polypeptides in urine can be used in coronary artery disease (CAD) and heart failure (HF).

1.2.4 Diabetes

Depending on the prediction by the World health organization, diabetes patients will continue to grow and reach at least 366 million by 2030 (Smyth and Heron 2006). It is necessary to recognize and control the progress of diabetes to induce both the incidence of the disease and its complications (Narayan et al. 2011). There are two main kinds of diabetes mellitus. Type 1 diabetes is due to deficient insulin production and needs daily insulin replenishment. Type 2 diabetes results from the body's ineffective use of insulin (Gavin et al. 1997).

There are many markers that can predict the diabetes process before abnormal blood sugar concentration appears. For type 1 diabetes, the correlation between disease and many factors has been found, such as immune response to islet autoantigen, gene expression profile of whole blood, proteomics of serum, circulating-miRNA (Gavin et al. 1997), proinsulin/C-peptide ratio (Truyen et al. 2005; Schölin et al. 2011; Sims et al. 2016), and DNA methylation pattern (Mirmira et al. 2016). DNA methylation can be an alternative for early diagnosis because islet β-cells express many genes in a nearly exclusive way. One example is the gene encoding preproinsulin (INS in humans and Ins1 and Ins2 in mice); this gene is usually hypomethylated in mouse and human islet β-cells at selective sites in promoter and coding regions than in other cells (Fisher et al. 2015; Lehmann-Werman et al. 2016). The hypomethylation form of cell-free circulating DNA (cfDNA) may reflect both autoimmune and alloimmune destruction of β cells (Lebastchi et al. 2013; Lehmann-Werman et al. 2016).

For type 2 diabetes, emerging biomarkers include organokines (Chung and Choi 2020), circulating miRNA (Zhu and Leung 2015), and metabolic markers (e.g., mannose (Lee et al. 2016) and α-hydroxybutyric acid (Cobb et al. 2016)). Adipokines are a wide range of cytokines secreted by adipose tissue. Abnormal secretion of adipokines is associated with insulin resistance and obesities, which make them an effective biomarker for diabetes screening and diagnosis (Jung and Choi 2014). Adiponectin is a kind of adipokine involved in glucose and lipid metabolism and also takes part in insulin resistance (Thanakun et al. 2014; Ojeda et al. 2015). Ojeda and his colleague have reported an electrochemical immunosensor that uses special electrodes (SPCEs) modified with functionalized double-walled carbon nanotubes (DWCNTs) and uses DWCNTs as platforms for further immobilization of specific antibodies (Ojeda et al. 2015).

1.2.5 Acute Diseases

Apart from chronic diseases, acute diseases are also a major killer of human health. Their disease duration is short, and patients' physiology can deteriorate rapidly in a

short time, a well-known example of which is the inflammatory storm during the COVID-19 pandemic (Russell et al. 2020). Usually, acute diseases include most of the severe infectious diseases, as well as the complications of septicemia, myocardial infarction, organ failure, etc. In addition to the pathogens that cause infection, some substances increase with complications. For example, the sharply increased inflammatory factors include interleukin, histamine, reactive oxygen metabolites, etc. However, it is important to note that the content anomalies of these nonspecific markers exist in other diseases; therefore, a combination of other markers for integrated diagnosis is required. At present, the detection of disease markers is relatively mature in terms of infectious diseases (shown in Table 1.1).

1.3 Emerging Technologies

Although current medical testing equipment can provide reliable test results, it often fails to meet the need for point-of-care applications and requires complex laboratory operations and personnel requirements. Over the past decade, the fusion of technologies such as microchannels, flexible electronics, and networked information has made diagnostic tools more portable, enabling rapid, real-time detection of a wider range of markers with high accuracy. Based on a quick review of the fundamentals of general biosensors, this section introduces the emerging trends of diagnostic tools from four aspects: in vitro diagnostic technology, in vivo diagnostic technology, wearable health testing devices, and decision assistance technology.

1.3.1 Fundamentals of Biosensors

1.3.1.1 Basic Mechanisms of Biosensors

Medical history, symptoms, signs, and auxiliary examinations are the core of medical diagnosis. Medical sensing technology uses signal conversion, amplification, and signal post-processions to provide clinicians and computers with original reference materials to enrich the evidence of medical diagnosis and predict the prognosis of patients' diseases (Fig. 1.5).

As shown in Fig. 1.5., there are various types of indicators that could be regarded as the inputs of healthcare biosensors (Table 1.2a). They could be captured by sensing elements, and subsequently, the signals produced by sensing elements could be amplificated (or sometimes transferred) to measurable electrical, optical, and physical signals (Table 1.2b). After necessary post-procession, the quality of signals could be further improved.

1.3.1.2 Evolution of Biosensors: From the Classical to the Next Generation

As shown in Fig. 1.6, the concept of next-generation diagnosis is a revolution that is developing extensively in the medical field. From the perspective of the medical world, the concept of next-generation diagnosis is not limited to molecular

Table 1.1 The biomarkers of most common infectious diseases

Pathogenic factors	Diseases	Biomarkers	Detection methods	Performances	
				Sensitivity	Specificity
Mycobacterium tuberculosis	Tuberculosis	mRNA (cytokine which responses to Mtb antigens: IFN-γ, IL-12β, IL-9, FOXP3, IL-10, IL-6, IL-8)	q-PCR (Li et al. 2015)	74.36%	84%
		DNA (special site)	PCR (Zhou et al. 2019) (detect NTM or MTBC)	100%	100%
		Protein (heparin-binding hemagglutinin adhesion–specific antibody)	ELISA (Sun et al. 2011)	77.08%	87.5%
Staphylococcus aureus	Various	Protein	Data-independent acquisition mass spectrometry (DIA-MS) (Liu et al. 2021c)	93.3%	88%
		Breath VOC	Gas chromatography–mass spectrometry (GC-MS) (Neerincx et al. 2016)	100%	80%
Salmonella typhi	Typhoid fever	Antibodies (blood or saliva)	Dot-EIA (Mohd Redhuan et al. 2017)	90.9% (salivary IgA), 90.9% (serum IgG)	N/A
Bacillus anthracis	Anthrax	Peptide (fingerprint)	Matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (Wei et al. 2020)	100%	100%
		Surface array protein	Immunochromatography test (ICT) (Puranik et al. 2020)	/	/
		Calcium dipicolinate (CaDPA)	ZnO quantum dots Functioned with europium ions (Eu3+) (Zhou et al. 2017)	/	/

Vibrio cholerae	Cholera	OmpW	Surface plasmon resonance (Taheri et al. 2016)	/	/
		D-amino acids (d-methionine and d-leucine)	Enzyme-based microfluidic chip (Batalla et al. 2015)	/	/
HIV	AIDS	miRNA	qRT-PCR (Munshi et al. 2014)	/	/
SARS-CoV-2	COVID-19	Antibody	IgM/IgG (Bin et al. 2020)	95.8%	98.5%
		RNA	RT-PCR (Chu et al. 2020; Corman et al. 2020)	/	
Influenza A virus	Influenza	Protein	ELISA (Jian-umpunkul et al. 2012)	/	
		RNA	Real-time PCR (Ilinykh et al. 2010)	/	
Hepatitis B virus	Hepatitis B	DNA	Structure-enhanced fluorescence polarization biosensor (Chen et al. 2015)	/	
		Hepatitis B surface antigen (HBsAg)	Automated fluorescent lateral flow immunoassay (FLIA) (Ryu et al. 2018)	99.8%	99.3%
Hepatitis C virus	Hepatitis C	antibody to HCV (anti-HCV)	Automated fluorescent lateral flow immunoassay (FLIA) (Ryu et al. 2018)	98.8%	99.1%
Dengue virus	Dengue	NS1 antibody	ELISA (Ahmed and Broor 2014)	73.5%	100%
		RNA	Real-time RT-PCR (Ahmed and Broor 2014)	79.4%	100%
Plasmodium vivax	Malaria	*P. vivax* lactate Dehydrogenase (LDH)	ELISA (Sousa et al. 2014)	/	/
Plasmodium falciparum		Plasmodium falciparum histidine-rich protein II (PfHRPII)	Magnetic bead-based ELISA (Markwalter et al. 2016)	/	/

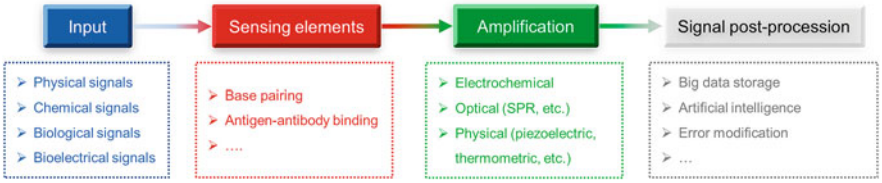

Fig. 1.5 Basic units of a medical sensing system

diagnostic tools brought by next-generation sequencing (NGS) but goes deeper into data storage, intelligent diagnosis, rapid disease screening, health monitoring, and more.

1.3.2 In Vitro Diagnostics

1.3.2.1 Liquid Biopsy

Liquid biopsy is the sampling and analysis of the nonsolid biological sample. It gives us noninvasive access to disease diagnosis and dynamic monitoring. In particular, in cancer, it contains detection, isolation, and further operation to circulating tumor cells, circulating tumor DNA/RNA, exosomes, and other biomarkers, which brings us genomic and epigenetic information about cancer. This information can help us in "precision medicine" and "point-of-care" treatment (Crowley et al. 2013; Soiza et al. 2018).

Biochips (e.g., Gene Chip, protein biochips, electrochemical biochips, microfluidic chips, and nanotechnology-based biochips) are playing an important role in liquidoid molecular diagnostics, and some of them are applied in point-of-care diagnosis, which potentially helps the development of personalized medicine. Many biochips with different properties have been developed, such as electrical biochips, to achieve rapid and multiplexing detection. DNA chips provide high throughput or easy access for sequencing and detection. Another trend in bio-chips is programmable bio-nano-chip (p-BNC), which often includes bio-sensitive elements such as field-effect transistors. p-BMC is a versatile multiplexed and multiclass bio- and chemical detection system for clinical and research use (McRae et al. 2015). This trend is generated by the need to deal with much information about potential biomarkers generated by today's advanced "omics" such as genomics, proteomics, and metabolomics (Hanash et al. 2008; Hunter et al. 2008) and the demand for a portable, inexpensive, and sensitive detection system (McRae et al. 2015).

Isolation of target cells from a liquid sample is usually the first step in a liquid biopsy; one of the core challenges is the usual need to deal with a large volume of samples with rare targets in complex backgrounds. Filtration-based micro-device brings us a solution for its high-throughput, label-free, and high recovery rate of target (Liu et al. 2021b). For example, a microcavity array for rapid and highly

Table 1.2 Main inputs and amplification approaches of biosensors

(a) Biosensors with different indicators

Indicators	Detection targets	Basic principles	Application
Physical indicators	Temperature	Common temperature sensors utilize the thermoelectric effect to convert heat to electrical characteristics such as conductor resistance by using thermocouples or thermistors	Versey et al. (2011)
	Pressure	Pressure sensors use a force collector to scale the strain, and its methods can be categorized into piezoresistive strain sensor, capacitive, electromagnetic, etc.	Graphene et al. (2020); Tao et al. (2020)
	Blood flow	Blood flow measurement utilizes laser Doppler effect or ultrasound Doppler effect. The frequency of the reflected light (or ultrasound) varies according to the blood-flow velocity	Ruiz-vargas and Arkwright (2019); Min et al. (2021); Surkova et al. (2021)
	Heart sound	Heart sound sensors generally are electronic stethoscopes, which use an acoustic transducer to convert the sound wave to an electrical signal. Electronic stethoscopes can be divided into air conduction and contact conduction	Pei et al. (2019); Liu et al. (2021a); Wang et al. (2021)
	Pulse	Heartbeat sensors utilize photoplethysmography, which measures changes in the intensity of light caused by the variance of the blood amount passing through the organ	Kwak et al. (2017)
	Respiration	Respiration can be measured with the chest strap that monitors the chest expansion during breathing or with a thermal mass flow sensor or pressure sensor to detect the respiratory air volume flow	Kanaparthi (2017); Yu et al. (2017)
Chemical indicators	Electrolyte	Ion concentration detection method varies. It can be detected via an ion-selective electrode (ISE), which converts the activity of the dissolved specific ion into an electrical potential	Shinwari et al. (2007); Melzer et al. (2014); Wang et al. (2019a)
	Saccharide	Saccharide sensor is usually based on the electrochemical method monitoring redox	Huang et al. (2009); Jina et al. (2014)

(continued)

Table 1.2 (continued)

(a) Biosensors with different indicators

Indicators	Detection targets	Basic principles	Application
		reaction generated by the hydrogen peroxide with the saccharide at the electrode	
Biological indicators	Protein	Protein can be targeted by various molecular probes. Aptamer-based biosensors (aptasensors) and antibody-based biosensors (immunosensors) can use those biological molecules bound with physically detectable signals (for example, fluorescence) for the detection of the target	Resende et al. (2018); Villalonga et al. (2020); Li and Lillehoj (2021)
	Nucleic acid	Electrochemical sensors can detect the electrical activities (change in resistance, capacitance, inductance, etc.) during the hybridization of the targeted DNA with tagged short DNA probes	Tabata and Miyahara (2019); Santhanam et al. 2020; Wu et al. (2020)
		Optical sensors can detect the optical activities during the hybridization of the targeted DNA with tagged short DNA probes via fluorescence, surface-enhanced Raman scattering, colorimetric assays, surface plasmon resonance, etc.	Aydın et al. (2020); Julker et al. (2021)
Bioelectrical signals (biophysical mechanism)	EEG/EMG/ECG	Electrophysiology detects the electrical properties of biological cells and tissues. It usually involves measurements of voltage or current	Onose et al. (2012); Lin and Jiang (2017); Level et al. (2019)

(b) Main technology types of biosensors

Types of biosensors	Detection device or principles	Brief descriptions
Electrochemical biosensors	Amperometric biosensor	Current produced by the oxidation could quantitatively reflect the amount of some certain substances
	Potentiometric biosensor (mostly field-effect transistors, FET)	By replacing the gate terminal in FET with an antibody or an enzyme, the physical and electrochemical changes happen in FET due to the change of pH, ionic force hydration, and redox response that will produce a change of the source flow in the drain

(continued)

Table 1.2 (continued)

(b) Main technology types of biosensors		
Types of biosensors	Detection device or principles	Brief descriptions
	Impedimetric detection	Impedimetric biosensors combine the analysis of both the R (resistance) and C (capacitance) of material, namely the analysis of the electrochemical impedance spectroscopy (EIS) by perturbating a small signal produced into a system at its equilibrium, and this small signal, when EIS is applied in biosensors, is generally produced by the biochemical activity that occurs when the detected substance meets the enzymes, nucleic acids, antibodies, and cells immobilized onto the electrodes' surface
	Voltammetric test	Voltammetry is an electrochemical technique in which a varying potential is applied to a working electrode in an electrochemical system, and the corresponding current is measured
Optical biosensors	Plasmonic resonance biosensors (including surface plasmon resonance, localized surface plasmon resonance, SPR imaging, etc.)	Plasmonic resonance occurs in free carrier-rich metal conductors or heavily doped semiconductor materials. The plasmonic resonance frequency is closely coupled with the external refractive index distribution, so small changes in concentration can affect the resonance mode. Sensitive signal conversion can be obtained by detecting information about incoming or transmitted light
	Evanescent wave biosensors (waveguide or optical fiber)	The evanescent wave arises from the manner in which light behaves when confined in an optical waveguide or fibers. It is sensitive to near-surface (less than 100 nm to a wavelength) fluorescent molecular excitation or biological binding events. For optical fibers, flexible mechanics and temperature measurement can be realized
	Spectroscopic analysis	Surface-enhanced Raman spectroscopy and fluorescence spectroscopy can reflect the concentration and fingerprint information of substances, which

(continued)

Table 1.2 (continued)

(b) Main technology types of biosensors		
Types of biosensors	Detection device or principles	Brief descriptions
		are widely used in high-throughput and high-precision material inspection. The spectral signal is received by a CCD or photodiode for further analysis
Magnetic biosensors	Alternating current (AC) susceptometry, Hall effect, or giant magnetoresistance effect	Utilizing paramagnetic or supra-paramagnetic particles, or crystals, which are bound with bioreceptors, to detect biological interactions. The binding of the bioreceptors will affect the magnetic particle properties that can be measured
Micro-electromechanical systems (MEMS)	Surface acoustic wave (SAW), cantilevers, micro-accelerometers, etc.	The resonant frequency of surface acoustic wave/cantilever or other mechanical vibration modes are very sensitive to the bonding events near the sensor side. Specific conversion of concentration information can be achieved by fixing biometric elements on the sensor surface. In addition, micromechanical sensors are also widely used in wearable biomechanical signal detections
	Piezoelectric effect, piezoresistive effect, thermo-electric effect, capacitive sensors, etc.	Microelectronic devices cover most bioelectrical signals' acquisition, stress, temperature, gas, and analyte measurement applications. For example, the piezoelectric effect and thermoelectric effect can directly convert physical quantities into electrical signals, which is very convenient for back-end signal processing

efficient tumor cell detection from blood was developed (Fig. 1.7a, d), which is mainly based on the differences in size and deformability between tumor cells and other cells (Hosokawa et al. 2010). A more complicated separable bilayer was reported to further reduce the mechanical stress on CTCs, which retains the ability to establish culture after capture (Fig. 1.7b). Some points may need further investigation in this area like purity increment, finding more cost-effective fabrication, and release of the cells from filter (Liu et al. 2021b).

Circulating free DNA (cfDNA) was another feasible biomarker for liquid biopsy. Due to the active and increasing cell proliferation, patients who have malignant tumors usually have a higher concentration of cfDNA (Schwarzenbach et al. 2008). Meanwhile, DNA is a stable chemical compound and has already been researched

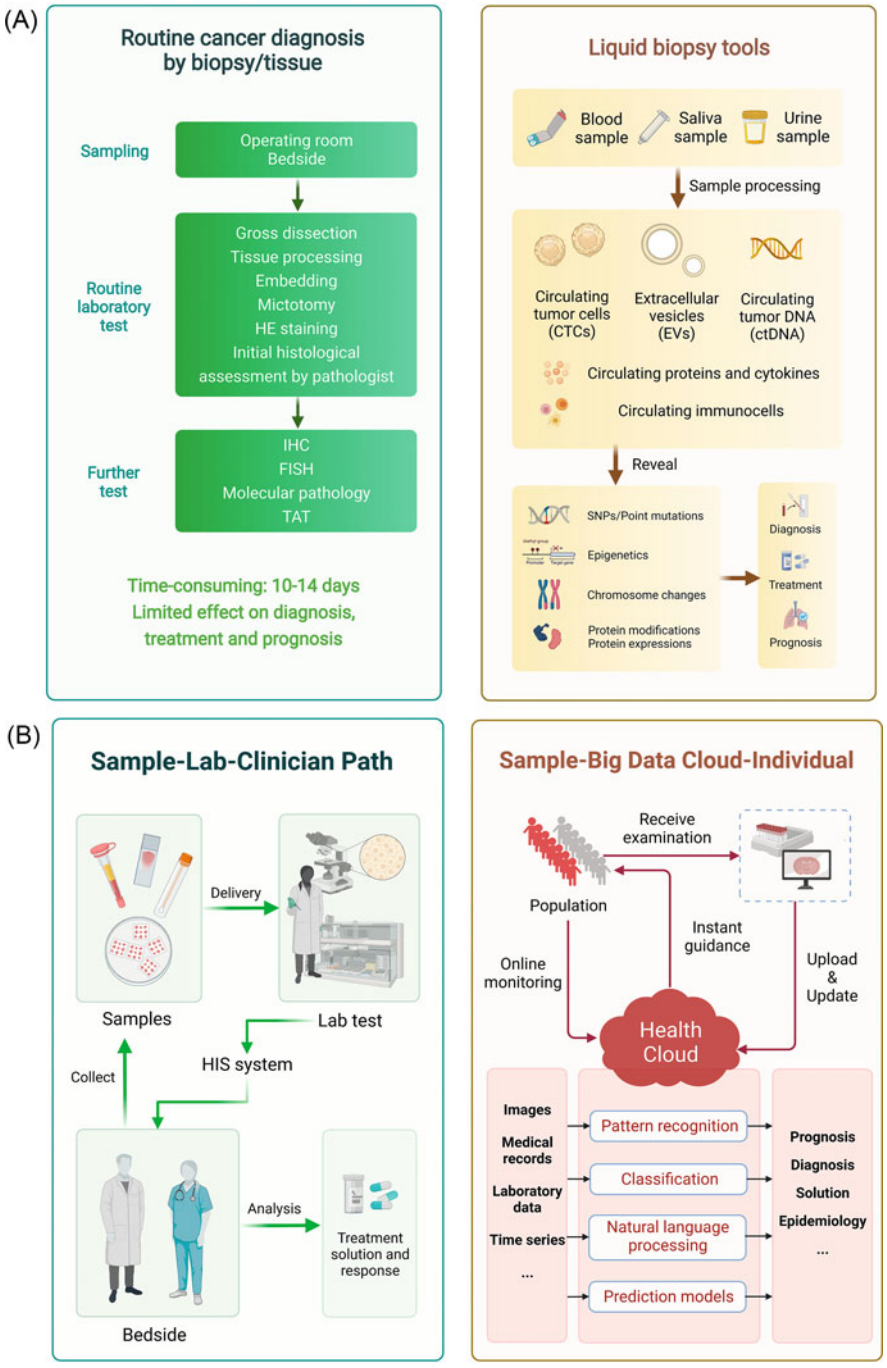

Fig. 1.6 Evolution from conventional diagnostics to next-generation diagnostics (NGD). (**a**) Liquid biopsy is changing the speed of diagnostics and the abundance of information by revealing the SNPs, epigenetics, chromosome changes, and the expression/modification of protein in a

for many years, which gives us lots of existing techniques for analysis. Some quantitative methods have been used to establish the relationship between cfDNA concentration and cancer, such as quantitative polymerase chain reaction methods (qPCR) (Spindler et al. 2014, 2015), DNA BEAMing, and digital droplet polymerase chain reaction (Sefrioui et al. 2015). Although these methods are advancing very well, the normal cfDNA level still needs to be tested in health cohorts, and consensus for the normalization strategy prevents clinical applications.

The exosome is essential to intracellular communication and metabolism in both physiological and pathological conditions. Some research shows that RNA and protein transport by exosomes can be a potential biomarker (Fig. 1.8). The complex informative composition of exosomes (DNA, RNA, protein, lipid, oligosaccharides, etc.) makes it suitable for multi-analyte testing (Yu et al. 2021). For example, researchers demonstrated a higher sensitivity in the detection of mutation in cancer patients by RT-PCR-based methods, which combine DNA and RNA detection. A new on-chip analysis target to exosomal miR-550, which suggests to be an indicator for cancer development, has been reported (Xu et al. 2020). This method includes rapid lysis of exosomes to release mi-RNA based on the surface acoustic wave (SAW), and the detection of this mi-RNA is achieved by ion-exchange nanomembrane. This detection can be performed in about 1.5 h with about 100-μL samples, which may provide a rapid, sensitive, and noninvasive approach to cancer diagnosis and prognosis (Taller et al. 2015).

These emerging liquid biopsy methods enable rapid and simple clinical diagnosis. However, some challenges remained in this area: for example, exosome production by cells and molecular content of exosome seem to be influenced by many factors. Also, the lack of standardization makes it difficult to get a promising conclusion in using exosomes.

1.3.2.2 Volatolomics

Volatolomics is an emerging frontier for rapid, noninvasive, and cost-effective diagnosis methods with many applications. The so-called volatile organic compounds (VOCs) are emitted from cells and their microenvironment, including, but not confined to, the VOCs from blood, breath, skin, feces, urine, and saliva

Fig. 1.6 (continued) molecular level, which assists the analysis of the diagnostic criteria, treatment solution, and prognosis prediction to a great extent. (**b**) The NGD is revolutionizing the clinical route in daily practice by turning the classic sample–laboratory–clinician path into an individual sample–big data cloud–individual analysis path, where the pattern recognition and classification algorithms, data storage system, natural language processing solutions, and image analysis are playing increasingly important roles. (**c**) The in vivo diagnostics will challenge the classical in vitro diagnostics since the continuous monitoring provided by wearable sensors, the delicate view captured by ingestible sensors, and the abundant biochemical information detected by implantable sensors could become a good supplement for discrete, invasive, and low-throughput in vitro testing. (**d**) After entering the omics era, high-throughput analysis methods and a wide range of biological sample sources (including volatolomics) provide more analysis methods and more comprehensive biomarkers. (Created with Biorender.com)

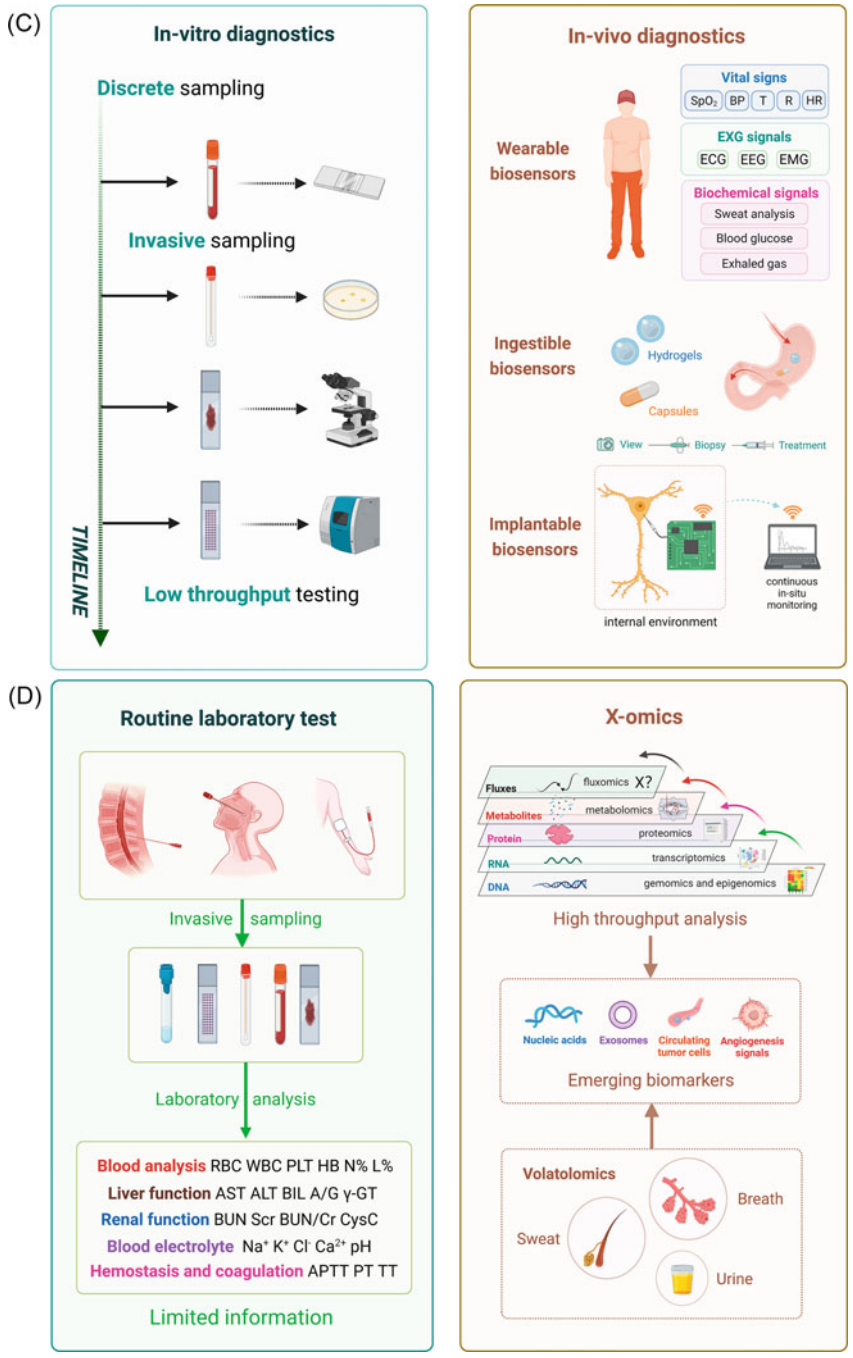

Fig. 1.6 (continued)

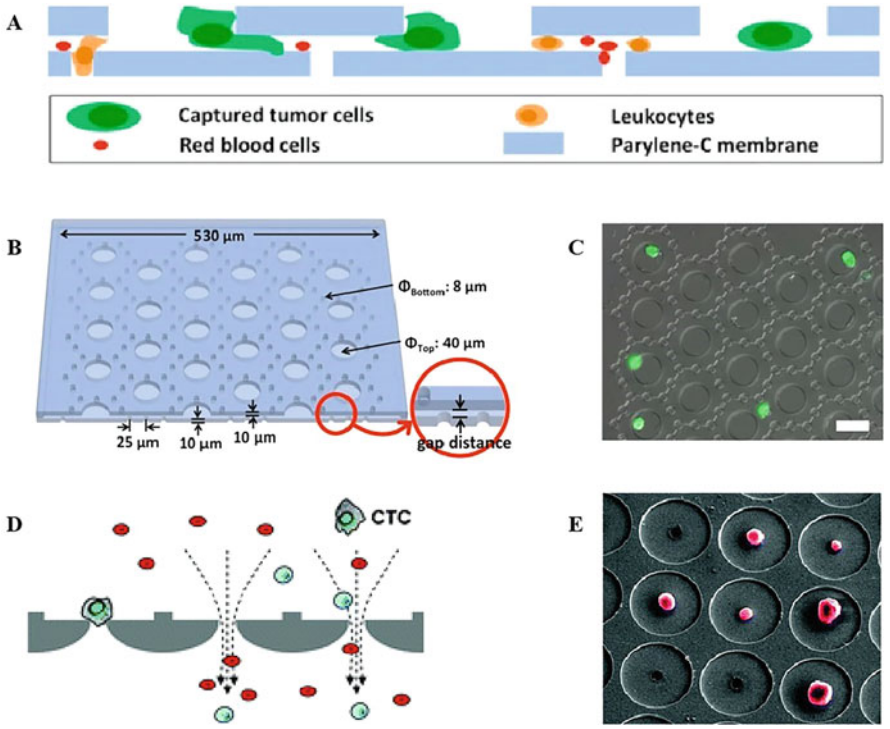

Fig. 1.7 A separable bilayer (SB) microfiltration device. (**a**) Schematic of device's cross-sectional view (the large top parylene-C pores form the edges, and the tumor cells are captured along them). (**b**) 3D view of an elemental unit model, including the gap distance in the inset. (**c**) Representative areas of the SB microfilter after filtration. MCF-7 breast cancer cells were GFP-expressing, which led to a green signal point on the filter (Da et al. 2014). (**d**, **e**) CTC recovery device equipped with the size-selective microcavity array. (**d**) Schematic of CTC recovery using the size-selective microcavity array. (**e**) SEM image of MCF-7 cells trapped on the microcavity array (Hosokawa et al. 2010)

(Broza et al. 2014, 2015; Vishinkin and Haick 2015). Volatolomics has been reported to have potential diagnosis value in myeloid leukemia (Dutta et al. 2018), cancer (Di Lena et al. 2016; Oguma et al. 2017; Chin et al. 2018; Guest et al. 2020), and numerous pathogenic bacteria (Djago et al. 2021). An induced volatolomics was reported in the diagnosis of respiratory disease. Researchers generated an engineered breath biomarker by local delivery of protease-sensing nanoparticles to the lung. The cleavage of the protease-sensing region will be accomplished by neutrophil elastase in pulmonary tissue, a protease with elevated activity in lung disease. After cleavage, the volatile reporters are released and are detected in exhaled breath (Chan et al. 2020). Notably, some obstacles remain in this area, including different confounding factors and lack of a standardized experimental procedure making it difficult to get an overview of the results (Fig. 1.9) (Di Lena et al. 2016; Djago et al. 2021).

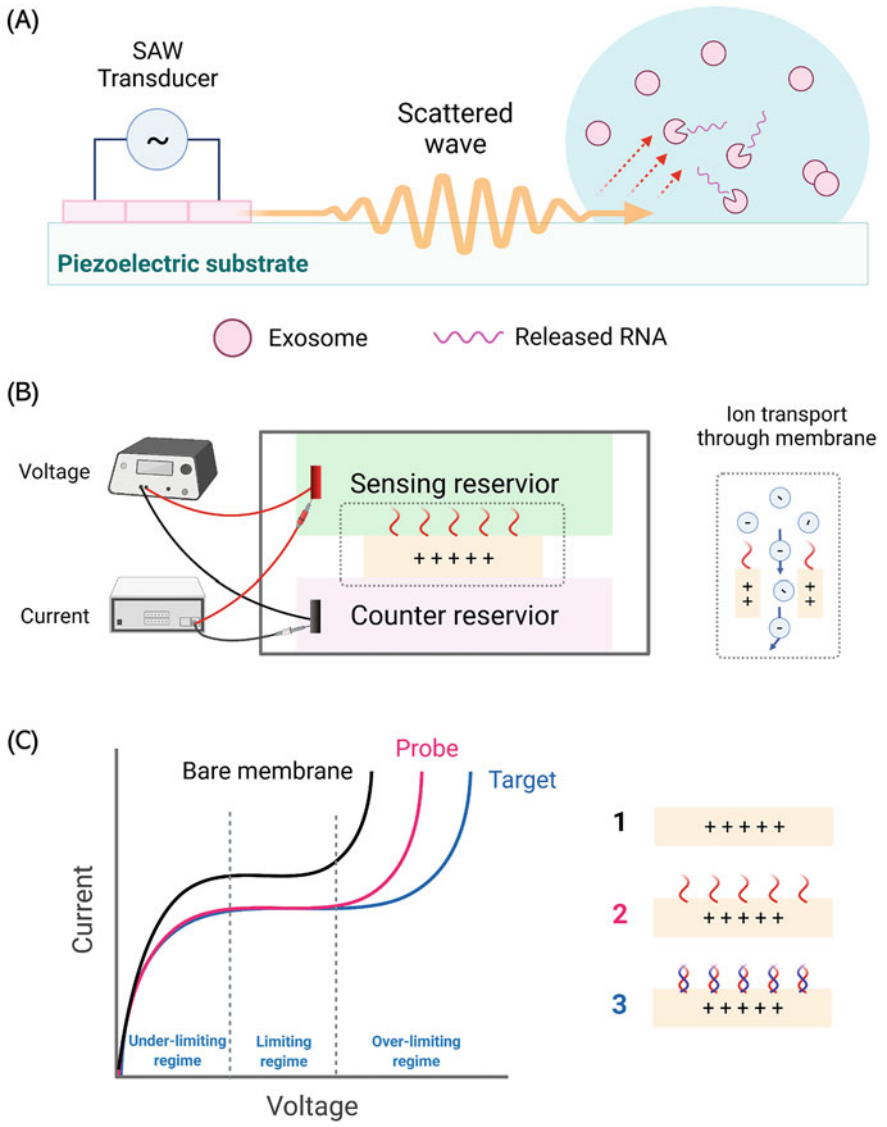

Fig. 1.8 A detector for exosomal RNA. (**a**) A side view of surface acoustic wave (SAW) device (SAW can lyse the exosomes, and then the exosomal RNA will be released and detected). (**b**) An ion-exchange nanomembrane sensor consists of two reservoirs separated by the membrane. RNA in the sensing reservoir hybridizes to complementary oligos immobilized on the surface of the membrane. (**c**) A characteristic current–voltage curve illustrating the under-limiting, limiting, and over-limiting regimes (Taller et al. 2015) (Redesigned with Biorender.com)

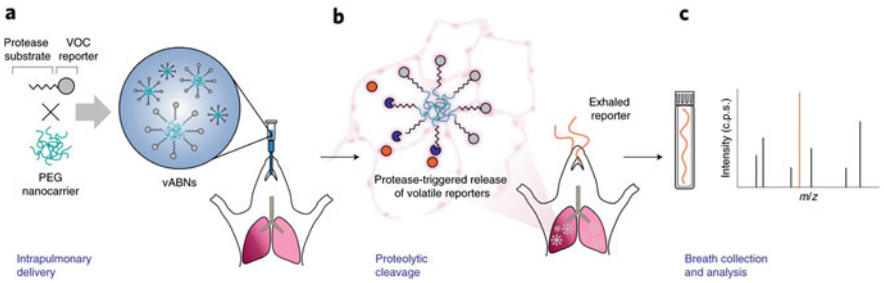

Fig. 1.9 An example of engineering synthetic breath biomarkers for respiratory disease. (**a**) Peptide substrates that are modified with VOCs are conjugated onto a multi-armed PEG nanocarrier, and then they are formulated into vABNs. Later, they are delivered into the lungs through intratracheal instillation. (**b**) VOC reporters are in a "gray" state when they are attached to the vABN, which means that they are undetectable and nonvolatile when the attachment remains. However, the extracellular proteases produced during respiratory disease could cleave surface-conjugated peptide substrates. In this way, the VOC reporters are released from vABNs, recover their "orange" state, namely of characteristic mass and volatility, and are exhaled. (**c**) Breath could be collected into a receptacle, and mass spectrometry could measure the VOC reporter concentration quantifiably (Chan et al. 2020)

1.3.3 In Vivo Diagnostics

One of the most common types of in vivo diagnosis is implantation devices, which can obtain physiological information in situ and rapidly. However, invasive operation, with a risk of infection together with usually higher fees, limited the use of these technologies (Li et al. 2021a). In some particular situations, in vivo diagnosis still has potential advantages, such as in intracranial pressure and electroencephalogram. To avoid the adverse effects of implanted sensors, some new technologies have been developed; many of these technologies have the same requirements as implantable therapeutic devices (Li et al. 2021a). For example, Kang et al. reported a new kind of bioresorbable silicon electronic sensor, which can continuously monitor the intracranial pressure and temperature. The signal was then transmitted by a biodegradable wire to a potentiostat for data transmission (Kang et al. 2016). Despite the fascinating promise of in vivo diagnostics, there are still some challenges that need to be solved for the further progress of this area. For instance, many of the bioresorbable devices may not have as complex functionalities as silicon-based chips. Also, further development of technologies that are fundamental in this area is necessary. These technologies include (1) in vivo biocompatibility that is more stringent than biocompatibility defined in wearable devices, and some of them are even fabricated by bioresorbable materials; (2) wireless communication, and this approach can help avoid discomfort and risk of infection when using wiring device; and (3) improved insertion strategies and mounting strategies. More details are covered in the chapter on "biologically compatible sensors" in this book (Fig. 1.10).

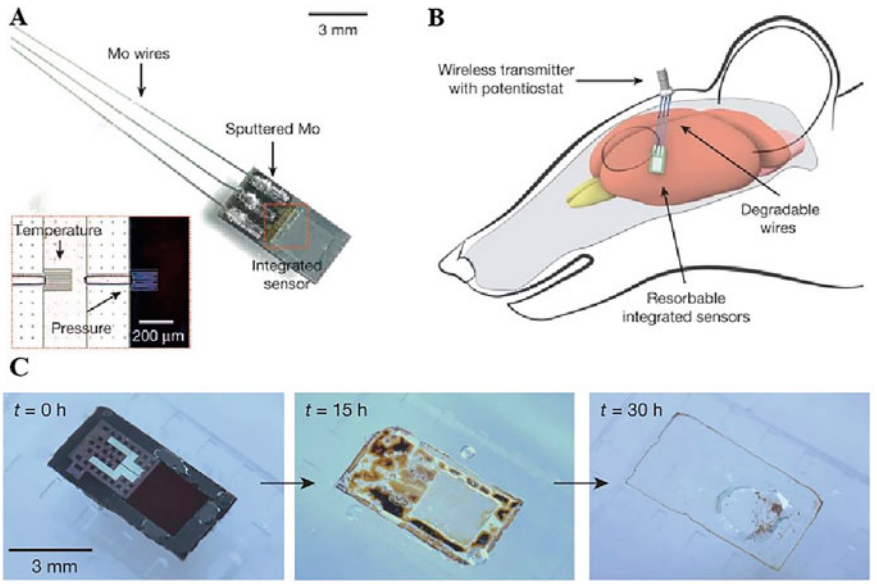

Fig. 1.10 Pictures of bioresorbable sensors detecting pressure and temperature. (**a**) The sensor was integrated with dissolvable metal interconnects and wires. As shown in the inset, the serpentine Si-NM structures form the sensing regions, where one that is not above the air cavity (left) responds only to temperature, and the one at the edge of the air cavity (right) responds primarily to pressure. (**b**) Diagram of a bioresorbable sensor system in a rat's intracranial space. For long-range detection and data transmission, there are electrical interconnects providing an interface to an external wireless data-transmission unit. (**c**) Pictures collected at several stages of accelerated dissolution of a bioresorbable pressure sensor upon insertion into an aqueous buffer solution (pH = 12) in a transparent PDMS enclosure at room temperature (Kang et al. 2016)

1.3.4 Wearable Health Monitoring Devices

In addition to in vitro and in vivo diagnosis, the skin, the body's largest organ, provides a valuable alternative diagnostic interface. Wearable devices can interact with them in a common way to obtain a variety of physiological health information. In contrast with traditional centralized healthcare services that require patients or samples to travel to the hospital, wearable sensing provides new insight into personalized medicine and point-of-care testing, as portable, wearable, remote, and timely features. Flexible sensors have become current trends in this area because of the mechanic mismatch and motion artifacts that occur between conventional rigid electronic materials and soft biological tissues. Technologies innovation in wearable sensors include, but not confined to, (1) new materials with special properties like flexible or stretchable, which can be used not only as substrate but also in sensors like some organic transistor (Kim et al. 2018; Cea et al. 2020); (2) sensor design, such as piezoelectric or piezoresistive; (3) device fabrication, like solution-based approaches or some mechanical-based printing; and (4) system integration not only

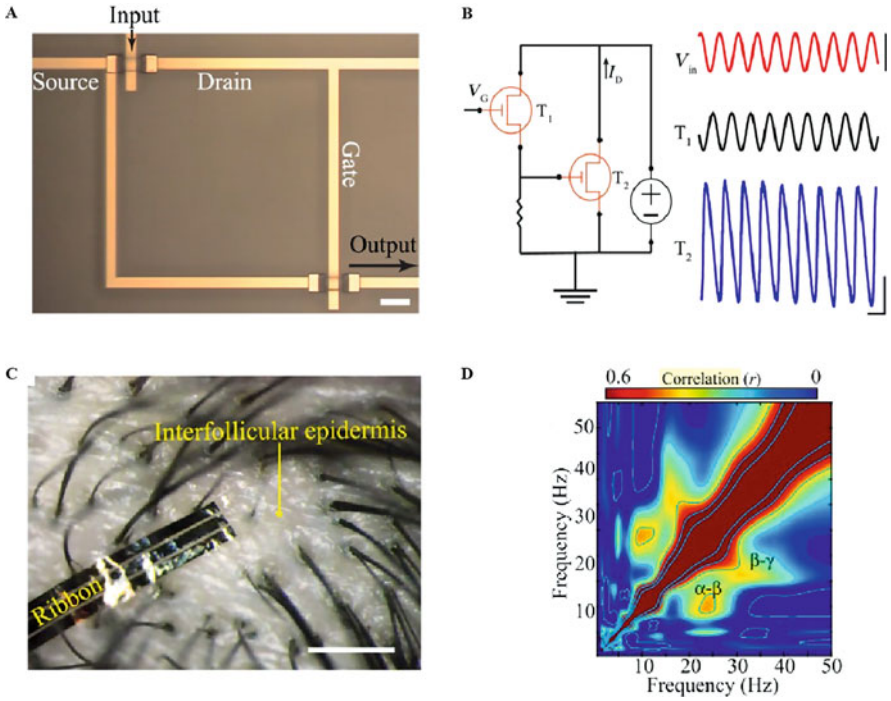

Fig. 1.11 An integrated ion-gated organic electrochemical transistor-based biosensor. (**a**) IGT-based NAND and NOR gates conform to the surface of orchid. (**b**) Temporal response of the output (O) drain current of a NOR (top) and a NAND (bottom) logic gate. (**c**) Picture of μ-EEG IGT conforming to human scalp, where devices were designed to fit the interfollicular epidermis (scale bar = 2 mm). (**d**) Comodulogram showing the cross-frequency coupling of the same recording epoch; significant coupling between α–β and β–γ is indicated (Spyropoulos et al. 2019)

with the form like an array, but some sensors also developed logic on the detection area. Spyropouls et al. reported an internal ion-gated organic electrochemical transistor that can be used in human electroencephalography (EEG). This device has a flexible substrate and gel-based biocompatible channel, which can be further integrated into amplifier logic (Spyropoulos et al. 2019). Some challenges still lie ahead before the daily use of wearable sensors in practical applications, such as the difficulty of distinguishing signals with physiological meaning from noise, the energy consumption of device, and the cost of device manufacturing (Wang et al. 2017). Further information on the features and design strategies of wearable devices can be found in the "biocompatible sensors" section of this book (Fig. 1.11).

1.3.5 Decision-Making Assistants

The development of Internet of things (IoTs) hardware promotes the fusion of multimodal information, especially represented by wearables and implantable devices. Data acquired by sensors need to be transmitted through wireless communication. These multimodal data constitute a health cloud concept that describes our physiological state. To minimize the probability of misdiagnosis, many algorithm strategies for decision fusion have been developed.

In general, decision fusion methods fall into three broad categories: probabilistic methods, evidential methods, and intelligent methods. Probabilistic methods represented by Bayesian theory use probabilistic and statistical foundations, which are effectively used in event fusion and are an efficient method for managing randomness (Antink et al. 2015). the theory of evidence relates to a combination of evidence to calculate the probability of an event. Fuzzy methods and artificial neural networks are examples of intelligent methods (Chowdhury et al. 2018; Köhler et al. 2015). Fuzzy-logic theory has been effectively used in fuzzy information processing and succeeds in making decisions and fusion systems for identifying and managing healthcare systems. The application of IoTs, information fusion, and artificial intelligence in multimodal sensing data-based diagnosis has initially been equipped with the function of a digital doctor. However, the biggest problem in the wide application of these decision assistants is still ethics and data norms.

1.4 Emerging Challenges

All of these emerging disease markers and detection technologies will be or are being used in the next generation of diagnostics, outlining a grand vision of medicine that enables precise diagnosis and disease intervention. However, we should also recognize that the next generation of diagnostics still faces challenges such as many scientific principles, engineering techniques, economic costs, and ethical challenges. Here we briefly analyze and look into some of these typical challenges:

1. **Sensitivity, accuracy, and reliability.** Although many studies have provided convincing experimental data, the actual clinical application is often faced with complex interference, and the accuracy and repeatability of the emerging sensors need to be compared with the reference technology and further cross-validation.
2. **Miniaturization and system integration.** Compared with the traditional diagnostic methods, the next generation of diagnostic technology inevitably requires direct contact with the human body to obtain physiological information in situ. But this poses a number of biocompatibility challenges. One of the most straightforward solutions is to implement a miniaturized device that integrates multiple sensing functions through appropriate packaging methods. However, this is a challenging system engineering problem, with difficulties such as power supply, signal transmission, and organizational rejection.

3. **Ethics-related issues.** The combination of IoTs technology and healthcare has given birth to the Health IoTs (H-IoTs). However, the application of H-IoTs technology also brings a series of ethical issues. For example, H-IoTs devices record personal health and activities with unprecedented scope and detail, leading to the emergence of ethical issues such as personal privacy in the H-IoTs scenario. In general, the main challenge facing H-IoT technology is how to scientifically design equipment and protocols, that is, to collect, share, process, and verify cross-domain data while achieving cost-effectiveness, advanced technology, scientific reliability, and ethics.
4. **Expense and patient compliance.** The cost of a single device is directly proportional to the intensity of technology, and the increasing cost of detection and deployment is also a challenge that cannot be ignored, although some optimized medical services can reduce administrative and operational costs. Some useful low-cost sensors have been developed in recent years (such as paper-based sensors), but there may be a trade-off between further cost reduction and more comprehensive and efficient diagnostic performance. Another challenge is patient compliance due to telemedicine. Because physicians cannot physically instruct patients to use specialized next-generation diagnostic equipment, the acquired data will be subject to motion artifacts and environmental interference or even completely ineffective. Standardized use is a viable solution to patient compliance.

Finally, we believe that driving basic research and development from the clinical application is also thought worthy of reference. Solving these problems for the next generation of diagnostics requires the collaboration of a variety of professionals, including electronic engineers, information scientists, and medical practitioners.

1.5 Conclusion

In this chapter, we systematically reviewed various concepts of next-generation diagnosis and sorted out some representative markers and sensor technologies in next-generation diagnosis. The most noteworthy points include the following two:

- **The core of next-generation diagnosis is precision medicine and individualized medicine.** The goal of next-generation diagnosis is to use omics technology and constantly update new discoveries in translational medicine to make the diagnosis and treatment of diseases individualized.
- **To truly realize the next generation of diagnosis, the advancement and innovation of sensor technology is an important foundation.** The basis of the next generation of diagnosis is the flourishing data technology, omics technology, and basic medicine. To make its concept fully close to the starting point and objective needs of clinical practice, it is necessary to have sensors to collect human signals. In order to improve patient compliance, this sensor-based collection must be efficient, accurate, low-cost, reliable, and ethical.

As witnesses in the medical–industrial interdisciplinary field, engineers and clinicians are looking forward to participating in the next-generation diagnostic revolution. The core of this revolution will be the close interaction of new sensor technologies and new disease markers. In this revolution, its participants are everyone who is interested in biosensing technology, and the beneficiaries will be a large number of people.

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