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REVIEW

From Diagnosis to Treatment: Recent Advances in Patient-Friendly Biosensors and Implantable Devices

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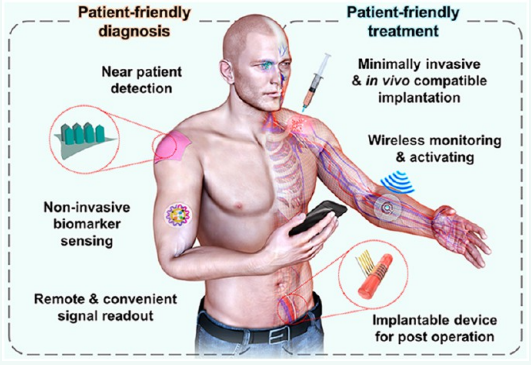
ABSTRACT: Patient-friendly medical diagnostics and treatments have been receiving a great deal of interest due to their rapid and cost-effective health care applications with minimized risk of infection, which has the potential to replace conventional hospital-based medical procedures. In particular, the integration of recently developed materials into health care devices allows the rapid development of point-of-care (POC) sensing platforms and implantable devices with special functionalities. In this review, the recent advances in biosensors for patient-friendly diagnosis and implantable devices for patient-friendly treatment are discussed. Comprehensive analysis of portable and wearable biosensing platforms for patient-friendly health monitoring and disease diagnosis is provided, including topics such as materials selection, device structure and integration, and biomarker detection strategies. Moreover, specific challenges related to each biological fluid for wearable biosensor-based POC applications are presented. Also, advances in implantable devices, including recent materials development and wireless communication strategies, are discussed. Furthermore, various patient-friendly surgical and treatment approaches are reviewed, such as minimally invasive insertion and mounting, *in vivo* electrical and optical modulations, and post-operation health monitoring. Finally, the challenges and future perspectives toward the development of the patient-friendly diagnosis and treatment are provided.



KEYWORDS: *patient-friendly diagnosis and treatment, point-of-care testing, portable and wearable biosensor, noninvasive biosensor, implantable devices, wireless communication, functional materials, biocompatibility*

There is an unprecedented challenge of providing health care and controlling diseases worldwide. Infectious and chronic diseases, such as Alzheimer's Disease (AD), cancer, heart disease, mental illness, stroke, acquired immunodeficiency syndrome (AIDS), and novel coronavirus 2019 (COVID-19), remain major global health threats.[1−14] In particular, the pandemic of COVID-19 has infected more than 90 million people in merely 13 months since the outbreak in January 2020.[15] The rapid increase in confirmed cases makes the prevention and control of COVID-19 extremely difficult, causing enormous economic loss and health care burden on the global community.[15,16]

One effective way to overcome the aforementioned challenges is to test a vast number of people and detect diseases at an early stage.[17−28] However, most of the current diagnostics are complex and are mainly suitable for centralized hospitals and laboratories, which require long testing time from hours to days.[29−36] Furthermore, timely large-scale disease diagnostics may be limited by medical resources, facilities, and the number of professionals in specific regions.[37] Therefore, there is an urgent need for patient-friendly diagnostic methods that are rapid, simple, accurate, and require low sample volumes and less testing reagents.[35] This is possible using portable and wearable biosensors for point-of-care testing (POCT), which allow patients to self-test without visiting health care facilities, hence, greatly reducing health care time and costs, as well as the risk of infection from contagious diseases.[35,38,39] The World Health Organization

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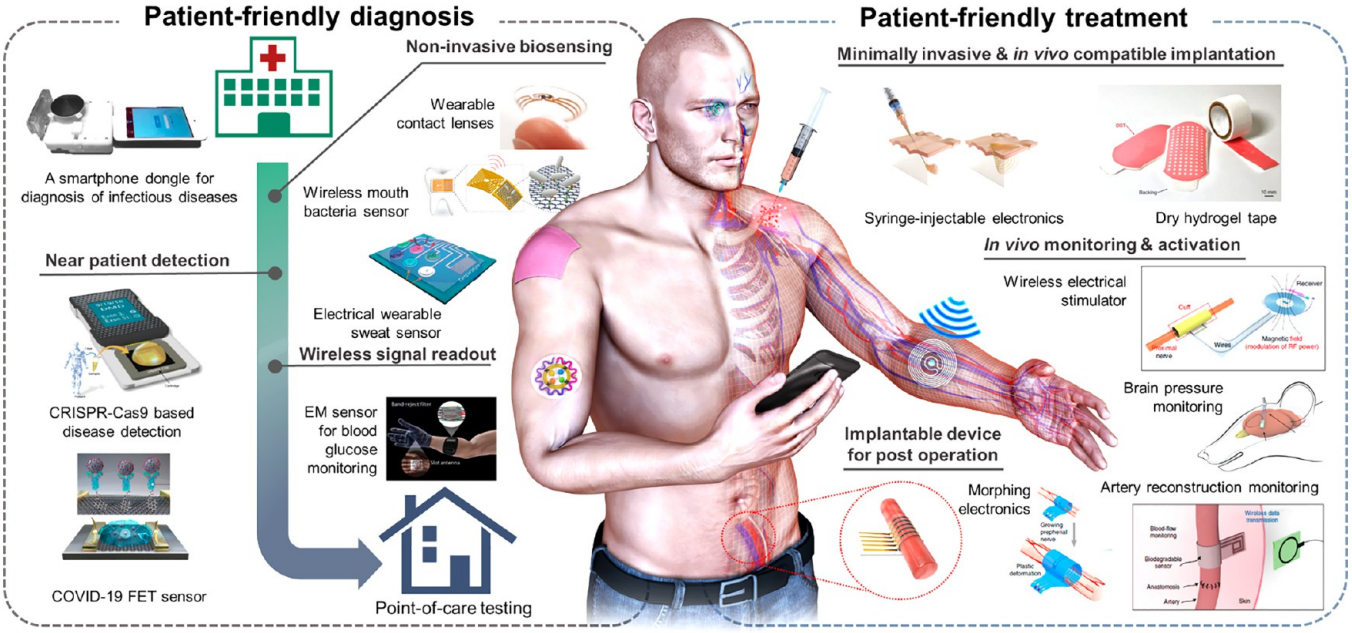

Figure 1. Schematic illustration of patient-friendly diagnosis and treatment. Reproduced in part with permission from ref 203 (copyright 2015 American Association for the Advancement of Science), ref 176 (copyright 2019 Nature Publishing Group), ref 104 (copyright 2020 American Chemical Society), ref 302 (copyright 2014 Nature Publishing Group), ref 317 (copyright 2012 Nature Publishing Group), ref 278 (copyright 2016 Nature Publishing Group), ref 330 (copyright 2020 American Association for the Advancement of Science), ref 386 (copyright 2015 Nature Publishing Group), ref 67 (copyright 2019 Nature Publishing Group), ref 63 (copyright 2016 Nature Publishing Group), ref 64 (copyright 2018 Nature Publishing Group), ref 68 (copyright 2019 Nature Publishing Group), and ref 73 (copyright 2020 Nature Publishing Group).

(WHO) issued the ASSURED criteria for POCT sensing platforms, which specified that POCT devices should be affordable, sensitive, specific, user-friendly (simple to perform in a few steps with minimal training), rapid and robust (results available in less than 30 min), equipment-free, and delivered to the end-users (deliverable to those who need them).[40] Over the past decade, a tremendous amount of portable and wearable POCT biosensors have been developed for cost-effective, disposable, or reusable diagnostic devices, suited for on-site detection and analysis.[41−46] The emergence of chemical and biological sensing platforms, lab-on-a-chip (LOC) systems, Internet of Things (IoT) technology, and soft, stretchable, and biocompatible electronics have greatly facilitated such advancement of portable and wearable biosensors.[35,47−55]

In addition to patient-friendly diagnosis, there is also an urgent need for patient-friendly treatment.[56,57] Conventional surgery-based medical treatments entail several disadvantages, including risk during operation, long recovery time after the operation, and huge economic burden.[58] In this regard, implantable devices have brought forth effective convenient treatment options.[58−61] Since the initial proof-of-concept demonstrations of implantable devices, the number of reported research in the related area dramatically increased over the past few years, resulting in a variety of implantable devices with desired functionalities.[62−65] For example, fabrication of implantable device with hydrogel enabled stable mounting of implantable devices on a human organ with no mechanical mismatch, eliminating the risk of inflammation and wound formation.[66,67] Implementation of a wireless communication system into implantable devices enabled seamless operation without the need of skin perforation for connecting the device outside the human body.[64,68,69] Furthermore, the use of functional materials such as biodegradable and self-healable materials eliminated the need for surgical removal of implantable devices after its use.[63,64,70−73]

In this review, we provide a comprehensive assessment of the state-of-art patient-friendly biosensor-based diagnosis and implantable device-based treatment (Figure 1). We discuss recent trends, key achievements, and the remaining challenges of patient-friendly biosensor-based diagnosis and implantable device-based treatment.

INTRODUCTION TO BIOSENSORS

In general, a biosensor is a device that measures biological or chemical reactions by generating signals proportional to the concentration of the analyte. Figures of merit of biosensors are sensitivity, selectivity, limit of detection (LOD), limit of quantification (LOQ), detection range, repeatability, and reproducibility. Details of these parameters can be found in the following book and articles.[74,75] A typical biosensor contains four basic units: bioanalytes, bioreceptors, signal transducers, and a signal readout system[76−79] (Figure 2). Bioanalytes are the specific biomarkers that are measured and evaluated as the indicators for health monitoring or disease diagnostics.[80] Common biomarkers include deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, toxins, hormones, cytokines, metabolites, ions, whole cells, viruses, and bacteria.[35,81] A bioreceptor is responsible for selective recognition of the bioanalyte, and the signal transducer translates the biorecognition event into a readable signal.[82] Finally, a signal-readout system displays the signal in digital forms.[49]

Bioreceptors. The selectivity of a biosensor is determined by the bioreceptor, which allows the specific binding of the

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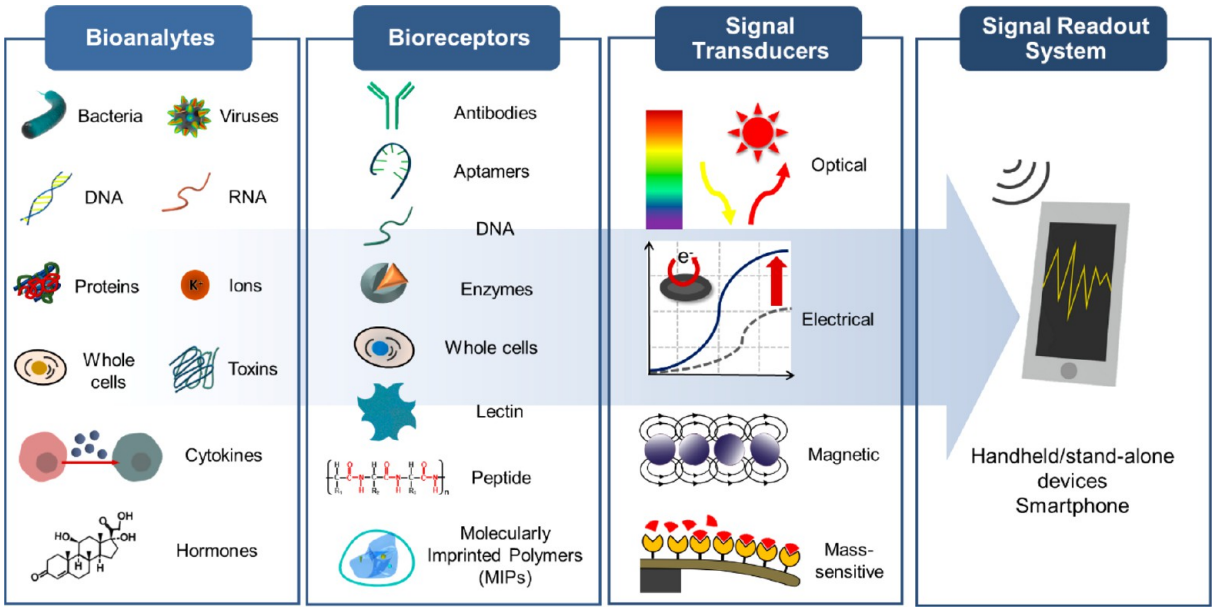

Figure 2. Schematic illustration of the four basic units of biosensors.

target bioanalytes. Natural bioreceptors include enzymes, antibodies, DNA, aptamers, lectin, peptides, and whole cells.[35,83−85] Particularly, aptamers offer flexibility in their structure design, which not only allow high sensitivity and selectivity toward target biomolecules but also enable the detection of recently discovered biomolecules.[86,87] Aptamers have several advantages as recognition elements when compared to traditional antibodies. They are small in size, chemically stable, and cost-effective.[86,87] Therefore, aptamers have attracted intense interest and found wide applications in diagnostics and therapeutics.[86,87]

However, natural bioreceptors have inherent drawbacks, such as limited stability and shelf life, high cost, labor-intensive synthesis, difficult purification process, and limited compatibility with most transducer surface.[88,89] To tackle these issues, considerable efforts have been made to mimic the interactions between biomolecules and natural bioreceptors. Molecular imprinting is the best-known technique to obtain antibody mimicking bioreceptors.[90] Molecular imprinting is based on the polymerization of functional monomer around targeted biomarkers through three different approaches: noncovalent assembly, covalent bonding, and ligand exchange.[90] The targeted biomarker is then removed to generate three-dimensional cavities in or on the polymerized substrate for specific recognition of the same biomarker.[90] Specific sites can be created for various biomarkers, including amino acids, hormones, drugs, metal ions, toxins, antibiotics, pesticides, nucleic acids, proteins, microorganisms, viruses, and cells.[49,90−92] Extensive studies which employ molecular imprinted polymers (MIPs) for biomarker recognition have been reported in both optical and electrochemical biosensors.[92,93]

It is of vital importance to ensure stable and reliable immobilization of a sufficient density of bioreceptors on the sensing surface.[50,94−96] Bioreceptors can be immobilized by either noncovalent binding or covalent binding depending on the functional groups on the sensing surface.[79,97−99] Noncovalent binding immobilizes the bioreceptors through physical adsorption (*e.g.*, van der Waals forces, hydrogen bonds, hydrophobic forces, and ionic interactions).[100,101] Generally, noncovalent binding does not cause chemical defects of the sensing surface; thus, it often negligibly affects the electrical properties of the sensing material. Moreover, the immobilization time for noncovalent binding is relatively short compared to that for the covalent binding. However, noncovalent binding suffers from chemical instability, low reproducibility, and poor durability due to its weak binding strength. In comparison, immobilization through covalent binding forms a strong and irreversible bonding through surface functionalization (*e.g.*, $-NH_2$, $-COOH$, $-OH$) or cross-linking chemicals, such as self-assembled monolayer (SAM) glutaraldehyde, carbodiimide hydrochloride (EDC) cross-linker, and *N*-hydroxylsulfosuccimide (NHS).[95,102] Covalent binding has been widely used in LOC sensing platforms owing to its high stability in the various sensing environments.[95] However, covalent binding often results in the formation of chemical defects on the sensing surface, potentially degrading the electrical properties of the transducing material, which commonly affects the sensing performance of electrical biosensors. To tackle this critical issue, many studies have been reported that minimizes defects on the sensing surface.[103,104]

Signal Transducers. A signal transducer in biosensor plays a critical role by generating a measurable signal that corresponds to the targeted biomarker concentrations.[35] Optical and electrical transducers are capable of delivering easy-to-use, rapid, label-free, and cost-effective analysis, making them suitable for miniaturized multiplexed portable and wearable biosensors, including general biosensors.[105−107] Optical biosensors are the most commonly reported class of biosensors, which transduce biological events using optical signals such as absorbance, fluorescence, chemiluminescence, and surface plasmon resonance.[108,109] Optical detections can be conducted by labeled or label-free methods.[108] Recent advances in patient-friendly diagnostics are mainly based on colorimetric and fluorescence biosensing platforms.[110,111] Due to the intrinsic color differences of nanoparticles, they have been widely used in optical biosensors.[112,113] Furthermore,

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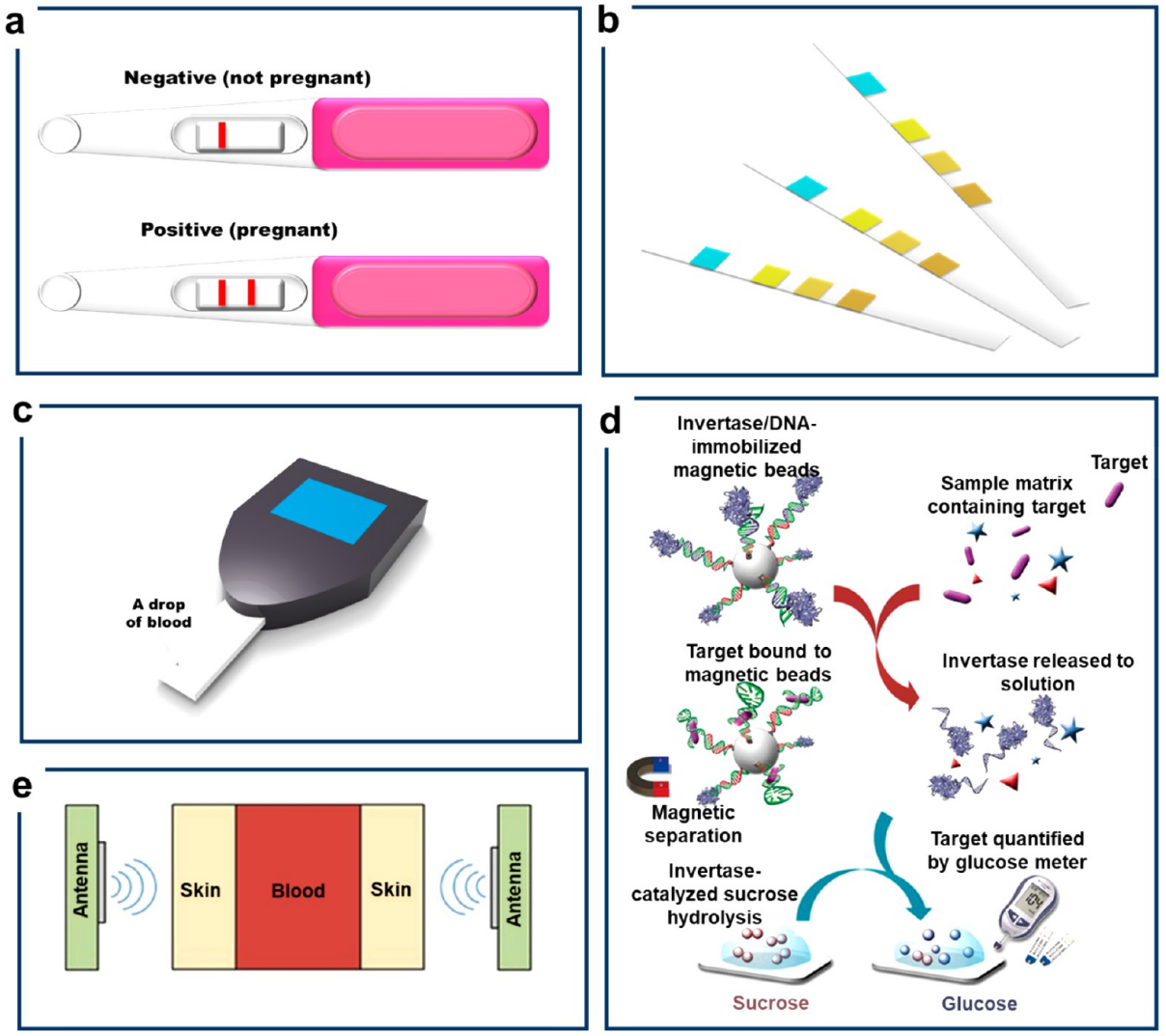

Figure 3. POC diagnosis utilizing commercialized portable biosensors. (a) Conceptual illustration of the colorimetric pregnancy test. (b) Conceptual illustration of urine test strips (dipstick tests). (c) Conceptual illustration of the personal blood glucose meter. (d) Schematic illustration of biosensing strategies of detecting a wide range of nonglucose targets using a personal glucose meter. Reproduced with permission from ref 142. Copyright 2011 Nature Publishing Group. (e) Design concept of a millimeter (mm) wave glucose sensor. The skin/blood/skin stacked structure is placed in between the two antennas. Adapted with permission under a Creative Commons CC BY License from ref 144. Copyright 2017 Nature Publishing Group.

nanoparticles can enhance or quench the optical signals, which improved the sensor performances.[114]

In regards to electrical biosensors, conductometry, potentiometry, amperometry, voltammetry, and impedimetry are the most common types of electrical transducing mechanisms.[115] The sensing material is essential to sensitively translate biological events into electrical signals.[115] In particular, nanomaterials, such as carbon nanotubes, graphene, and nanoparticles, have been commonly adopted to facilitate a high surface area to volume ratio, a large active area of immobilizing bioreceptors, and a rapid charge transfer, leading to the improvement in the sensitivity, detection range, and reaction time.[116−118]

The biological events can be recognized based on the formation of an electrical double layer (EDL) generated by the electrolytes under a continuous electric field and by direct charge transfer that occurs when the biomarkers bind to the bioreceptors.[102,119−121] Regardless of this type of detecting mechanisms, it is important to fabricate the transducing layer with a large surface area for biorecognition. The nanoscale transducing film can be fabricated into a thin and highly dense layer or a three-dimensional structure.[102,122,123] This film morphology can enhance the current signal produced by the redox reaction of amperometry-based biosensors using enzymes and amplify the scattering effect in conductimetry-based biosensors because of the high surface area to volume ratio.[118,124] For potentiometry-based biosensors, when the detection of biomarkers occurs outside of the EDL, the Debye length screening effect can shield the charge on the biomarkers, making it difficult for the biomarkers to be detected. Details of the Debye length effect can be found in the following articles.[102,122,123] Diluted buffer solution which has lower ionic strength has been commonly used to increase the effective screening length (the Debye length) on the interface, through which charge screening can be reduced.[125,126] For biomarkers where diluted buffer solution cannot be used (*i.e.*, ionic strength cannot be lowered), a porous and biomarker-permeable polymer layer, such as

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polyethylene glycol (PEG), can be incorporated into the signal-transducing layer to increase the Debye length by modifying the dielectric properties of the electrolyte.[127]

Moreover, nonspecific binding can occur at the interface between the transducer and nontargeted bioanalytes, which generates background noise and reduces sensing performance. Therefore, this phenomenon should be addressed as a fundamental problem for biosensor design. In order to reduce nonspecific binding, biomaterials, such as bovine serum albumin (BSA), have been deposited on the transducers to reduce the surface energy of the signal-transducing surface.[128]

In addition to optical and electrical biosensors, radio frequency (RF), microwave (MW), millimeter wave (mmW), and terahertz (THz) biosensors employ capacitive sensing mechanisms (measuring permittivity in terms of capacitance or scattering parameters). These sensors have utilized interdigitated capacitors, resonators, and microstrip structures.[129−131]

Signal Readout System. Stand-alone/hand-held diagnostic platforms integrated with digital signal readout systems such as smartphone applications (apps) are rapidly emerging as potential cost-effective alternatives to the centralized hospital or laboratory-based diagnostics.[49,132] These digital signal readout systems offer qualitative and quantitative detection results for various targets ranging from small molecules to pathogens.[35,133−138]

PORTABLE BIOSENSORS

Recent Trends in Portable Biosensors. *POC Diagnosis Utilizing Commercialized Portable Biosensors.* Early developments in portable biosensing devices have enabled them to be applied in a wide range of disease diagnosis and monitoring settings, including commercially available colorimetric pregnancy tests that detect human chorionic gonadotropin (hCG)[139] (Figure 3a), dipstick test that detects various pathological changes in a patient's urine, including ketone, glucose, and pH[140] (Figure 3b), and electrical personal blood glucose meter that detect glucose concentration in blood[49,141,145] (Figure 3c). Subsequently, taking advantage of the wide availability and low cost of the pocket-sized personal glucose meter and the selective binding ability of DNA aptamers, Lu *et al.* demonstrated a method using a glucose meter to quantify nonglucose targets, such as cocaine, adenosine, interferon-gamma (IFN-γ) of tuberculosis, and toxic metal ions[142] (Figure 3d). Apart from the cases stated above, other commercial tests for *Escherichia coli* O157, influenza A and B viruses, *Helicobacter pylori*, human immunodeficiency virus, tuberculosis, and malaria have also achieved success.[146]

Moreover, the rapid growth in electromagnetic (EM) wave biosensors has aroused great interest among researchers due to their merits of minimal or noninvasive label-free diagnostic process and cost-effectiveness.[105] For example, since blood permittivity depends on the blood glucose levels, the transmission coefficient variation of the blood is correlated to its glucose levels (Figure 3e). One commercially available RF biosensor for glucose monitoring is the hand-held device named Glucowise (MediWise, London, UK), which is a noninvasive, 100% pain-free device that allows glucose level monitoring without the need for skin piercing.[105,143,144]

In recent years, driven by the high exposure to infectious diseases throughout the world, there has been a rapid growth in developing fully integrated optical or electrical portable biosensors for patient-friendly diagnostics.[44,147−149] Specifically, diagnosis based on LOC platforms, enabled by miniaturization, integration, and automation of multiple assay procedures on a single chip, facilitated the translation of biosensors to POC settings.[150,151]

Recent Trends in Optical Portable Biosensors. In particular, immunochromatographic lateral flow assays (LFAs, also known as dipstick tests) and microfluidics-based fully integrated biosensing platforms have been extensively studied for the development of optical LOC sensing platforms.[105,152] In particular, paper-based LFA technology has undergone rapid development as they meet the ASSURED requirements for POCT applications.[153] The colorimetric method has been predominantly used in LFA for multiplexed detection owing to its simplicity and visual readout. Conventional LFA results are mainly based on Au nanoparticle (NP) accumulation induced colorimetric signals, and they can be read out by the naked eye. It is a simple and rapid detection strategy. However, quantification of biomarker concentration is difficult, and sensitivity needs further improvement.[154] Hence, recent LFA developments have been focusing on improving sensitivity, which exploit various chemical recognition and signal amplification strategies.[155] For instance, quantum dots (QDs) have been used in fluorescent immunosensors for the detection of critical biomarkers, such as C-reactive protein (CRP), RNA, and carcino-embryonic antigen detection.[156−158]

Recent Trends in Electrical Portable Biosensors. In addition to optical biosensors, field-effect transistor (FET)-based electrical biosensors integrated with wireless communication systems are emerging for POCT applications due to their attractive properties, such as high sensitivity and miniaturized devices.[159,160] Generally, a FET is composed of several layers: source, drain, gate electrodes, channel, and dielectric layer; however, in biosensing platforms, the dielectric layer is replaced with ionic liquid that contains the biomarkers.[161,162] Among different types of semiconducting materials, nanomaterials have been commonly used as the channel material to improve the sensing performance, including graphene, carbon nanotubes, and metal nanowires.[79,116,163] Due to their high surface to volume ratios and reactive chemical functional groups, biosensors utilizing these materials can provide rapid testing results with high sensitivity.[49,118,164−166] Though the signal analysis from FET-based biosensors is relatively complex, it can be simplified by converting the drain current−gate voltage (I−V) transfer curve into resistance.[167−170]

Using the aforementioned detecting methods, various types of biomarkers can be detected by portable biosensors for the diagnosis of different diseases. Depending on the targeted biomarker, we discuss three main portable sensing platforms below: molecular assay-based biosensors, immunoassay-based biosensors, and biosensors for cells and related biomarkers.

Molecular Assay-Based Portable Biosensors. The pathogenicity of human diseases is very complex and commonly affected by various chemical and physical substances. Detecting genetic mutation or the presence of the genetic material of specific pathogens is one of the standard diagnostic methods for the confirmation of patients' pathological states.

Since its introduction in the mid-1980s, polymerase chain reaction (PCR) has been considered as the gold standard for molecular diagnosis, enabling the amplification of target

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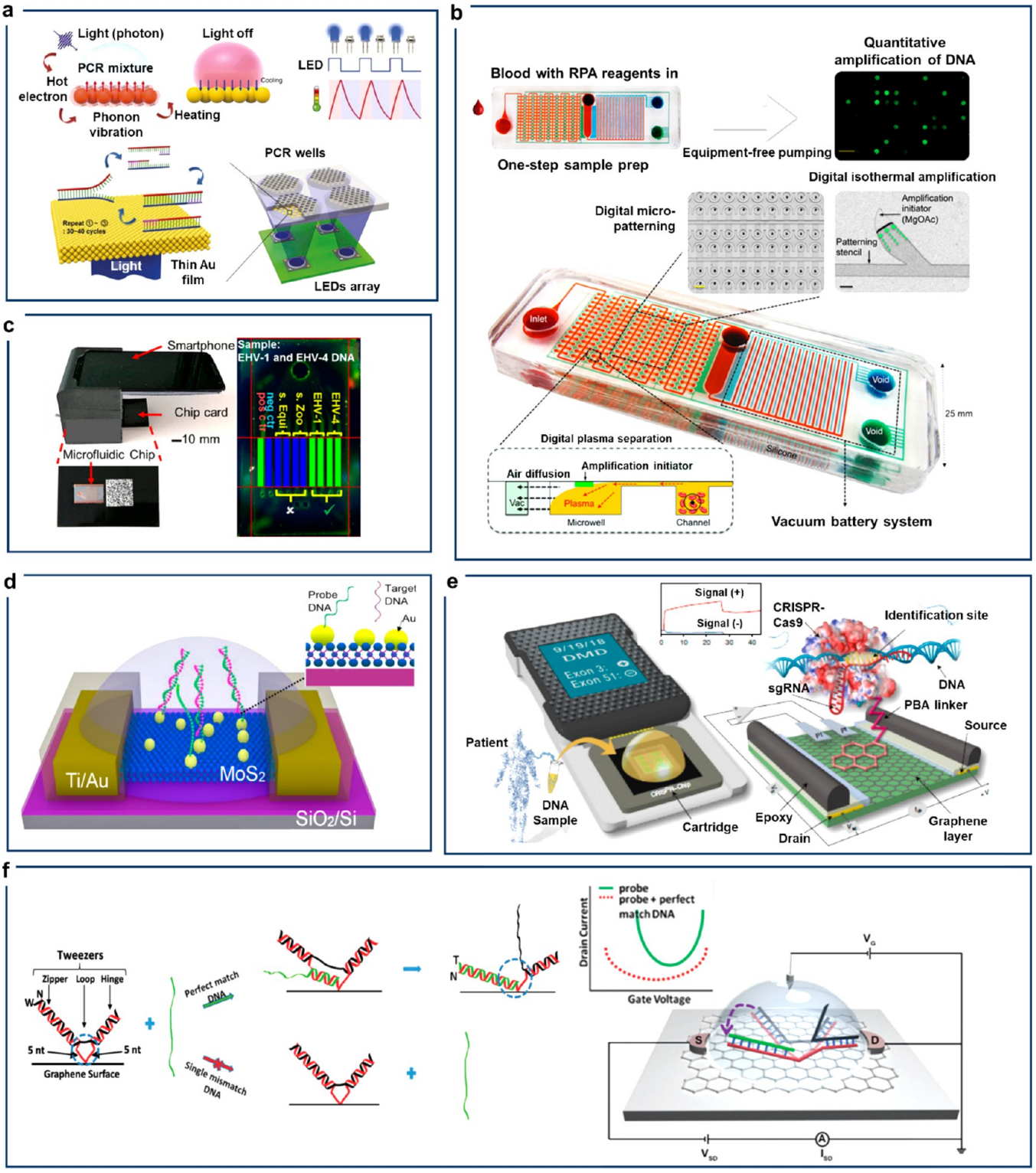

Figure 4. Optical and electrical molecular assay-based portable biosensors for POCT. (a) Ultrafast photonic PCR with plasmonic photothermal light to heat conversion and subsequent heating of the PCR mixture through photon−electron−phonon couplings. Adapted with permission under a Creative Commons CC BY License from ref 171. Copyright 2015 Nature Publishing Group. (b) Self-powered integrated microfluidic POC low-cost enabling (SIMPLE) portable chip for digital quantitative nucleic acid testing directly from human blood samples *via* recombinase polymerase amplification (RPA). Adapted from ref 172. Copyright the authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC) http://creativecommons.org/licenses/by-nc/4.0/. Copyright 2017. (c) Smartphone-based fluorescence microscopy with multiple flow channels/microfluidic chip for multiplexed bacteria and virus detection by loop-mediated isothermal amplification (LAMP). Reproduced from ref 173. Copyright 2017 American Chemical Society. (d) Schematic illustration of MoS_2- and AuNP-based field-effect transistor immobilized with probe DNA for down syndrome diagnosis. Reproduced from ref 175. Copyright 2019 American Chemical Society. (e) Schematic illustration of a graphene field-effect transistor-based biosensor detecting target

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Figure 4. continued

nucleotide sequences by utilizing CRISPR-Cas9 as the bioreceptor. Reproduced with permission from ref 176. Copyright 2019 Nature Publishing Group. (f) Design of the DNA nanotweezer, which could place longer DNA sequences horizontally and closer to the graphene transistor surface than conventional double-stranded DNA probe design. Reproduced with permission from ref 177. Copyright 2018 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim Publishing Group.

templates containing just a few molecules to detectable levels. For the amplification of RNA targets, reverse transcription PCR (RT-PCR) is needed, in which RNA strands are first reverse transcribed into their DNA complement, followed by amplification of the resulting DNA using standard PCR. Though the PCR-based test provides sensitive and quantitative molecular testing results, there are several limitations associated with conventional PCR, such as the need for bulky equipment for rapid and precise temperature control, several hours of assay time, and complicated operation requiring trained technicians.[178] Moreover, PCR is sensitive to the presence of inhibitors in biological samples.[179]

Recently, the field of molecular diagnostics has shifted from the centralized diagnostic model to decentralized patient-centered POC settings. The essential features of POC molecular diagnosis platforms include integrated sample preparation and signal amplification systems, as well as miniaturized sensing devices.[35,148] Appropriate sample preparation is the first essential step for sufficient nucleic acid amplification.[180,181] In this regard, it is ideal to integrate sample preparation steps with the enzymatic reaction into a single platform.[147,182] Moreover, as mentioned above, traditional PCR needs to be supplanted as it requires bulky equipment for thermocycling. In this regard, recent research has turned toward low thermal inertia PCR or isothermal nucleic acid amplification methods for the development of chip-based PCR.[147,181,183]

Ultrafast chip-based PCR, characterized by low power consumption, compact size, and simple operation, is ideal for timely POC molecular diagnosis. To achieve ultrafast PCR, Lee *et al.* introduced a photonic PCR method, utilizing plasmonic photothermal light to heat conversion *via* photon−electron−phonon coupling[171] (Figure 4a). They used gold (Au) thin film for photonic heat conversion owing to its plasmon-assisted high optical absorption (approximately 65% at 450 nm, the peak wavelength of the light-emitting diode heat source). The plasmon-excited Au film was capable of rapidly heating the surrounding solution to over 150 °C within 3 min. Using this method, ultrafast thermal cycling of 30 cycles from 55 °C (temperature of annealing) to 95 °C (temperature of denaturation) is accomplished within 5 min. This simple, robust, and low-cost approach could be integrated into a variety of devices, including on-chip thermal lysis and heating for isothermal amplifications.[171]

Isothermal PCR makes use of enzymes to perform strand separation, eliminating the need for thermal cycling.[181] Many researchers have reported isothermal PCR-integrated with the lateral flow and microfluidic devices to achieve autonomous, portable, and low-cost molecular diagnosis.[172,174,184,185] In particular, Lee *et al.* reported a self-powered integrated microfluidic POC low-cost enabling (SIMPLE) chip capable of on-site nucleic acid detection without sample preparation steps[172] (Figure 4b). This simple chip allowed rapid quantitative digital nucleic acid detection directly from human blood samples ($10-10^5$ copies/μL of methicillin-resistant *Staphylococcus aureus* DNA, ~30 min) *via* isothermal recombinase polymerase amplification (RPA, explained below).[172]

Multiplexed isothermal molecular diagnostic platforms are also critical in POC molecular diagnosis due to the increasing need to rapidly identify infectious viral and microbial pathogens in resource-limited settings. In this regard, Cunningham *et al.* reported a platform for multiplexed analysis of disease-specific DNA sequences[173] (Figure 4c). It utilizes a smartphone camera as the signal acquisition device, and it is connected to a hand-held "cradle" that interfaces the phone with a silicon-based microfluidic chip embedded within a credit-card-sized cartridge. By the insertion of loop-mediated isothermal amplification (LAMP, explained below) reagents into the distinct lanes of the microfluidic chip, respiratory pathogen target nucleic acid sequences can be detected through fluorescent signals when excited with light-emitting diodes (LEDs). A software app running on a smartphone analyzes the fluorescent signal automatically. Notably, this sensing platform achieved detection limits comparable to those obtained by laboratory-based methods.[173]

Isothermal amplification methods for COVID-19 diagnosis are also considered to be promising testing technologies to halt this global health crisis. Without the control and prevention of transmission through early detection, COVID-19 would spread rapidly and eventually lead to higher mortality. The "gold standard" test for COVID-19 is based on RT-PCR. However, the RT-PCR test takes 3 h or longer to complete and requires extensive human labor. The method was also limited by the shortage of RNA extraction kits and the number of real-time PCR machines in the centralized hospital or laboratories.[174]

Two isothermal techniques, LAMP and RPA, are considered to be the two most promising techniques for rapid and sensitive diagnosis of COVID-19. LAMP uses a strand-displacing DNA polymerase together with four specially designed primers containing regions of complementarity to six target sequences. Since LAMP includes primers that anneal to six specific target regions, it is highly sequence-specific.[181,186] Due to its merits, LAMP is the most widely used isothermal protocol for the diagnosis of COVID-19.[187−190] RPA uses a recombinase to catalyze strand invasion of a primer into double-stranded DNA (dsDNA). Single-stranded binding proteins are included to stabilize the open duplex structure and a strand-displacing DNA polymerase extends the primer.[181,191] Combination of RPA and LAMP into a two-stage amplification protocol, termed RAMP, exhibits high specificity and enhanced sensitivity due to dual amplification. It also shows a higher tolerance to inhibitors.[192] By utilizing RAMP reaction, Song *et al.* were able to improve sensitivity by 100-fold over that of RT-PCR or LAMP alone in mimic patient samples containing nasal swabs from healthy volunteers, inactivated HIV particles, and other pathogens with synthesized COVID-19 DNA sequences.[193] It provides an early proof-of-concept for an extremely sensitive method that can detect down to just a few viral RNA copies for POCT.[193] In addition, a group of Cas nucleases, including

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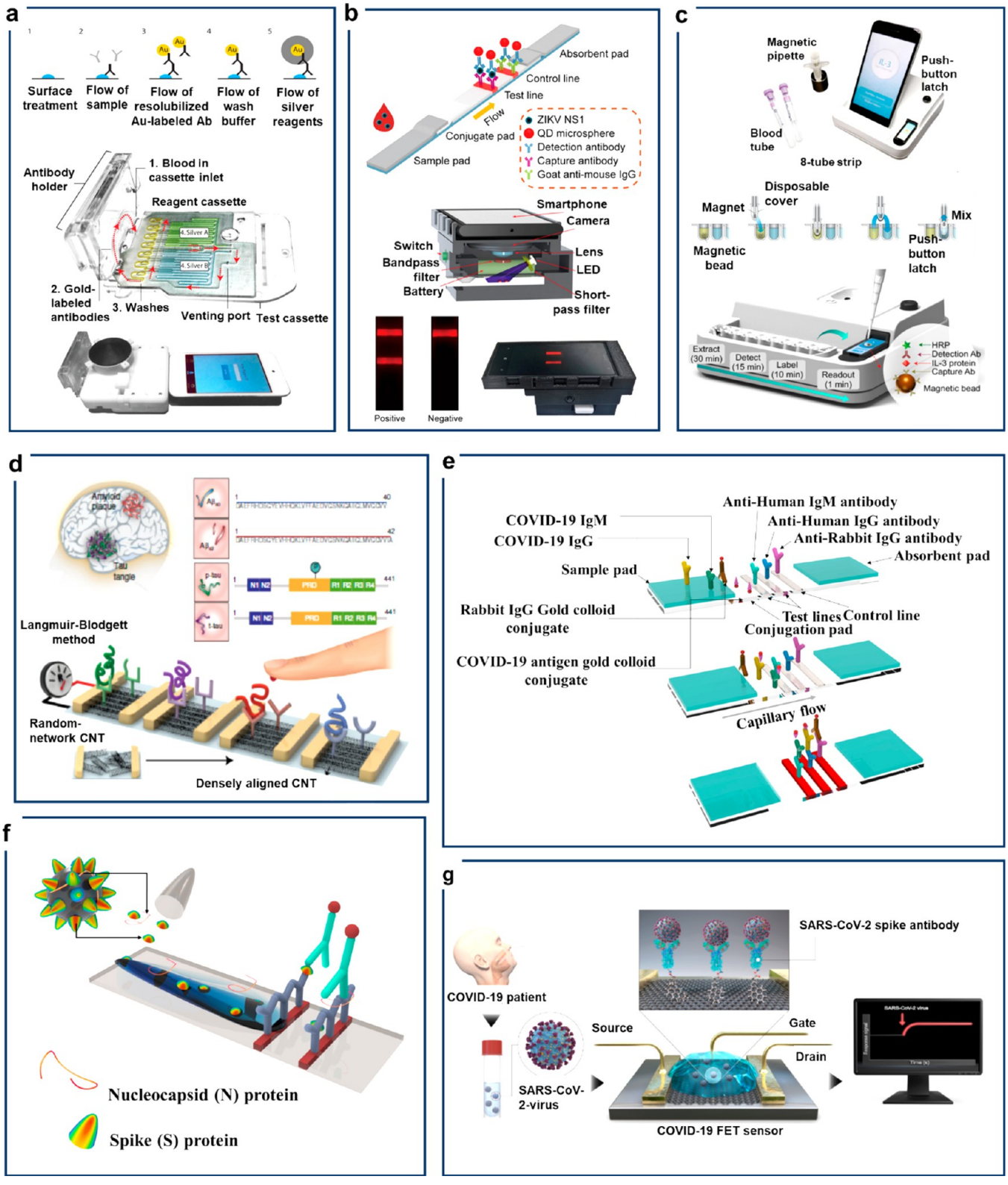

Figure 5. Optical and electrical immunoassay-based portable biosensors for POCT. (a) Smartphone dongle-based portable biosensor for POC diagnosis of infectious diseases. Reproduced with permission from ref 203. Copyright 2015 American Association for the Advancement of Science. (b) Smartphone-based fluorescent LFIA platform for the detection of Zika virus (ZIKV) NS1. Reproduced with permission from ref 204. Copyright 2019 Elsevier B.V. (c) Schematic illustration of the integrated biosensor for detecting sepsis. The sepsis-related biomarker was captured with magnetic beads labeled with the specific antibodies, and a magnetic pipet was utilized for target biomarker extraction. Reproduced from ref 205. Copyright 2018 American Chemical Society. (d) Highly aligned and packed carbon nanotube (CNT) film fabricated by the Langmuir−Blodgett process, sensing four representative biomarkers of Alzheimer's disease ($A\beta_{42}$, $A\beta_{40}$, total tau proteins, phosphorylated tau proteins) in human plasma. Adapted with permission under a Creative Commons CC BY License from ref 167. Copyright 2020 Nature Publishing Group. (e) Schematic illustration of current serological test for COVID-19

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Figure 5. continued

diagnosis based on colorimetric LFIA. Adapted with permission under a Creative Commons CC BY License from ref 206. Copyright 2020 Wiley Online Library. (f) Conceptual illustration of viral antigen-based diagnostics of COVID-19. (g) Graphene-based FET sensor for COVID-19 diagnosis by immobilizing the SARS-CoV-2 spike antibody onto the graphene channel *via* the $\pi-\pi$ interaction linker. Reproduced from ref 104. Copyright 2020 American Chemical Society.

Cas 12 and Cas 13, was recently discovered to have DNA or RNA cleavage activities, respectively.[194,195] Multiple assays based on clustered regularly interspaced short palindromic repeats (CRISPR) techniques combined with LAMP or RPA can harness highly specific nucleases to achieve fast readouts and sensitivity down to a few viral RNA copies within 60 min.[196,197] CRISPR detection can be coupled to LFA readouts, which is an attractive option for patient-friendly at-home testing for COVID-19.[174] Colorimetric or fluorescent dyes are commonly used in the signal acquisition methods for these amplification techniques.[174]

An alternative to PCR has been demonstrated by an electrical biosensor, which provides high detection sensitivity without amplification steps. Through various attempts, researchers have successfully lowered the detection limit of specific DNA sequences to the femtomolar levels by utilizing electrical sensing devices.[169,175,176,198−200] For instance, Zhang *et al.* successfully integrated the chemical vapor deposition (CVD)-grown MoS_2 and Au nanoparticles (AuNPs) in FET-based biosensor for the early diagnosis of Down syndrome by detecting fetal DNA fragments (chromosome 21 as the target DNA, chromosome 13 as the reference DNA) in human plasma[175] (Figure 4d). The selective detection of trisomy chromosome 21 in maternal blood achieved a limit of detection of 100 aM with a wide detection range of chromosome 21 target DNA from 10 aM to 10 fM.[175]

Recently, a wireless data communication technique was utilized to enable fully integrated electrical molecular diagnostics platforms that exhibit high sensitivity without DNA/RNA amplification. For example, Aran *et al.* fabricated a wireless CRISPR-based graphene FET (g-FET) biosensor for the diagnosis of genetic disorder-related disease[176] (Figure 4e). The CRISPR technology provided specific gene-targeting capacity while the g-FET provided high sensitivity.[201,202] In comparison to commercial PCR-based diagnosis of the Duchenne muscular dystrophy (DMD) disease, the g-FET-based biosensor was more rapid and sensitive with a lower LOD (1.7 fM). In order to simplify the detection signal (*i.e.*, transfer curve), the authors defined a response threshold value to convert the current signal, which indicates either DMD positive or negative. Using this binary format, the reliability of clinical diagnosis has been demonstrated with real patients. In addition, diagnostic data are capable of being transported wirelessly to hand-held devices such as smartphones. The CRISPR-integrated electrical biosensor is potentially a promising biosensing platform that can be applied to on-site diagnoses of a variety of diseases such as COVID-19, based on LAMP-CRISPR or RPA-CRISPR SARS-CoV-2 RNA sensing strategies.

In another work, carried out by Lal *et al.*, a portable graphene FET-based wireless biosensor that could detect single nucleotide polymorphism (SNP) mutations by a DNA strand displacement-based probe was demonstrated[177] (Figure 4f). Remote transition of the SNP-sensed signal ($I-V_g$ curve) to the smartphone was achieved *via* the Bluetooth module. The authors focused on improving the detection limit by optimizing the structure and the sequences of a three-dimensional DNA probe, also known as the "DNA nanotweezer". Using this optimized probe, they reached the detection limit to a picomolar range without amplification process.[177] It should be noted that for wireless biosensors to be used effectively for POC diagnosis, issues such as large power consumption of wireless communication systems and low efficiency of data transmission should be addressed.[95]

Immunoassay-Based Portable Biosensors. An immunoassay is a biochemical test that measures the presence of biomarkers using antibodies or antigens, which also plays an important role in on-site diagnosis of various kinds of diseases.[207] In this section, we introduce different optical and electrical POCT immunoassay technologies for the diagnosis of high fatality diseases.

Millions of people are infected and living with human immunodeficiency virus (HIV) globally.[208,209] The conventional representative approach for HIV testing is enzyme-linked immunosorbent assay (ELISA).[210] However, it is complicated and time-consuming and it also suffers from low sensitivity.[210] Therefore, it is not suitable for patient-friendly diagnosis.[205,210] To solve these issues, a fully laboratory-quality immunoassay that can run on a smartphone accessory has been introduced by Sia *et al.* for HIV and syphilis diagnosis[203] (Figure 5a). This low-cost dongle replicates all mechanical, optical, and electronic functions of a laboratory-based ELISA without requiring any stored energy; all necessary power is drawn from the smartphone. The dongle that contains three antibodies (*i.e.*, HIV antibody, treponemal-specific antibody for syphilis, and nontreponemal antibody for active syphilis infection) could perform rapid triplex immunoassay in 15 min. Rwandan health care workers used this dongle to test whole blood obtained *via* fingerpicks from 96 patients. This work suggests that integrating microfluidics with recent advances in consumer electronics can make certain laboratory-based diagnostics accessible to almost any population with access to smartphones.[203]

Zika virus (ZIKV), a mosquito-borne flavivirus, has spread rapidly in South and Central America, as well as the Caribbean since 2015 and poses a global public health emergency.[211] Recently, Wang *et al.* developed a smartphone-based fluorescent lateral flow immunoassay (LFIA) platform for the highly sensitive POC detection of Zika virus nonstructural protein 1 (ZIKV NS1)[204] (Figure 5b). Quantum dot microspheres were utilized as probes in fluorescent LFIA because of their extremely bright fluorescence signal. This approach can achieve quantitative POC detection of ZIKV NS1 within 20 min with high selectivity and sensitivity. This smartphone-based fluorescent LFIA platform holds considerable potential in rapid and accurate point-of-care detection of ZIKV NS1 in resource-limited settings.[204]

Sepsis is a life-threatening organ dysfunction that results from the body's response to infection.[212,213] Despite significant advancements in the understanding of the pathophysiology of this clinical syndrome, sepsis remains

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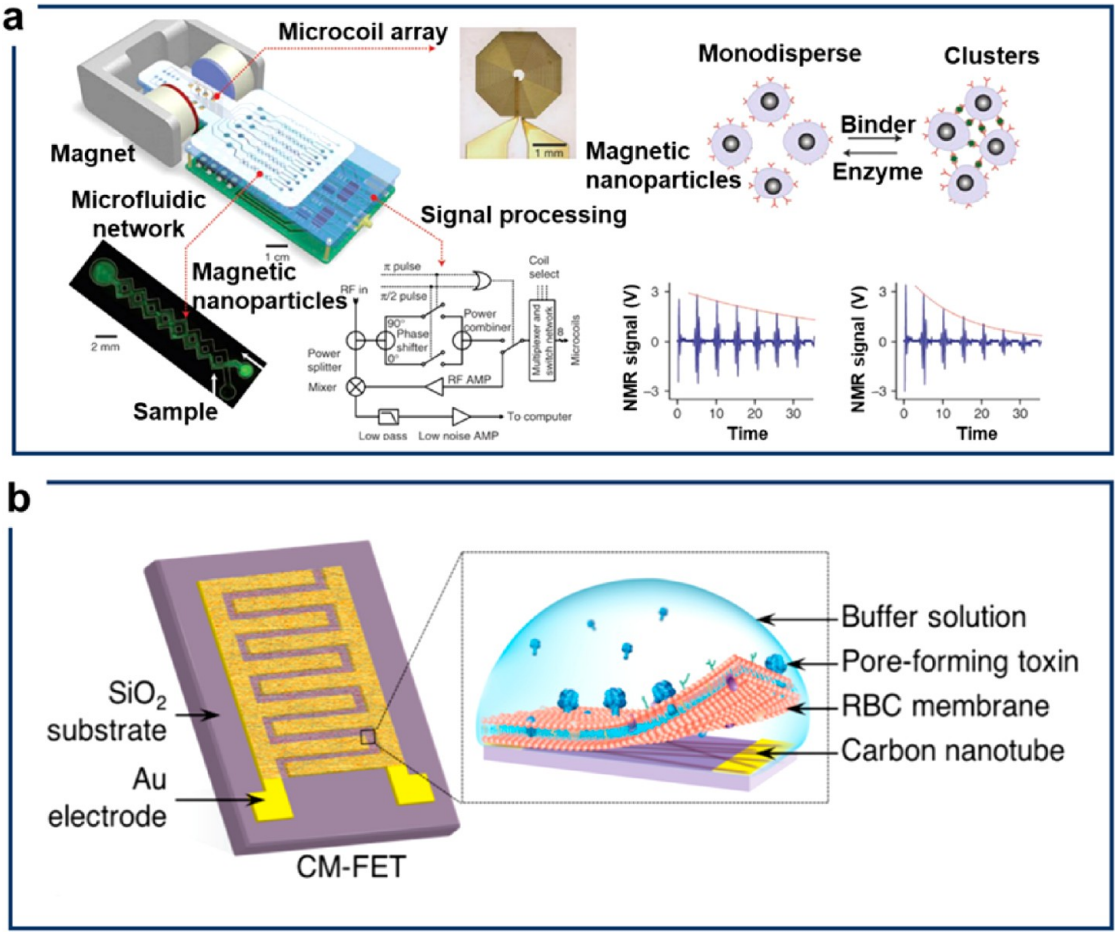

Figure 6. Optical and electrical portable biosensors for cells and related bioreceptors. (a) Miniaturized diagnostic magnetic resonance (DMR) biosensor for detection and molecular analysis of cells. Reproduced with permission from ref 233. Copyright 2008 Nature Publishing Group. (b) Fabrication of carbon nanotube field-effect transistor deposited with red blood cell (RBC) membrane and the schematic detection diagram of pore-forming toxin from bacteria. Reproduced from ref 234. Copyright 2019 American Chemical Society.

one of the major causes of morbidity and mortality in critically ill patients.[214] The sepsis–diagnostic sensor fabricated by Lee *et al.* exhibited clear advantages compared to the ELISA method.[205] They developed a disposable kit for blood processing and amperometric diagnostic sensor integrated into a single, portable, and POC sensing system (Figure 5c). They also designed a magnetic pipet that enables the rapid transport of magnetic beads to the sample for continuous sample processing. The magnetic beads increased the surface area that could capture biomarkers, leading to higher sensitivity and specificity in the testing of clinical samples. Moreover, controller units for signal processing were integrated into the system, such as an analog to digital converter (ADC), a digital to analog converter (DAC), and a microcontroller unit (MCU), leading to transmission of amperometric data *via* Bluetooth to the signal readout device.[205]

Alzheimer's disease (AD) is one of the representative diseases targeted by portable diagnostic sensors so that it could replace the conventional clinical diagnosis of AD, such as neuropsychological tests and neuroimaging.[215] AD causes severe cognitive decline and irreversible memory loss, but early diagnosis of AD can slow down this disease progression with early treatment.[8] Highly sensitive electrical biosensors can potentially enable early diagnosis of AD, thus improve the survival rate of AD patients. Park *et al.* constructed a densely aligned carbon nanotube-based resistive biosensor in a LOC form to detect multivariate AD biomarkers in human plasma[167] (Figure 5d). This device can detect AD biomarkers rapidly and conveniently by analyzing the change in resistance of the sensors using a multimeter. Owing to the densely aligned monolayer carbon nanotube film generated *via* the Langmuir–Blodgett method, this work successfully achieved femtomolar levels of the limit of detection and high diagnostic sensitivities for all four AD biomarkers. This was attributed to the increase in sensing surface area, leading to an increase in the density of immobilized bioreceptors. Moreover, the different combinations of the concentration ratio of the four AD biomarkers yielded higher diagnostic accuracy than those of individual biomarkers. This work demonstrated the highly selective and reliable multiplexed sensing of AD biomarkers in clinical blood samples by improving the carbon nanotube film morphology.[167]

Early and rapid detection of SARS-CoV-2 is of vital importance for the prevention of COVID-19 and to perform timely treatments. Though the positive sensitivity for current standard molecular diagnosis by qRT-PCR is higher than 90% during the initial days of infection (days 1–3), it dramatically decreases after day 6 due to the low viral load in patients' upper respiratory system.[21,216–219] Due to the high false-negative rate and long turn-around time of molecular testing,

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immunoassay is recommended as a complementary test in addition to the standard RT-PCR-based diagnostics.[16,220]

Immunoassays for COVID-19 detection can be classified into two different categories: serological test and viral antigen detection.[16] Current commercially available serological tests detect immunoglobin M (IgM) and immunoglobin G (IgG), which not only provide evidence of viral identification, but also information on the infection history. However, due to the production periods of IgM and IgG, serological testing for COVID-19 should be conducted when symptoms have been presented for at least 3−6 days.[221,222] Nevertheless, they are invaluable tests which may provide critical epidemiological clues on COVID-19.[223,224] Health care experts have emphasized the significance of serological tests for random large-scale testing in order to diagnose suspected patients with negative qRT-PCR results and screen asymptomatic patients.[225,226] Current serological tests are mainly based on conventional colorimetric LFIA, which detects IgM and IgG antibodies in human blood[222] (Figure 5e).

Most advanced COVID-19 diagnostic method is the viral antigen-based rapid test, which can detect the presence of viral structure protein in the early stage after infection. The structural proteins have been extensively researched as the main target viral antigens for coronavirus detection and therapeutics.[227−229] POCT biosensors targeting SARS-CoV-2 structural proteins as antigens may provide rapid and large-scale screening for COVID-19. Current efforts on antigen-based COVID-19 diagnostics is focused on nucleocapsid (N) protein and the spike (S) glycoprotein of SARS-CoV-2[230−232] (Figure 5f). Kim *et al.* recently succeeded in developing a graphene FET-based biosensor that rapidly detects the COVID-19 viruses in the clinical samples of COVD-19 patients[104] (Figure 5g). This sensor achieved a limit of detection of 1 fg/mL from the spiked buffer solution by covalently immobilizing the SARS-CoV-2 spike antibody *via* the interface coupling linker (1-pyrenebutyric acid *N*-hydroxysuccinimide ester). It shows high selectivity toward the SARS-CoV-2, exhibiting no response to other proteins related to Middle East Respiratory Syndrome (MERS). Significantly, the clinical application of this COVID-19 sensing platform was demonstrated by detecting SARS-CoV-2 from the COVID-19 patients' nasopharyngeal swabs.[104]

Portable Biosensors for Cells and Related Biomarkers. Rapid and accurate measurement of cells as biomarkers in tissue and fluid samples is a major challenge in biosensor design. In order to tackle this issue, Weissleder *et al.* reported the development of a miniaturized diagnostic magnetic resonance (DMR) system for multiplexed, quantitative, and rapid analysis of cells.[233] Using magnetic particles as a proximity sensor to amplify molecular interactions, the hand-held DMR system can perform measurements on unprocessed biological samples. The capability of the DMR system has been tested using it to detect bacteria, identify small numbers of cells and analyze them on a molecular level in real-time, which also measures a series of protein biomarkers in parallel. The DMR technology shows promise as a robust and portable diagnostic device[233] (Figure 6a).

In addition, cells could be utilized as bioreceptors in biosensor design. Zhang *et al.* constructed a carbon nanotube (CNT)-based FET coated with the membranes of red blood cells (RBCs).[234] Deposition of the cell membranes on the CNT has been utilized as an alternative bioreceptor instead of the conventional bioreceptors[234] (Figure 6b). Immobilization of biomarkers on cell membranes does not rely on molecular structures or chemical properties of the target biomarkers; therefore, it exhibits detecting capability of biomarkers with complicated and unknown molecular structures.[234−236] The human body underdoes hemolytic activity, where the RBC membrane absorbs and neutralizes various types of pore-forming toxins (PFTs) that are highly fatal to humans.[237] Therefore, this RBC membrane-coated FET sensor could be developed into a versatile biosensing platform that detects alive pore-forming bacteria with fast and accurate signal readout.

WEARABLE BIOSENSORS

Necessity of Noninvasive Diagnosis. Currently, the majority of clinical tests and commercialized POCT biosensing platforms are based on blood or serum analysis.[238] Although some disease-related biomarkers exist at very low concentrations in human blood, the relatively high correlation between these biomarkers and diseases offers high reliability for health care monitoring.[49,239] However, conventional invasive blood sample collection often requires the disruption in the outermost layer of the human skin (the stratum corneum), making them inconvenient and increasing the risk of infection of patients during diagnosis.[82] For example, blood-based glucose diagnosis resulted in a 67% reduction in patient compliance in routinely monitoring capillary blood glucose concentrations.[240] In this regard, noninvasive detection-based biosensors with high reliability to disease diagnosis are particularly attractive for patients who are repetitively subjected to invasive blood withdrawal procedures over a long-term and those that are in the "critically" ill stages under intensive care, such as immunodeficiency patients who suffer from cancer and AIDs. Noninvasive detection methods are also beneficial for pregnant women and pediatric patients.[241]

Recent Trends in Wearable Biosensors. The aforementioned benefits motivate the development of wearable biosensors based on noninvasive sample collection methods. In this review, we define wearable biosensors as those worn or attached on the skin or other surfaces of the human body (*e.g.*, skin, eyes, and teeth). Early efforts in wearable sensors have focused on physical sensors that monitor mobility and vital signs, such as steps, calories burned, heart rate or blood pressure, respiration rate, skin temperature, and brain activity.[39,82,242,243] Recent interest in wearable biosensors is also being focused on clinically relevant biomarker monitoring through chemical reactions.[244,245] Advances in biological sample collection and processing, rapid analysis through miniaturized fluidic devices, and smartphone-based facile data analysis have enable wearable biosensors to provide continuous, real-time physiological information *via* dynamic, noninvasive or minimally invasive measurements of biomarkers in biological fluids, such as sweat, tears, saliva, and interstitial fluids (ISF).[49,82,239] For the wide acceptance of wearable biosensors in clinical diagnosis, a deep understanding of the relation between biomarkers in blood and noninvasively accessible physiological fluids is essential.[49] Furthermore, since many of the disease-related biomarkers in noninvasively accessible physiological fluids are more than 10-fold lower than that in serum samples,[49] highly sensitive and selective noninvasive wearable sensors are crucial.

Material Selection Criteria for Wearable Biosensors. For wearable biosensor-based patient-friendly diagnosis, it is

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necessary to replace the bulky and rigid substrates and electronic components typically used in conventional biosensors with skin-like flexible and stretchable materials for enhanced wearability and functionality.[48,206] In this section, we discuss the essential properties for wearable biosensing materials, including flexibility, stretchability, transparency, adhesion property, water repellency, selective permeability, and biocompatibility.[54,246]

Flexibility and Stretchability. The sensor's mechanical properties should closely match that of human epidermis for intimate contact with the skin for reliable data collection and comfort. In this regard, a Young's modulus from 2 to 600 kPa and stretchability from 30 to 100% are required.[54,247,248] The most widely used substrate material for wearable sensors is poly(dimethylsiloxane) (PDMS) (elastic modulus: 360−870 kPa).[249] Other soft materials, such as poly(vinylpyrrolidone) (PVP), ethylene−vinyl acetate, Tegaderm, Ecoflex, and Parylene, can afford significant weight and thickness reduction with improved mechanical compliance at the interface and enhance conformability on the skin.[48] Recently, a non-Newtonian fluid, shear thickening fluid (STF), has emerged for wearable electronics due to its reversible transition capability from a fluid-like to a solid-like state. When a sudden force is applied, viscosity increases dramatically but recovers to its initial state immediately when applied stress is relieved.[250] STF-based wearable electronic textiles have been fabricated for body armors with variable flexibility and conductivity depending on the applied deformation.[251,252] In addition, STF-processed Kevlar fabrics (STKF) exhibit an EM interference shielding effect as high as 27 dB.[253]

Transparency. High optical transparency of wearable biosensors is required to keep them invisible during daily activities, especially for contact-lens-based biosensors.[54,254] For example, graphene and its hybrid with metal nanowires have been utilized in the design of contact-lens-based biosensors, providing sufficient transparency (>91%) with high flexibility and stretchability to ensure mechanical reliability, comfort, and unobstructed vision.[255,256]

Adhesion Property. Adequate or tunable adhesion through chemical, van der Waals, or electrostatic force guarantees proper strain transfer between two distinct surfaces, through which reliable data can be attained with enhanced user comfort and convenience.[54] In this regard, various strategies have been developed to enhance the adhesion property of biosensing materials. For example, Liu *et al.* showed that by electropolymerizing a covalently bonded polydopamine (PDA) phase within polypyrrole (PPy) hydrogels leads to significant increase in conductivity and adhesion compared to pure PPy hydrogels.[246]

Water Repellency. Despite the advanced adhesion of biosensors with mechanical properties similar to human epidermis, it is not effective for use in extreme situations such as aquatic or arid environments.[257] Adhesion of wearable sensors under such conditions can be enhanced by imparting water repellent properties through structural or chemical treatment. Such a strategy can be used to make a sweat sensor that is unaffected by the surrounding water during showering or swimming, and it prevents the evaporation of collected sweat.[257] Various flexible polymer substrates are intrinsically hydrophobic, such as silicon rubber, Ecoflex, PDMS, parylene, and poly(styrene−isoprene−styrene) (SIS); hence, they naturally possess water repellent properties.[54,257,258] These hydrophobic polymers can also robustly adhere to human skin.[259,260]

Selective Permeability. Moreover, highly selective permeability is required for wearable biosensors to maintain the sensing performance of certain applications. In terms of a sweat-based biosensor, a sweat gland can be blocked due to the stagnant sweat, which may cause skin inflammation. Thus, it is important to ensure the breathability of a wearable biosensor for long-term wearing and tight adhesion.[54,261] In terms of contact-lens-based biosensor, oxygen permeability is necessary to prevent oxygen deficiency and enhance the accuracy of continuous metabolite monitoring.[262] In addition to these functions, selective permeability is essential for long-term use and continuous monitoring of wearable sensors in harsh environments, such as in human mouth (in human saliva). Recent reports successfully demonstrated the tunability of selective permeability by controlling the porosity and pore size of the substrate materials, which prevents the accumulation of unwanted molecules from the external environment on the sensor surface.[263,264,214]

Biocompatibility. Lastly, the biocompatibility of the sensing materials needs to be carefully examined when the wearable biosensor is attached to human skin, eyes, or teeth. Ionic conducting polymers, such as hydrogel and nanofibrils, have been widely used in patient-friendly biosensors due to their excellent biocompatibility.[265−269] In particular, biomimicking nanofibril biopolymers, including silk, chitin, and cellulose, are highly ordered architectures with desired mechanical strength, anisotropy, flexibility, and optical properties.[270] These properties render nanofibrillar biopolymers promising candidates for strong, sustainable, and biocompatible materials for wearable biosensors.[270]

Sweat-Based Noninvasive Wearable Biosensors. As a representative biological fluid, sweat is of particular interest owing to its relative ease of noninvasive collection and its rich content of important biomarkers including electrolytes (*e.g.*, Na^+, K^+, and Ca^{2+}), small molecules, metabolites (*e.g.*, lactate, urea, and glucose), hormones, proteins, and exogenous agents.[274] Recent attempts to collect sweat and detect sweat biomarkers simultaneously involve direct contact of wearable biosensors on the skin where fabric or paper substrates accumulate sweat for both optical and electrical assessment.[271]

Optical Sweat-Based Wearable Biosensors. Current optical wearable POC biosensors, including colorimetric and fluorescent sensing devices, are capable of analyzing biomarkers in human sweat according to the change of color or fluorescent signal. Colorimetric detection of biomarkers is one of the most widely used strategies for POC applications due to its straightforward operation and convenient readout.[275] Due to its simplicity, colorimetric response in functionalized porous substrates is widely applied in optical wearable sensors, which enables the detection of chemical information in sweat.[271] The color change induced by the bioanalytes is proportional to the bioanalyte concentration, which is visible to the naked eye and can also be measured by a digital camera/smartphone with imaging processing algorithms. Colorimetric wearable sensors provide rapid and cost-effective sensing methods about the state of wellness and progression of diseases.[49,276,277]

In addition to time-variant changes in the concentration of sweat biomarkers, well-established colorimetric wearable sensors are capable of analyzing other physiological parameters, including local sweat loss/rate without requiring battery-

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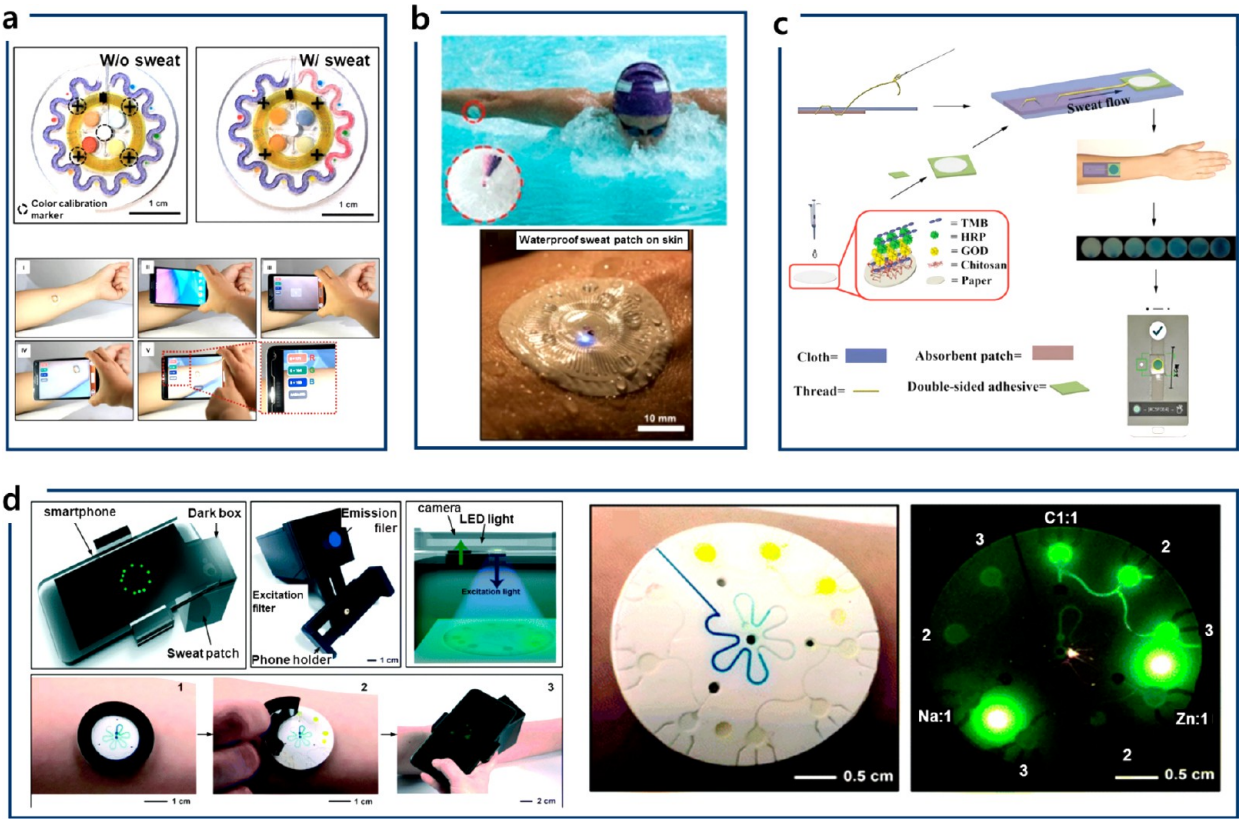

Figure 7. Optical wearable biosensors for noninvasive monitoring of bioanalytes in sweat. (a) Schematic illustration of a soft, wearable microfluidic device for the capture, storage, and colorimetric sensing of sweat. Reproduced with permission from ref 271. Copyright 2016 American Association for the Advancement of Science. (b) Waterproof, electronics-enabled, epidermal microfluidic device for sweat collection, biomarker analysis, and thermography in aquatic settings. Adapted from ref 257. Copyright the authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC) http://creativecommons.org/licenses/by-nc/4.0/. Copyright 2019. (c) Fabrication of a wearable μTPAD and its application for *in situ* sweat glucose sensing with a smartphone as the signal readout. Reproduced with permission from ref 272. Copyright 2019 Springer Nature Switzerland AG. (d) Fluorometric skin-interfaced microfluidic device and smartphone imaging module for *in situ* quantitative analysis of sweat chemistry. Reproduced with permission from ref 273. Copyright 2018 Royal Society of Chemistry.

powered actuators or active valves.[277] Recently, advances in soft hybrid electronics and microfluidic systems have enabled the development of optical sweat sensors that can non-invasively capture and interrogate sweat.[239] For instance, the soft, flexible, and stretchable microfluidic device developed by Rogers *et al.* is capable of harvesting and storing sweat from human skin and measuring sweat rates as well as sweat biomarkers, including chloride, glucose, lactate, and pH.[271] The addition of colorimetric assays in the form of dry reagents built within the microfluidic chamber allows for colorimetric analysis. The devices can be mounted at multiple locations on the body without chemical or physical irritation (Figure 7a). This colorimetric sensing approach allowed simple, rapid quantitative assessment of the instantaneous rate and total volume of sweat loss, pH, as well as the concentration of chloride, lactate, and glucose in the sweat.[271] Reference color markers (true white and black) on this device allowed white balancing to eliminate the dependence on lighting conditions of practical relevance (daylight, shadow, and various light sources), which enabled the device to have precise readout under various lighting conditions.[271] Recently, another colorimetric multifunctional microfluidic system developed by Rogers *et al.* has accurate assessments not only of the total loss of sweat and sweat rate but also pH and temperature of sweat, and chloride, glucose, and lactate in physiologically relevant ranges.[46] The colorimetric signal readout is performed by digital image analysis through RGB values. Field studies conducted on healthy volunteers show testing results that match conventional lab-based measurement systems.[46]

One of the major challenges to sweat sensors is collecting a small quantity of sweat for diagnostics without contamination under extreme situations such as aquatic or arid environments.[273] To tackle this issue, a water-proof wearable biosensor that can collect sweat underwater while maintaining robust adhesion in an airtight and water-tight fashion in the presence of viscous drag forces has been developed.[257] This was enabled by the use of SIS (a high-water barrier hydrophobic material) membrane and the small diameter of the outlet aperture[257] (Figure 7b). The SIS membrane was shown to have water permeability of 4.6×10^{-8} g-m/mm^2/h/Pa. It is significantly lower in water absorption and sweat loss than that of PDMS, which was commonly used in previously reported systems. In particular, devices made with SIS can store sweat for 4 h at 37 °C with less than 20% loss, while PDMS devices of comparable geometry exhibited ~100% loss within 3 h. As a means to detect physiological changes, colorimetric dyes containing red and blue water-soluble

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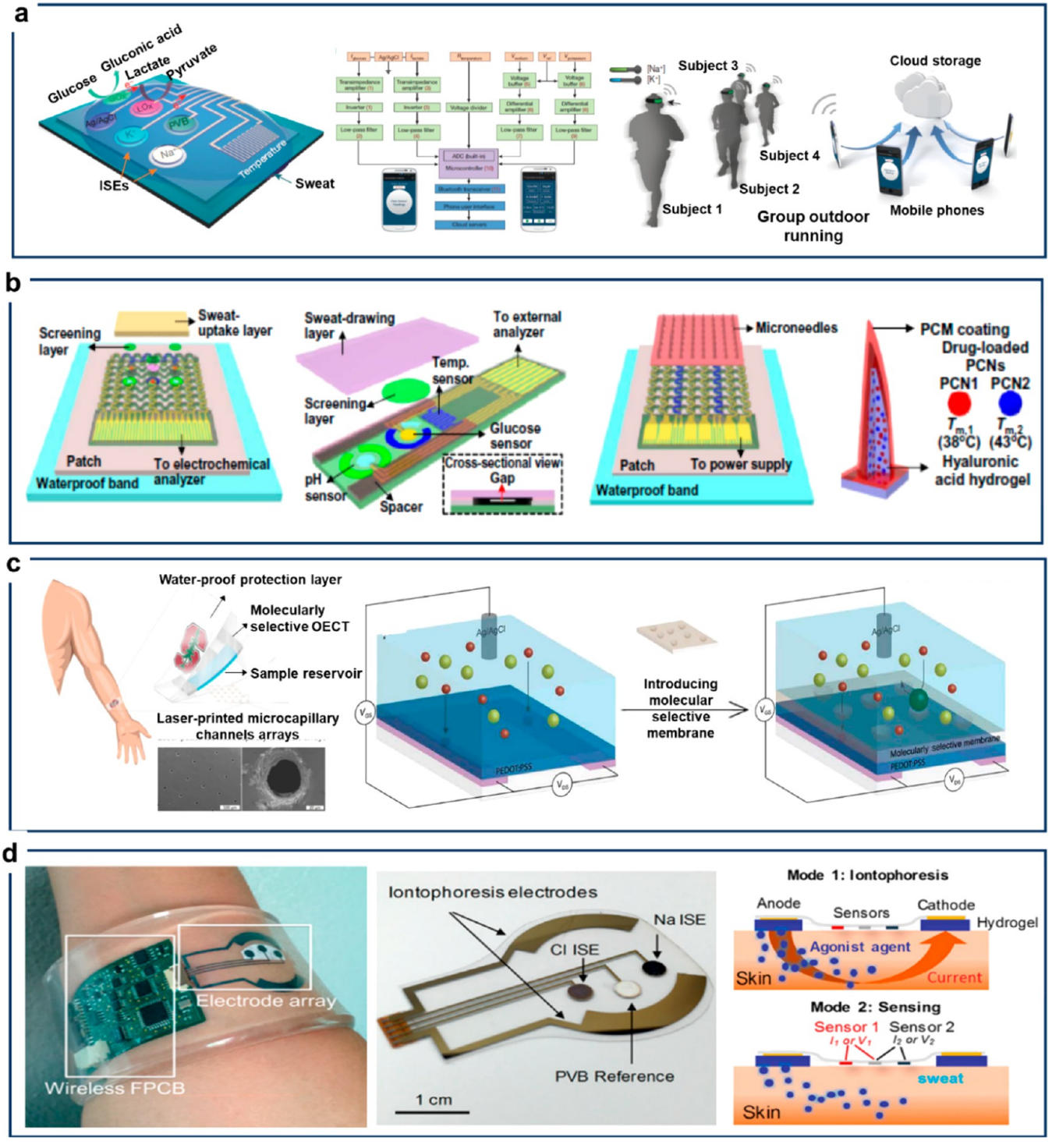

Figure 8. Electrical wearable biosensors for noninvasive monitoring of bioanalytes in sweat. (a) Schematic diagram of a wearable sweat sensor array containing glucose, lactate, sodium ion, potassium ion, and temperature sensor, enabling signal readout process through a controller unit embedded in a FPCB. The device is utilized for monitoring the hydration status of runners by transmitting the signals to a cloud server *via* the smartphone. Reproduced with permission from ref 278. Copyright 2016 Nature Publishing Group. (b) Schematic illustrations of a wearable glucose monitoring patch, a disposable glucose monitoring strip, and a microneedle array for drug delivery in response to the increased sweat glucose level. Adapted from ref 279. Copyright the authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC) http://creativecommons.org/licenses/by-nc/4.0/. Copyright 2017. (c) Schematic illustration of an integrated cortisol patch sensor composed of a water-proof protection layer, sweat reservoir, and PEDOT:PSS-based OECT with a molecularly selective membrane (MSM). Adapted from ref 39. Copyright the authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC) http://creativecommons.org/licenses/by-nc/4.0/. Copyright 2018. (d) Image of an iontophoresis-based sweat sensor integrated with FPCB and schematic illustration of

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Figure 8. continued

the iontophoresis and biomarker detection process. Adapted with permission from ref 280. Copyright 2017 National Academy of Sciences Publishing Group.

particles with different dissolution rates were preinjected into the wearable sensor, thereby generating a volume-dependent color gradient as the devices were filled with sweat. Alternatively, a silver chloranilate suspension that reacts with sweat resulted in a colorimetric response corresponding to the concentration of chloride. Hence, this wearable sweat sensor provides real-time measurement of sweat rate, sweat loss, and chloride concentration *via* optical readout.[257]

In addition to soft and flexible material-based microfluidic systems, Lu *et al.* developed a wearable thread/paper-based analytical device (μTPAD) containing a cotton thread and a functionalized filter paper for noninvasive, quantitative, and *in situ* monitoring of human sweat glucose with the assistance of a smartphone[272] (Figure 7c). The amount of enzymes and reagents on the filter papers was optimized to achieve the high-performance colorimetric sensing of glucose with a dynamic range of 50−250 μM and a detection limit of 35 μM. The device's simplicity and wearability make it a low-cost wearable sensor for human sweat analysis.[272]

Though colorimetric-based soft and stretchable microfluidic devices are the most widely used optical sweat-based wearable biosensor, the main drawback of colorimetric assays is that they are only suitable for a relatively narrow range of biomarkers, and they can provide insights about sweat concentration and dynamics only at discrete points of time.[277] In this regard, fluorescent-based sweat detection could serve as a complementary approach to colorimetric detection.[273] A soft, skin-interfaced microfluidic system composed of a network array of microchannels and microreservoirs prefilled with fluorescent probes that selectively react with target analytes in sweat has been developed, providing quantitative and rapid analysis of biomarkers in sweat[273] (Figure 7d). Chloride ion, sodium ion, and zinc ion in sweat have been analyzed by the fluorescent wearable sensor with accuracy that matches conventional laboratory-based techniques.[273]

As stated above, fluorescent detection has advantages over that of colorimetric detection, such as providing continuous quantitative analysis of a wider range of sweat biomarkers. However, fluorescent image analysis requires the intergradation with a dark shielded box with excitation and emission filters of LED light for picture capturing with a smartphone, while colorimetric image capturing and analysis does not require strict light condition.[273] As a result, the cost of the sweat-based optical wearable biosensor can increase. Therefore, such a compromise should be considered when designing the biosensor.

Electrical Sweat-Based Wearable Biosensors. Compared to that of optical sweat-based wearable biosensors, the output signal of electrical sweat-based wearable biosensors can be directly interpreted by signal analysis software, negating the need for colorimetric or fluorescent images. In addition, electrical sweat sensors exhibit quantitative signals, unlike colorimetric optical sweat sensors that exhibit qualitative signals. There are various detecting mechanisms in electrical sweat sensors that detect biomarkers *via* noninvasive sample collecting methods, but a majority of them are fabricated into amperometric or potentiometric electrochemical platforms due to their simple architectures and straightforward signal analysis.[49,56,278,279,281−286] Javey *et al.* demonstrated one of the key papers in wearable sweat-based biosensors by fabricating a fully integrated biosensing system on a flexible polyethylene terephthalate (PET) substrate, which can selectively and simultaneously detect glucose, lactate, sodium ion (Na^+) and potassium ion (K^+) in sweat.[278] In this approach, concentrations of sodium and potassium ions were detected through the potentiometric mechanism[287] (Figure 8a). Their sensor showed stable attachment on different body parts including wrist and forehead and exhibited stable sensing performance of sodium and potassium ions in exercise-induced sweat. They monitored the hydration status of the running people according to the variation in ionic concentration *via* the flexible printed circuit board (FPCB). Furthermore, the collected data were wirelessly transmitted to a cloud server through IoT system for further signal analysis.[95]

As another example of fully integrated electrical wearable sweat sensor, Kim *et al.* fabricated an amperometric glucose sensor integrated with a thermally responsive microneedle array in both patch and strip form[279] (Figure 8b). This system was also functionalized as a drug delivery system for the treatment of hyperglycemia, enabling efficient management of the sweat glucose concentration without causing discomfort (*i.e.*, finger pricking) to the patients. To further improve the accuracy of their sensing system, the authors integrated other sensors to monitor pH, temperature, and humidity for real-time signal calibration. After a certain amount of sweat was collected through the sweat uptake layer, the glucose sensor detected the glucose level based on the variation in amperometric signals, while signal calibration occurred simultaneously. When the glucose level indicated a state of hyperglycemia, the microneedle array delivered two types of diabetes drugs into the patient's epidermis.[279]

In addition to potentiometric and amperometric sweat sensors, organic field-effect transistors (OFETs) and organic electrochemical transistors (OECTs) can be utilized for electrical sweat-based wearable biosensors.[70,288−291] OFETs detect biomarkers based on the changes in charge density and/or mobility of the semiconducting material (manifests as changes in the transfer curve characteristics such as threshold voltage and transconductance), which can occur due to biomarker surface accumulation or charge scattering in the interfacial region. OECTs also detect the change in transfer curve characteristics, except that they detect electrochemical reaction of the targeted biomarker with the bioreceptor, leading to ion penetration and change in the doping state throughout the channel; hence, OECTs possess a limited range of detectable biomarkers.[292−294]

In order to extend the range of detectable biomarkers using OECT wearable biosensors, Salleo *et al.* modified the structure of their OECT-based biosensor by adding porous molecularly selective membrane (MSM) layer, through which cortisol in human sweat was detected without the need for redox reaction.[39] They fabricated a tailor-made cortisol-sensing system by cross-linking porous MSM layer synthesized with cortisol-detectable MIPs. Subsequently, when the cortisol binds to the MIPs, the MSM layer functioned as an ionic

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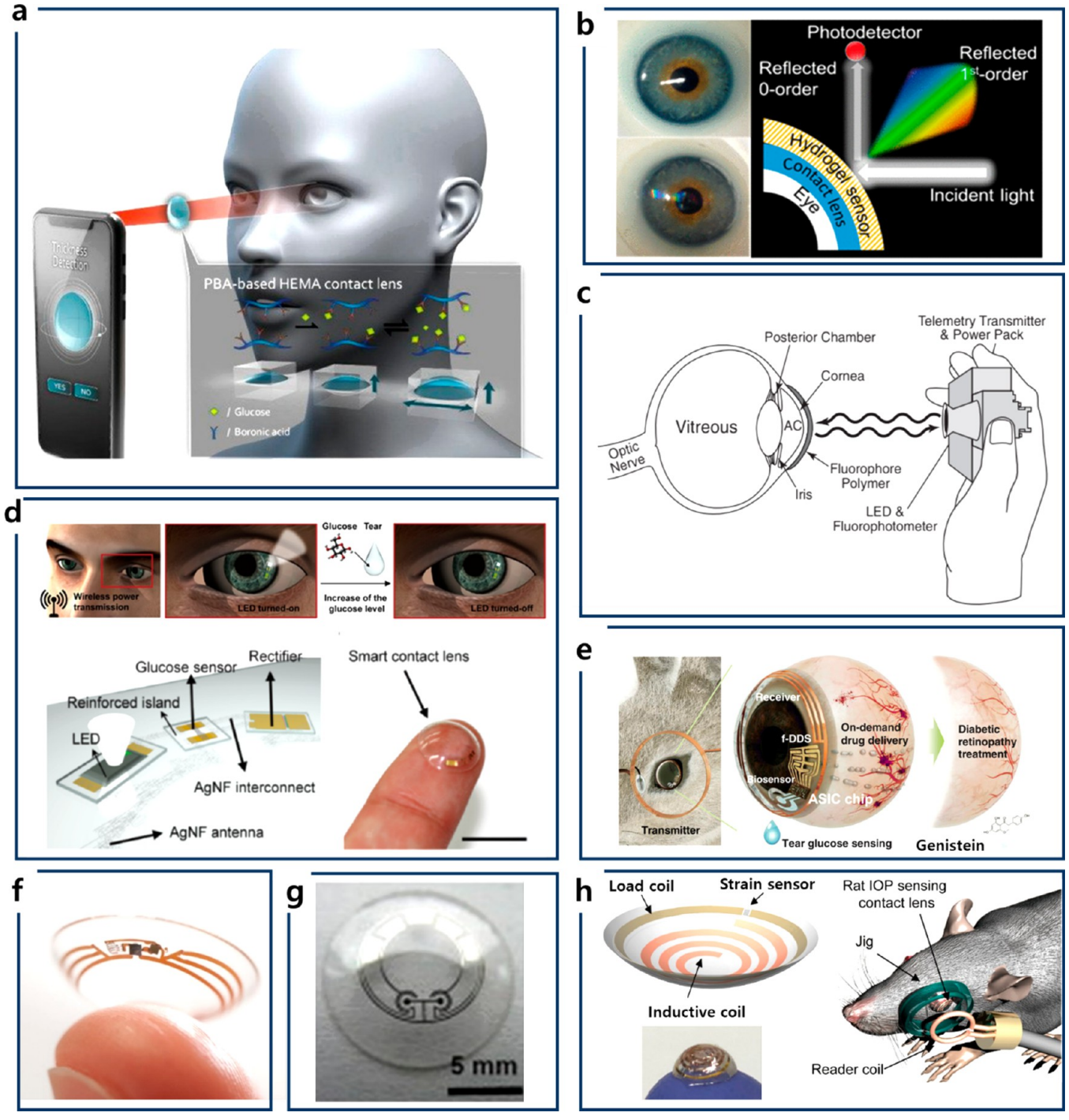

Figure 9. Contact-lens-based biosensors for noninvasive monitoring of bioanalytes in tears. (a) System of using a smartphone for detecting the thickness of the PBA-based HEMA contact lens. Reprinted with permission under a Creative Commons Attribution (CC BY) License.[298] Copyright 2018 Multidisciplinary Digital Publishing Institute (MDPI). (b) Wearable contact-lens-based biosensor for continuous glucose monitoring using a smartphone. Reproduced from ref 299. Copyright 2018 American Chemical Society. (c) Fluorescent contact lens glucose sensor. Reproduced with permission from ref 300. Copyright 2006 Mary Ann Liebert, Inc. (d) Soft, smart contact lens integrated with wireless circuit, glucose sensor, and LED display. Adapted from ref 254. Copyright 2018 the authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC) http://creativecommons.org/licenses/by-nc/4.0/. Copyright 2017. (e) Schematic illustration for *in vivo* diabetic diagnosis and therapy using smart contact lens. Reprinted from ref 301. Copyright the authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC) http://creativecommons.org/licenses/by-nc/4.0/. Copyright 2020. (f) Contact-lens-based biosensor under co-development by Google and Novartis. It measures glucose concentration in tears using a miniaturized electrochemical sensor embedded into a hydrogel matrix. Reproduced with permission from ref 302. Copyright 2014 Nature Publishing Group. (g) Electrical contact lens for lactate detection. Reproduced with permission from ref 303. Copyright 2012 Elsevier B.V. (h) Wireless IOP sensing contact lens for the eye of a rat. Reproduced from ref 304. Copyright 2020 American Chemical Society.

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barrier that lowers the drain current of the channel (Figure 8c). This sensor was attached to the forearm of human to monitor the concentration of cortisol from the exercise-induced sweat.[39]

The above-mentioned wearable biosensors extracted sweat through natural perspiration (*e.g.*, exercise).[278,284,295,296] This type of extraction leads to a different chemical composition in sweat compared to that in sweat at a state of rest, which may not accurately represent the state or health condition of the patient.[280,297] To attain sweat at a state of rest, iontophoresis has been utilized.[281] Iontophoresis stimulates the sweat glands locally by delivering sweat-inducing cholinergic compounds while applying mild electronic current using anode and cathode electrodes.[241,281] Delivered cholinergic compounds enhance the transport of sweat that contains charged and polarized biomarkers. Davis *et al.* integrated iontophoresis technology with a wearable sodium and chloride ion sensing array[280] (Figure 8d). A sufficient amount of sweat was extracted by applying 1 mA of current, which allowed accurate sodium and chloride ion concentration analysis, and enabled early diagnosis of cystic fibrosis. Furthermore, the integrated FPCB in this wearable sensor eliminated the necessity of external data analysis.[280]

Tear-Based Noninvasive Wearable Biosensors. Similar to sweat, tears are also considered to be an attractive diagnostic biological fluid that can be obtained in a noninvasive manner. Unlike blood, which has various components and requires invasive methods to obtain, tears are less complex than blood and can be easily collected. Tears do not possess a large range of biomarkers like blood, but they contain both low- and high-molecular-weight compounds, such as protein, peptides, lipids, metabolites, and electrolytes. When analyzing changes in the concentration of these biological chemicals, it also provides an opportunity for the diagnosis of eye-related diseases.[82,262,305−308]

Smart contact lenses have been utilized as a noninvasive biomarker detecting and monitoring platform, through which glucose, lactate, and intraocular pressure can be detected.[225,306,309] For instance, a contact-lens-based wearable biosensor was introduced by Asher *et al.* using optical measurement of glucose in tears based on glucose-responsive hydrogels.[310,311] These hydrogels contained molecular recognition agents to detect glucose in tear and photonic crystals to diffract visible light to various wavelengths. Specifically, the volume of the hydrogel changed according to the variation of glucose concentration, and the photonic structures enabled quantification of the glucose concentration using holographic images.[310,312,313] Here, a multilayered periodic structure was formed within a polymer matrix that was functionalized with boronic acid derivatives, which can bind to carbohydrates covalently and reversibly.[312] Phenylboronic acids (PBAs) have been commonly used in holographic contact-lens-based biosensor for glucose monitoring.[298,299] Chen *et al.* fabricated a PBA-based poly(2-hydroxyethyl methacrylate (HEMA) contact lens that exhibits reversible swelling/shrinking due to glucose binding, which changes its thickness.[298] The difference in thickness can be detected in a picture taken by a smartphone and analyzed using software[298] (Figure 9a). Another PBA-based holographic contact-lens-based biosensor was fabricated by Butt *et al.* for continuous monitoring of glucose at physiological conditions[299] (Figure 9b). Initially, a photonic microstructure was printed on a glucose-selective hydrogel film functionalized with PBAs. Upon binding with glucose, the microstructure volume swelled, resulting in the change of Bragg diffraction, which can be monitored *via* a smartphone app.[299] This biosensor showed high sensitivity, fast response time, and short saturation time. The combination of such optical biosensors with smartphone cameras and algorithm-based monitoring is expected to further advance these sensing platforms toward fully integrated systems. It is anticipated that this sensing platform will facilitate the development of reusable, equipment-free POC diagnostic devices for diabetes monitoring.

Additionally, fluorescence contact-lens-based wearable biosensors employing Förster resonance energy transfer (FRET) as the detecting mechanism with a hand-held photofluorometer was proposed for noninvasive monitoring of glucose in tear (Figure 9c). The fluorescence signal increased proportional to the glucose concentration.[299,300] Also, the authors claimed that during 3 h of clinical trial testing, this biosensor was comfortable and well tolerated by the patient, and the blood glucose level was well-correlated with the tear glucose level.[300]

Park *et al.* constructed a smart contact-lens-based biosensor to continuously monitor the physiological and chemical information in tears.[254] Their substrate contained mechanically reinforced islands for the placement of various components such as glucose sensor, rectifier, LED, and the coils for antenna, through which mechanical stability of the device was achieved (Figure 9d). Furthermore, sufficient amount of light was capable of passing through the substrate because it is composed of materials with similar refraction index. Using this sensing system, the authors were able to detect the tear glucose concentration without interference from other biomolecules in tears. Furthermore, the authors visualized the threshold glucose concentration for diabetes in real-time by turning a LED (integrated on the contact lens) on and off.

Recently, Hahn *et al.* developed a smart contact lens that can simultaneously conduct continuous glucose monitoring and treatment of diabetic retinopathy[301] (Figure 9e). This smart contact lens contained ultrathin and flexible electrical circuits and a microcontroller chip for real-time electrochemical biosensing, on-demand controlled drug delivery, wireless power management, and data communication system. The contact lens was inserted into a diabetic rabbit, and the rabbit's tear glucose levels were measured. Its accuracy was validated by conventional invasive blood glucose testing; moreover, the possibility of simultaneous treatment was demonstrated by releasing the trigger drugs from reservoirs.[301]

Despite the successful demonstrations of various contact lens wearable biosensors, the safety of these devices needs to be further examined. Google and Novartis have thus far made the most notable progress of contact lens wearable biosensors, which consist of wireless control chip, miniature electrochemical transducer, and antenna on a soft contact lens platform, with a glucose sensor embedded within a hydrogel matrix[302] (Figure 9f). However, this product is being delayed as it still requires further clinical trials.[82] Sufficient clinical testing is essential and necessary to ensure the safety of contact lens wearable biosensors prior to commercialization.

An alternative way to make tear-based biosensor is to develop an eyeglasses-based sensing platform. For instance, Wang *et al.* developed an eyeglasses sensing platform with electrochemical detection system and its wireless electronic backbone positioned outside of the eye.[314] Their sensing

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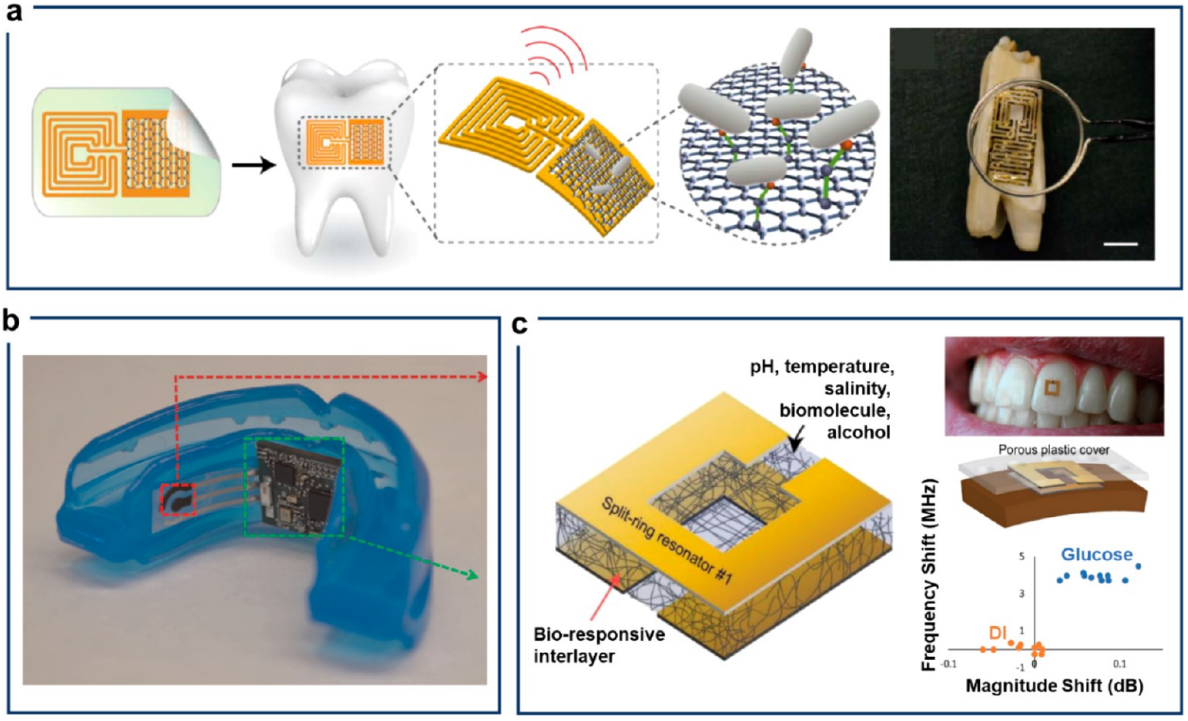

Figure 10. Electrical wearable biosensors for noninvasive monitoring of bioanalytes in saliva. (a) Fabrication process of a wireless tooth-attachable biosensor by printing graphene onto a bioresorbable silk substrate. The pathogenic bacteria can be detected by the peptides, which is immobilized on the graphene surface. Reproduced with permission from ref 317. Copyright 2012 Nature Publishing Group. (b) Image of mouthguard-based amperometric biosensor for noninvasive detection of uric acid in saliva. It contains a wireless circuit board to transmit the signal outside of the mouth. Reproduced with permission from ref 318. Copyright 2015 Elsevier B.V. Publishing Group. (c) Tooth-mountable RF-trilayer sensor for wireless monitoring of oral cavity and food consumption. Reproduced with permission from ref 319. Copyright 2018 Wiley-VCH Verlag GmbH Publishing Group.

platform collected stimulated tears into an external flow detector mounted on the eyeglasses pad. Integration of wireless electronic circuitry into the eyeglasses frame, thus leading to a fully portable, convenient to use, yet fashionable wearable sensing platform.

Apart from glucose monitoring, Parviz *et al.* developed an amperometric enzymatic L-lactate sensor on a polymer substrate molded into contact lens shape for potential *in situ* monitoring of L-lactate levels in tears[303] (Figure 9g). This sensor exhibits a fast response time and sufficient resolution for the measurement of physiological concentration of L-lactate. However, since this sensor employs an enzymatic reaction, the safety of this contact lens sensor needs to be further examined for its clinical applications.

Monitoring intraocular pressure (IOP) is also important for health care and diagnosis.[315] An early approach for IOP monitoring was conducted on enucleated pig eyes using a wireless contact lens sensor (CLS).[316] Very recently, Park *et al.* fabricated a contact lens strain sensor, which can detect detailed changes in IOP[304] (Figure 9h). This contact lens IOP wearable sensor was utilized to monitor intraocular islet transplantation as an alternative procedure to treat diabetes. This smart contact lens can transmit the real-time IOP values wirelessly using an antenna.

Saliva-Based Noninvasive Wearable Biosensors. Saliva is a complex fluid consisting of many components such as amino acids, ions, proteins, sugar, nucleotides, microorganisms, metabolites, enzymes, hormones, and ions.[307] Many of the biomarkers pass directly from blood to saliva, making it a promising sample for noninvasive accurate diagnosis. It has therefore been widely used in both portable and wearable biosensing systems.[82]

Recent progress of saliva-based wearable biosensors mainly focused on electrical wearable sensors. For example, McAlpine *et al.* fabricated a saliva-based wearable sensing platform consisting of a passive wireless graphene-based resistive sensor that could detect pathogenic contamination.[317] Specifically, the sensing platform consists of a parallel LRC resonant circuit with a gold inductive coil for wireless communication and interdigitated capacitive electrodes in contact with graphene to form the resistive sensor. Graphene was functionalized with antimicrobial peptides (AMPs), and the variation in graphene resistance upon bacterial binding changed the bandwidth of the resonance curve, enabling wireless monitoring (Figure 10a). AMP is a genomic bioreceptor which binds to various pathogenic bacteria, including *Escherichia coli* (*E. coli*), *Helicobacter pylori* (*H. pylori*), and *Staphylococcus aureus* (*S. aureus*). Furthermore, they also demonstrated the bacteria sensing capability in human saliva at real-time.

Another wearable saliva-based electrical biosensor was developed by Wang *et al.*, where the detection of biomarkers is based on a dielectric sensing mechanism that monitors the change in impedance in response to the change in biomarker concentration in liquid media.[317,320] Their sensing system was in a form of an enzyme (uricase)-based mouthguard integrated with Bluetooth wireless communication, through which varying levels of salivary uric acid (UA) in saliva was monitored[318] (Figure 10b). Abnormal levels of UA indicate various diseases, including hyperuricemia, gout, Lesch-Nyhan

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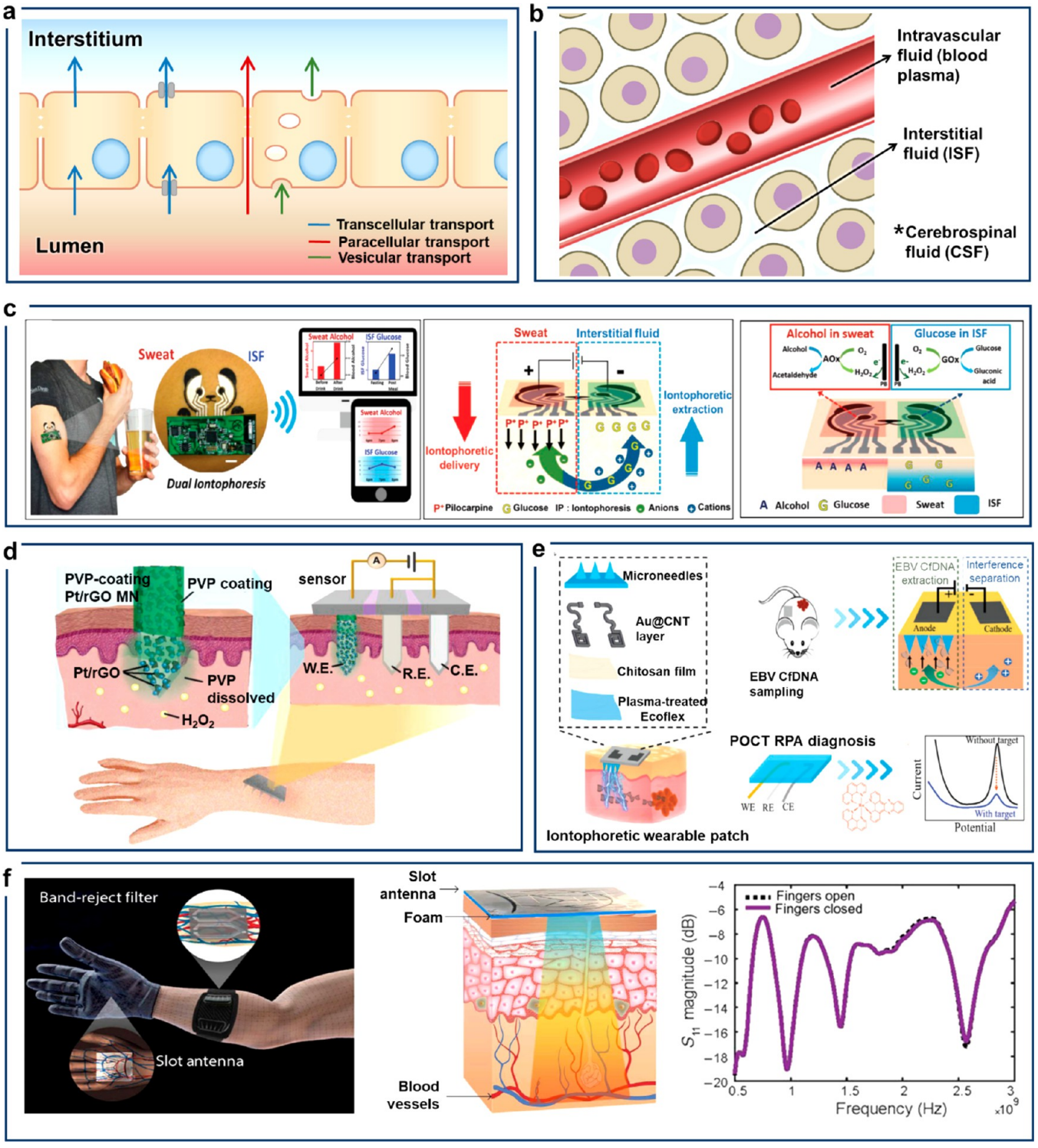

Figure 11. Extracellular fluid-based wearable biosensors. (a) Extraction of biomarkers in extracellular fluid through transcellular, paracellular, or vesicular transport paths. Adapted with permission from ref 239. Copyright 2019 Nature Publishing Group. (b) Different types of extracellular fluid, including intravascular fluid (blood plasma), interstitial fluid (ISF), and cerebrospinal fluid (CSF). (c) Description of dual-iontophoresis-based tattoo biosensor for the detection of glucose in ISF and alcohol in sweat with minimized skin irritation. Adapted with permission under a Creative Commons CC BY License from ref 327. Copyright 2018 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim Publishing Group. (d) Amperometric wearable biosensor integrated with a conductive microneedle array coated with rGO and Pt NPs for the detection of H_2O_2 in ISF within the epidermis. Reproduced with permission from ref 328. Copyright 2019 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim Publishing Group. (e) Patch-type wearable biosensing system integrated with a microneedle array and dual-iontophoresis system for the extraction of the Epstein−Barr virus (EBV) cell-free DNA (CfDNA) for cancer diagnosis. Reproduced with permission from ref 329. Copyright 2020 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim Publishing Group. (f) EM sensor mimicking vasculature anatomy for noninvasive blood glucose monitoring. There is a negligible effect on the output wireless signal due to the opening and closing of the fingers. Adapted from ref 330. Copyright 2020 the authors, some rights reserved; exclusive licensee

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Figure 11. continued

syndrome, and renal syndrome.[318,321−324] High levels of UA also implicate a high future risk of type 2 diabetes and its complications.[325] The acquired data were capable of being transmitted to smartphones, laptops, and other consumer electronics for on-demand processing, diagnostics, or storage.[318]

Since the above-mentioned dielectric sensing device contains radio frequency identification (RFID) electronics for signal readout, the sensing system is relatively bulky compared with other POC biosensors.[326] In order to overcome this drawback, Omenetto *et al.* fabricated a miniaturized passive dielectric tooth-attachable saliva sensor by employing a broadside-coupled split-ring resonator (BC-SPR).[319] They used porous silk film or poly(*N*-isopropylacrylamide) (PNIPAM) hydrogels as the bioresponsive interlayer between two split-ring resonators (Figure 10c). This sandwich structure enhanced the sensor performance by concentrating the electric field within the sensing layer. Furthermore, Omenetto *et al.* demonstrated *in vivo* functionality by adhering this sensor on a human tooth. The shift in resonance frequency in response to food ingestion was monitored.[326]

Extracellular Fluid-Based Wearable Biosensors. Noninvasively accessible biological fluids, such as sweat, saliva, and tears, are created by diffusion from the blood vessel through the cell membrane (transcellular), space between the cells (paracellular), and *via* vesicular transport[239] (Figure 11a). Therefore, since the noninvasively accessible fluids have to go through these transport steps, the biomarker concentrations in these fluids have relatively low correlation with the health conditions of the patient, compared to those in human blood. Additionally, the concentration changes of biomarkers in these biological fluids have a certain degree of time delay compared to that of their concentrations in blood. These intrinsic limitations can pose a restriction on the breadth of possible diagnostic applications.

Extracellular fluids are regarded as a more reliable biomarker resource for wearable biosensing applications because these fluids are created by direct diffusion through the interface of the capillary vessels.[239,331−333] Extracellular fluid refers to body fluids outside the cells of any multicellular organism, including interstitial fluids, intravascular fluids (blood plasma), and cerebrospinal fluids (CSFs) (Figure 11b). Among these three biological fluids, ISF and blood are frequently used in wearable electrical biosensors. Recently, methods of detecting biomarkers in ISF and blood through minimally invasive and noninvasive techniques have been developed. These topics will be discussed below.

Interstitial Fluid-Based Minimally Invasive Wearable Biosensors. Minimally invasive ISF collection can be classified based on the location of ISF extraction: extraction from outside the epidermis and within the epidermis.[239] A dual-iontophoretic system can conduct the ISF extraction outside the epidermis, whereas the microneedle array can conduct the ISF extraction process from both outside and within the epidermis.

The dual-iontophoresis system stimulates and extracts both sweat and ISF simultaneously through iontophoresis (explained above in the section Electrical Sweat-Based Wearable Biosensors) and reverse iontophoresis that extracts biomarkers to the outside of the skin surface *via* electromigration and electro-osmosis.[334,335] This system has been extensively studied for application in wearable biosensors.[280,327,336] Wang *et al.* developed a fully integrated tattoo-based amperometric biosensor that detects the concentration of ethanol in sweat and glucose extracted from ISF after food consumption[327] (Figure 11c). The authors prevented intermixing of the two biological fluids by collecting them separately at the anode and cathode and by coating the electrodes with a biocompatible hydrogel with different pore sizes. The hydrogel also prevented unwanted skin irritation. This skin-attachable, dual-iontophoretic, amperometry-based biosensor can be further developed to extract and detect multivariate biomarkers in different biological fluids efficiently.[327]

Withdrawing ISF outside the epidermis using iontophoresis causes discomfort to the patients and may cause skin irritation under extended exposure to an electrical current.[337,338] More importantly, the extraction of ISF outside the epidermis may result in high variability in chemical composition.[339] One way to overcome these limitations is to insert the sensing element into the epidermis using a microneedle array. For instance, Xie *et al.* fabricated a microneedle array patch that functioned as the reference, working, and counter electrodes of an amperometric H_2O_2 sensing system[328] (Figure 11d). The surface of the working electrode was deposited with reduced graphene oxide (rGO) and Pt NPs to offer fast charge transfer and to increase the accessibility of adsorption and electrocatalysis of H_2O_2, respectively.

Kong *et al.* fabricated a wearable electrical biosensor that contains both hydrogel-based microneedle array and dual-iontophoresis system to extract the target biomarker from ISF[329] (Figure 11e). They successfully demonstrated the extraction of the Epstein−Barr virus (EBV) cell-free DNA (CfDNA) for cancer diagnosis. Through reverse iontophoresis, EBV CfDNA was concentrated at the anode, and it was subsequently captured and extracted within the epidermis through a microneedle array. This sample collection method led to an improvement in the capture efficiency and accurate screening of EBV CfDNA. Furthermore, they demonstrated the potential for *in vivo* detection of EBV CfDNA fragments by adhering their wearable biosensor to tumor-bearing immunodeficient mice at both early and advanced stages of EBV CfDNA-related cancer.[329]

Blood-Based Noninvasive Wearable Biosensors. Blood contains various types of biomarkers, and unlike other biological fluids, such as sweat, saliva, tears, and ISF, there is no time lag issue. Therefore, disease diagnosis based on blood is commonly accurate. For instance, blood glucose is the standard biomarker for diabetes diagnosis and treatment, but noninvasive disease diagnosis based on glucose in human blood remains a formidable challenge.

Eid *et al.* provided an approach for painless, needle-free, and continuous glucose monitoring through EM wave multisensing system targeting different on-body locations[330] (Figure 11f). Since glucose levels in blood alter the dielectric

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Table 1. Comparison of Different Portable Biosensor Performances

detection methods	biomarker	LOD, LOQ, sensitivity, and specificity	dynamic range	multianalysis	detection time	biosensing device	sensing material	ref
fluorescence	DNA		10−10^5 copies/μL		∼30 min	self-powered integrated microfluidic chip	magnesium acetate, silicone (PDMS)	172
fluorescence	DNA	LOD: 5−50 copies/ μL	5 × 10^2 and 5 × 10^6 copies/mL	yes	∼30 min	silicon-based microfluidic chip and smartphone	silicon wafer	173
field-effect transistor	chromosome 21 fragments (DNA)	LOD: <100 aM	0−200 aM		400 s	field-effect-transistor-based biosensor	molybdenum disulfide (MoS_2) film, gold nanoparticles, silicon wafer	175
field-effect transistor	DNA fragments related to DMD disease	1.7 fM			<15 min	field-effect-transistor-based CRISPR−chip	graphene, dCas9 CRISPR complex carboxylated magnetic beads (MBs)	176
absorbance	HIV and syphilis antibody, anticardiolipin antibody, IgM	sensitivity: 92−100% specificity: 79−100%		yes	<15 min	smartphone dongle	plastic cassettes, gold nanoparticles, silver ions	203
colorimetric detection	IgM, IgG antibodies against SARS-CoV-2	sensitivity: 88.66% specificity: 90.63%		yes	<15 min	colorimetric lateral flow immunoassay	gold nanoparticles, nitrocellulose (NC) membrane, plastic pad, and glass fiber conjugate pad	206
fluorescence	Zika virus nonstructural protein 1	LOD: in buffer 0.045 ng/mL, in serum 0.15 ng/mL	0.01−1000 ng/mL		<20 min	smartphone-based fluorescent lateral flow immunoassay	quantum dot microspheres, NC membranes, plastic cassettes	204
amperometry	cytokine interleukin-3 (IL-3)	<10 pg/mL sensitivity: 91.3% specificity: 82.4%			<1 h	integrated biosensor for sepsis (IBS) with a microcontroller unit and a Bluetooth module	magnetic beads, magnetic pipet	205
resistance	AD core biomarkers (t-tau, p-tau_{181}, Aβ_{42}, and Aβ_{40})	sensitivity: 90.0% selectivity: 90.0% LOD: 2.13 fM LOQ: 2.72 fM	10^0 −10^6 fM	yes		chemiresistive biosensor	single-walled carbon nanotube, silicon wafer	167
field-effect transistor	SARS-CoV-2 spike protein and SARS-CoV-2 virus	spike protein: 1 fg/mL in phosphate-buffered saline and 100 fg/mL clinical transport medium SARS-CoV-2 virus: in culture medium (limit of detection [LOD]: 1.6 × 10^1 pfu/mL) and clinical samples (LOD: 2.42 × 10^2 copies/mL)				field-effect-transistor-based biosensor	graphene, silicon wafer	104

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Table 2. Comparison of Biomarker Concentrations in Different Biological Fluids

biomarker		concentration range in human serum	concentration range in sweat	concentration range in saliva	concentration range in tear	concentration range in interstitial fluid	ref
metabolic biomarker	glucose	3.3−6.7 mM	10−200 μM	0.22−0.72 mM	0.013−1 mM	4.1−6.9 mM	109,271,337342,343
	lactate	0.36−1.3 mM	5−20 mM	0−0.4 mM	2−5 mM	0.5−10 mM	271,303,344,345
	cortisol	44.9−145 ng/mL	0.1−139.9 ng/mL	1.2−9.8 ng/mL	0−1306 nM		346,347
	uric acid	200−400 μM	2−10 mM	100−250 μM			348,349
immunological biomarker	IgG	407−2170 mg/dL	IgG1 1640 pg/mL 1gG2 292 pg/mL 1gG3 74pg/mL IgG4 43 pg/mL	10.5 mg/mL		similar concentration to human serum	350−352
	IgM	24−791 mg/dL	69 pg/mL	1.2 mg/mL		lower quantity to human serum	350−352
ionic biomarker	Na^+	136−145 mM	10−100 mM	20−80 mM	80−161 nM	135−145 nM	241,273,345,353
	Ca^{2+}	2−2.6 mM	0.41−12.4 mM		0.4−1.1 mM		239,345
	K^+	3.5−5 mM	1−18.5 mM	30−100 mM		3.5−5 mM	241,345
	Cl^-	98−107 mM	10−100 mM	20−100 mM	106−130 mM		271,273
nucleic acids	DNA	10−15 μg/mL		84 μg/mL	714 ng/mL		354,355
	RNA	308 μg/mL		1945 μg/L	564 μg/L		356

Table 3. Pros and Cons of Noninvasive Accessible Biological Fluids for Wearable Biosensors

biological fluids	pros	cons
sweat	•readily obtainable biological fluid	•difficult to produce enough sweat for analysis, sample evaporation, sample contamination, sample collection, normalization of sample volume, and complexity of sweat secretion
	•suitable for noninvasive sample collection on various spots on human body	•clinical value of sweat not yet fully evaluated
tears	•the composition less complex than blood	•the correlation between biomarkers in tear and blood is unclear
	•biomarkers diffuse directly from the blood	•signal is sensitive to ambient temperature and light
	•the concentration of biomarkers exhibits a close correlation with that in blood	•miniaturization of the power supply is critical to prevent eye irritation
	•contains a variety of biomarkers	•long-term monitoring with contact-lens-based biosensors may cause discomfort to the patients
	•continuous access to the biological fluid without the need for induction or extraction	•continuous stimulation of tear is needed for glasses-based biosensors
saliva	•readily accessible noninvasive biological fluid	•biofouling by the rich salivary biomarkers can reduce the sensing performance
	•it contains many of the biomarkers directly diffused from the bloodstream	•the concentration of many biomarkers in saliva are lower than that in blood, requiring highly sensitive biosensing techniques
		•gum bleeding can contaminate the saliva, which can lead to a false positive signal
		•tight encapsulation of the biosensing device and the use of biocompatible selective permeable materials are essential
interstitial fluid	•minimally invasive accessible biological fluid	•high dilution factor during bioanalytes extraction by reverse iontophoresis
	•the concentration of biomarkers in ISF shows a reliable correlation with that in blood	•the obtained sample quantity is low
	•sample collection efficient and reproducible	•long extraction time and biomarker concentration can vary during collection; the time to reach steady-state is highly dependent on the initial biomarker concentration of the extraction spot
		•certain types of biomarkers cannot be extracted, such as proteins and cholesterol

properties of the blood, their system measured glucose levels in a noninvasive manner without a time lag. A high correlation (>0.9) between the system's physical parameters and that of the actual blood glucose level was observed under human trials. These results were attributed to their sensor's vasculature anatomy-inspired tunable EM topologies that can be aligned with the body curvature and adjusted to small movements while focusing on the effective tailoring of EM waves.[330]

Recently, a blood collection device without needle injection has emerged as an alternative blood collection approach for clinical monitoring of human biomarkers in blood. The commercialized TASSO-M20 wearable device is suitable for near-patient blood sample collection for people of all ages.[228] The TASSO-M20 wearable device includes a Tasso button, sample pod, and the Tasso OnDemand kit. Currently, a research team is using the TASSO-SST OnDemand device to test for COVID-19 antibodies in serum. The collected samples are mailed back from people confined to their homes, keeping them out of clinics. Though this device is designed for blood sample collection only, it shows vast potential to be integrated into future blood-based noninvasive biosensors.

Challenges and Future Perspectives for Patient-Friendly Biosensors. Current portable and wearable biosensors still require further development in terms of sensitivity, selectivity, response time, continuity, reproducibility, and stability to provide comparable testing results with those in centralized laboratories. In particular, reducing false-negative and false-positive testing results is critical for their commercialization and clinical acceptance.

Though portable biosensors have been widely applied for POCT, a large number of portable biosensors are mainly designed for invasive sampling. We selected some of the most

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Table 4. Comparison of Different Noninvasive Wearable Sensor Performances

detection methods	biomarker	sensitivity/LOD	dynamic range	multianalysis	reusability	signal readout system	sensor material	cost-effectiveness	ref
colorimetric	the total volume of sweat loss, pH, chloride, lactate, glucose in sweat	sweat harvest rate: ∼1.2 to 12 μL/h color change <1 min glucose: ∼200 μM changes in units: 0.5 pH 0.2 mM chloride 0.3 mM lactate 0.1 mM glucose	approximately lactate: 1.5−100 mM chloride: 100−800 mM pH: 5.5−8.5 glucose: 1−10 mM	O	one-time use	smartphone	PDMS, pHEMA hydrogel mix, filter paper	low cost	271
colorimetric	glucose	∼35 μM	50−250 μM	O	one-time use	smartphone	cotton thread and functionalized filter paper	low cost	272
fluorometric	Cl^-, Na^+, Zn^{2+} total sweat lost and rate	sweat harvest rate: 0.8 μL/min	Cl^-: 5−100 mM Zn^{2+}: 1−20 μM Na^+: 5−100 mM	O	one-time use	smartphone with a dark box	white silicone material, PDMS, PMMA-coated bare wafer, a black silicone formulation	relatively expensive	273
amperometry, potentiometry	glucose, lactate, Na^+, K+ in sweat	2.35 nA/μM (glucose), 220 nA/mM (lactate)	glucose: 0−200 μM lactate: 0−30 mM Na^+: 10−160 mM K^+: 1−32 mM	O	one-time use	a flexible printed circuit board (FPCB)	PEDOT:PSS covered electrode	low cost	341
OECT	cortisol in sweat	2.68 μA/dec	0.01−10.0 μM	not shown	one-time use	not mentioned	PEDOT:PSS	relatively expensive	39
amperometry	glucose in sweat	high (not mentioned in a quantitative value)	10 μM to 1 mM	not shown	one-time use	not mentioned	Prussian blue-deposited porous gold electrode disposable strip	low cost	357
resistive	glucose in tear	∼22.72%/mM	0.1−0.9 mM	O	one-time use	wireless display (LED pixel, rectifier, and antenna)	disposable graphene FET-based contact lens	expensive	254
resistive	pathogenic bacteria in saliva	not shown	not shown	O	one-time use	wireless communication *via* resonance frequency (RF)	graphene/silk hybrid	relatively expensive	358
amperometry	uric acid in saliva	2.32 μA/mM	up to 1 mM	O	4 h with 10 min intervals	a Bluetooth low energy (BLE) chip	Prussian blue-deposited carbon electrode	low cost	318
dielectric	common liquid environments in human mouth and glucose	0.6 MHz in 1 g/L of glucose	glucose: 1−100 g/L	O	one-time use	wireless communication *via* a conformal RF sensor composed of an active layer encapsulated between two reverse-split ring resonators portable minivector network analyzer (VNA) attached to a tablet or cell phone	silk hydrogel or a responsive poly(*N*-isopropylacrylamide), PNIPAM-based hydrogel gold	relatively expensive	319,359

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well-known portable biosensors and listed their performance in Table 1. Compared with blood-based invasive sampling methods, noninvasive sampling methodologies are beneficial to and preferred by most patients. Recent advances in fully integrated wearable biosensors utilizing noninvasive sampling strategies enable diagnosis in a patient-friendly manner.

Sweat, tears, saliva, and ISF are the most well-known noninvasive or minimally invasive accessible biological fluids. Although a blood-based noninvasive biosensor based on EM monitoring technology is rapidly emerging for patient-friendly diagnosis, this technique is only in its beginning stages, and its clinical applicability needs to be proven under various conditions. We compared the concentrations of biomarkers in different biological fluids in Table 2. Below, we discuss the strengths and drawbacks of each biological fluid and their associated wearable sensing technologies (summarized in Table 3). We also selected some of the most well-known wearable biosensors and listed their performance in Table 4.

Sweat. Sweat is the most readily obtainable biological fluid, and it is suitable for noninvasive sample collection on various spots on the human body because sweat glands are distributed across the entire human body. However, the main limitations of using sweat as clinical samples include difficulty to produce enough sweat for analysis, sample evaporation, sample contamination, sample collection, and normalization of sample volume.[340] In addition, its practical applications have been limited by the variation of bioanalyte concentrations collected from different parts of the body, and the change in biomarker concentration in sweat is a delayed response of human body to a given disease.[35] Furthermore, the clinical value of using sweat as a diagnostic biological fluid needs to be carefully examined.

Many of these sweat-based diagnosis issues are being resolved by bringing wearable biosensors into nearly immediate contact with sweat. However, only knowing the sweat generation rate is inadequate to predict the actual biomarker sampling intervals without a detailed microfluidic and transport model between the sweat glands and the sensors. Due to the complexity of the sweat secretion, simultaneous and multiplexed screening of target biomarkers are crucial for accurate measurements by wearable biosensors.[341] Therefore, a deeper understanding of the sweat chemistry and transport mechanism, along with biomarker partitioning and microfluidic transport models will facilitate the growth of sweat-based wearable biosensors.[341]

Tears. The composition of tears is less complex than blood, but they nevertheless contain a variety of biomarkers. For example, contact-lens-based wearable biosensors mostly provide continuous glucose monitoring in their normal physiological range (Table 2). However, some critical issues need to be considered for these sensors. First, though biomarkers in tears diffuse directly from the blood, the correlation between the biomarkers in tears and blood is unclear.[35] Second, the contact-lens-based wearable biosensors being directly exposed to ambient temperature and light lead to their short lifetime due to the degradation of the embedded enzymes. Third, miniaturization of the power supply is critical to prevent eye irritation. Moreover, long-term monitoring with contact-lens-based biosensors may cause discomfort to the patients. Therefore, development of a fully integrated multiplex contact-lens-based biosensing system for continuous biomarker monitoring remains a big challenge.[35] Though a glasses-based tear sensing platform eliminates the necessity of direct eye contact with the biosensing system, a menthol tear stick is inconveniently needed to stimulate tearing.[314]

Saliva. Since saliva is a readily accessible noninvasive biological fluid which contains many of the biomarkers directly from the bloodstream, saliva-based diagnosis has advanced rapidly in recent years. Though several saliva biomarkers (*e.g.*, hormones, metabolites, or antibodies) have been used in clinical settings, potential biofouling by the rich salivary protein content limited the development of oral wearable biosensors. Moreover, the concentration of many biomarkers in saliva is lower than that in blood, requiring highly sensitive biosensing techniques. Furthermore, potential gum bleeding can also lead to contamination or false signals.[82] Hence, tight encapsulation of the biosensing device and the use of biocompatible selective permeable materials are essential for saliva-based biosensors.

Interstitial Fluid. Minimally invasive sampling methods, such as iontophoresis, reverse iontophoresis, and microneedles, have been developed to induce both sweat and ISF. Since nutrients directly diffuse from cells to ISF, analytes in ISF show reliable correlations to that of the analytes in blood. Though reverse iontophoresis is efficient and reproducible, the quantities of bioanalytes obtained at the skin surface are small, and the dilution factor can be as high as 10−100-fold.[241] As a result, the duration of sample collection may be too long and the biomarker concentration can vary with time during collection. Moreover, the time to reach the steady state during reverse iontophoresis is highly dependent on the initial biomarker concentration of the extraction spot, and this may lead to misdiagnosis.[241] Additionally, reverse iontophoresis does not work for certain biomolecules (*e.g.*, proteins that are too large to be quantitatively extracted, lipophilic biochemicals such as cholesterol), limiting the number of detectable biomarkers.[241,329]

Most wearable devices have focused primarily on single measurements, which makes it difficult for standardization; in this regard, simultaneous noninvasive monitoring of multiple biomarkers is needed. Such multiplexed analysis can not only provide a broader analysis of the physiological state but also enable active calibration and correction of the signal response. Moreover, the incorporation of multiple sensing approaches for the same bioanalyte, and the use of a wider range of biomarkers taken from a wider range of biological fluids can furthermore improve the reliability of biosensors. These improvements can ultimately speed up the development of clinical therapies for diseases.[82]

Below are some of the current remaining challenges of wearable biosensors that need to be addressed: (1) a better understanding of the correlation between bioanalyte concentrations in sweat, tear, saliva and ISF with that in blood to improve diagnostic reliability, (2) development of reusable and cost-effective wearable biosensing platforms, (3) biomarker recognition site regeneration for repeatable detection and continuous monitoring, (4) expansion of biomarker detection range, (5) exploring various types of noninvasive accessible biological fluids, such as urine, mucus and semen, and (6) personalized calibration since every person is unique in terms of symptoms and biomarker levels.[45,87]

In addition to addressing the aforementioned challenges, to progress toward commercialization of wearable biosensors, the sensors should meet the requirements for integration into conventional electronic circuits and wireless systems, such as constant electrical properties under ambient conditions,

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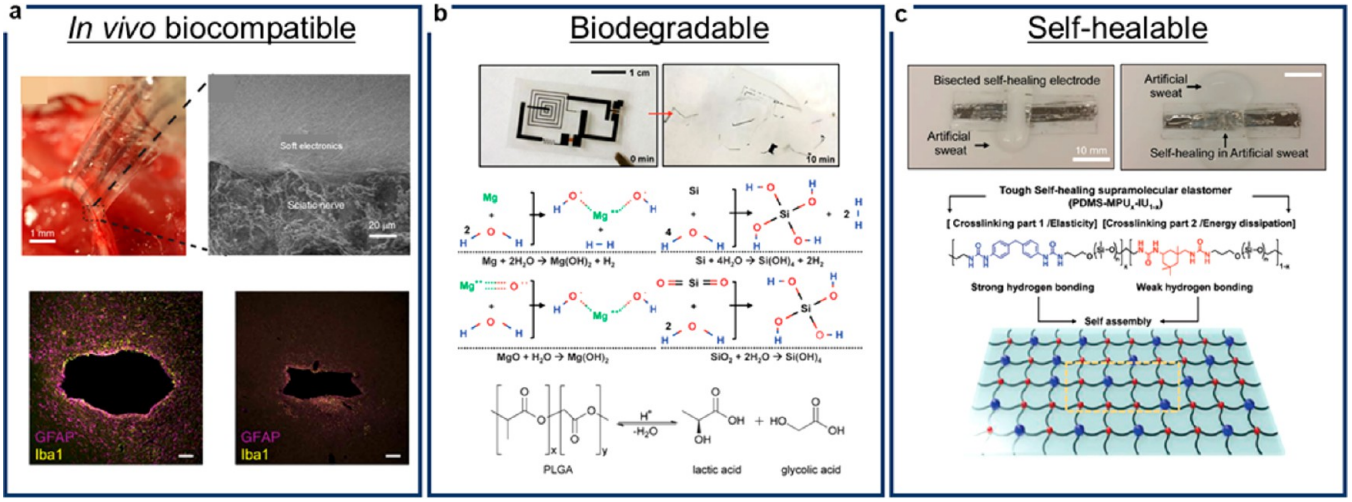

Figure 12. Required material properties for implantable devices. (a) Photograph of an *in vivo* biocompatible material-based implantable device (top) and *in vivo* biocompatibility test (bottom). Reproduced with permission from ref 73. Copyright 2020 Nature Publishing Group. Reproduced with permission from ref 368. Copyright 2019 the authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC) http://creativecommons.org/licenses/by-nc/4.0/. Copyright 2019. (b) Photograph of a biodegradable material-based device (top) and its degradation mechanism (bottom). Reproduced with permission from ref 369. Copyright 2012 American Association for the Advancement of Science. (c) Photograph of a self-healable material-based device (top) and its healing mechanism (bottom). Reproduced with permission from ref 370. Copyright 2018 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim Publishing Group.

sensor to sensor uniformity, and excellent frequency response. Additionally, ensuring the accuracy and stability of wearable biosensors are critical to their commercialization. Moreover, there is a massive demand to reduce sample to answer time and enhance accuracy through advanced diagnostic algorithms, such as machine learning and artificial intelligence. Finally, assuring the privacy and security of wearable biosensors needs to be properly addressed for digital health care applications. Since wearable biosensors are small in size and have the ability to store a large amount of data, it is highly likely that the device and the stored data may be lost or even hacked.[45] Development of encrypted wearable biosensors with tracking capabilities is needed to ensure safe and secure use of wearable biosensors.

There is still plenty of room for POC portable and wearable biosensors to grow. Along with the aforementioned issues, a large number of clinical studies relating each biological fluid to medical disorders are needed to underpin the widespread clinical acceptance of portable and wearable biosensors. Hence, for portable and wearable biosensors to leap forward toward commercialization, collaborative research and partnership between academia, industry, and hospitals are of critical importance. With these efforts in effect, portable and wearable biosensors have the potential to become the dominant diagnostic tools for patient-friendly health care in the future.

PATIENT-FRIENDLY TREATMENT

Introduction to Patient-Friendly Treatment. Implantable devices refer to medical devices that have specific functions beyond passive mounting for fixation.[57,360−363] There have been many implantable devices that were approved by the FDA; some of which have been industrialized recently, such as cochlear, heart pacemaker, and vagus nerve stimulator.[360−363] Although traditional implantable devices enable effective medical care and treatment, they can also cause side effects and are generally costly to the patients.[58] To solve these issues, patient-friendly implantable devices based on different materials and device architectures are being introduced that minimize the burden on the patient while pursuing functions that could not be performed.[56,57] In this section, we discuss various aspects of implantable devices such as material selection, required specifications, and possible clinical uses.

Material Selection Criteria for Implantable Devices. The materials for implantable devices require a set of properties similar to those of wearable devices mentioned above. However, implantable devices must have *in vivo* biocompatibility (Figure 12a), which is more stringent than that of biocompatibility defined for wearable electronics.[56,57,364−366] *In vivo* biocompatibility testing generally requires experimentation since inner body reactions are difficult to predict because too many factors are involved.[365,366] Usually when foreign materials are introduced in the human body, unintended biological reactions (so-called host response) can occur, causing malfunction of tissues or organs. Gold, titanium, PDMS, and Ecoflex are the most well-known biocompatible materials in medical research.[57] Moreover, since tissues and organs are generally soft (*i.e.*, spinal cord and brain have modulus of 100 Pa to 100 kPa), the presence of hard and stiff material may cause a wound or inflammation.[367,368] Therefore, along with biocompatibility, mechanical suitability should also be carefully considered. It is important that the mechanical properties of the device match that of the tissue or organ to which it is adhered. Furthermore, even if the device is biocompatible and sufficiently soft, if the overall device is too bulky, biological rejection reactions can still occur.[368] Therefore, miniaturization is also important for implantable device design.

Though an implantable device fabricated with biocompatible and soft materials improves their suitability to clinical applications, it is still risky to keep foreign components in the body for an extended period, as side effects such as inflammation, malfunction, and deformity of tissues and organs can be induced. Therefore, a secondary surgery is

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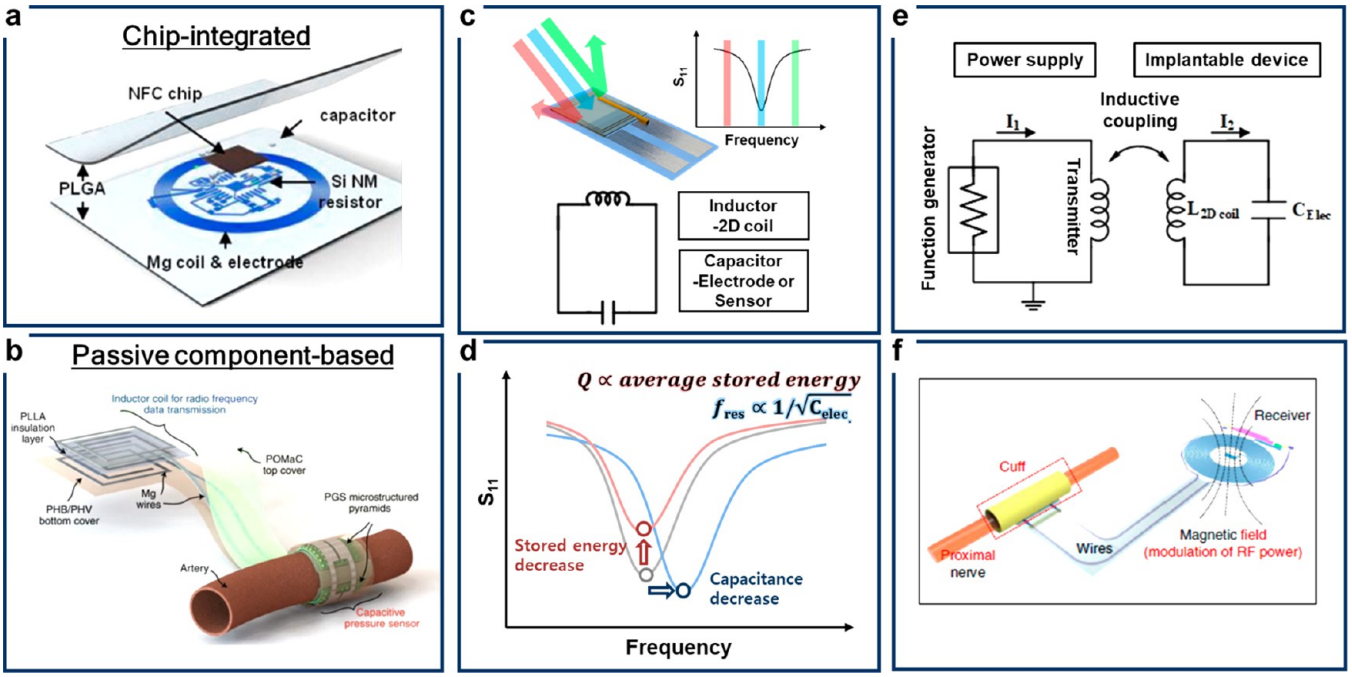

Figure 13. Wireless communication for implantable devices. (a) Schematic illustration of a chip-integrated wireless implantable device. Reproduced with permission from ref 63. Copyright 2016 Nature Publishing Group. (b) Schematic illustration of a passive component-based implantable device. Reproduced with permission from ref 69. Copyright 2019 Nature Publishing Group. (c) Schematic illustration of EM wave storing of LC resonator (top) and its equivalent circuit (bottom). Reproduced with permission from ref 376. Copyright 2019 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim Publishing Group. (d) Conceptual depiction of S_{11} spectrum variation according to the change of capacitance and stored energy. Reproduced from ref 372. Copyright 2020 American Chemical Society. (e) Equivalent circuit of wireless power transfer system. (f) Schematic illustration of an inductive coupling-based implantable device. Reproduced with permission from ref 64. Copyright 2018 Nature Publishing Group.

often required to remove the implantable device after it serves its purpose. The need for an additional surgery deters many patients from implanting medical devices in the first place. As a means to address this issue, transient implantable devices (devices made up of biodegradable materials) have been introduced[369] (Figure 12b). These types of devices can be completely dissolved in the human body through the metabolic processes.[63,64,68] Typically, magnesium (Mg), molybdenum (Mo), and zinc (Zn) have been used as conductors, silicon (Si) nanomembrane (NM) or zinc oxide as semiconductors, and silicon oxide (SiO_X) and nitride (SiN_X) as insulators. Polymers containing an ester group such as poly(lactic-*co*-glycolic acid) (PLGA), polycaprolactone (PCL), or poly(glycerol sebacate) (PGS) have been utilized as substrates. These materials, in general, can be cleaved by water atoms in the blood, and their byproducts are soluble and can be absorbable by the body. The initial demonstrations of biodegradable implantable devices were shown to have functionalities comparable with those of conventional electronics, making them highly promising for future implantable electronic applications.[369]

In some cases, it is necessary to continuously monitor and treat disease for an extended period of time. One of the issues of having the implantable device inside the body for a long time is its potential break down and malfunction.[72,370] This can occur due to the repeated motion of the tissues and organs and their change in size over time. In this regard, self-healable materials that employ a reversible bonding chemistry with energy dissipation mechanism are potentially of high value (Figure 12c), so that the implantable device can last a long time in the body and constantly adapt to different geometries.[72,73,370] Recently, various self-healing mechanisms with several possible material candidates have been reported, which allows the development of adaptable, durable, and suturing/glue-free implantable devices.

Wireless Communication for Implantable Devices. It is often necessary for implantable devices to communicate (transmit signal and energy) with an out-of-body device. Also, since it is often infeasible for implantable devices to have their own power source, power needs to be supplied from an out-of-body source.[56,64,68] Conventional implantable devices address these issues *via* wiring; however, such wire-based implantable devices have several key drawbacks, such as patient discomfort, the complexity of implantation, and the risk of infection.[62,64] Wireless implantable devices, in this regard, present solutions to these drawbacks. In general, there are two main types of wireless communication devices: passive component-based devices and communication chip-integrated devices.[63,68] Passive component-based devices communicate with a transmitter or a reader through near EM field variation, whereas communication chip-integrated devices measure the electrical signal transmitted by the electronic chip that is integrated with the implantable device. There are trade-offs between these two types of devices. Chip-integrated devices have a relatively long-range communication and can implement complex functionalities such as frequency modulation and closed-loop feedback process (Figure 13a). However, these devices usually require rigid and bulky electronic chips and a power supply for activation, which makes them less suitable to be implanted into the human body. On the other hand, passive component-based wireless implantable devices do not require a rigid and bulky electronic chip, nor an

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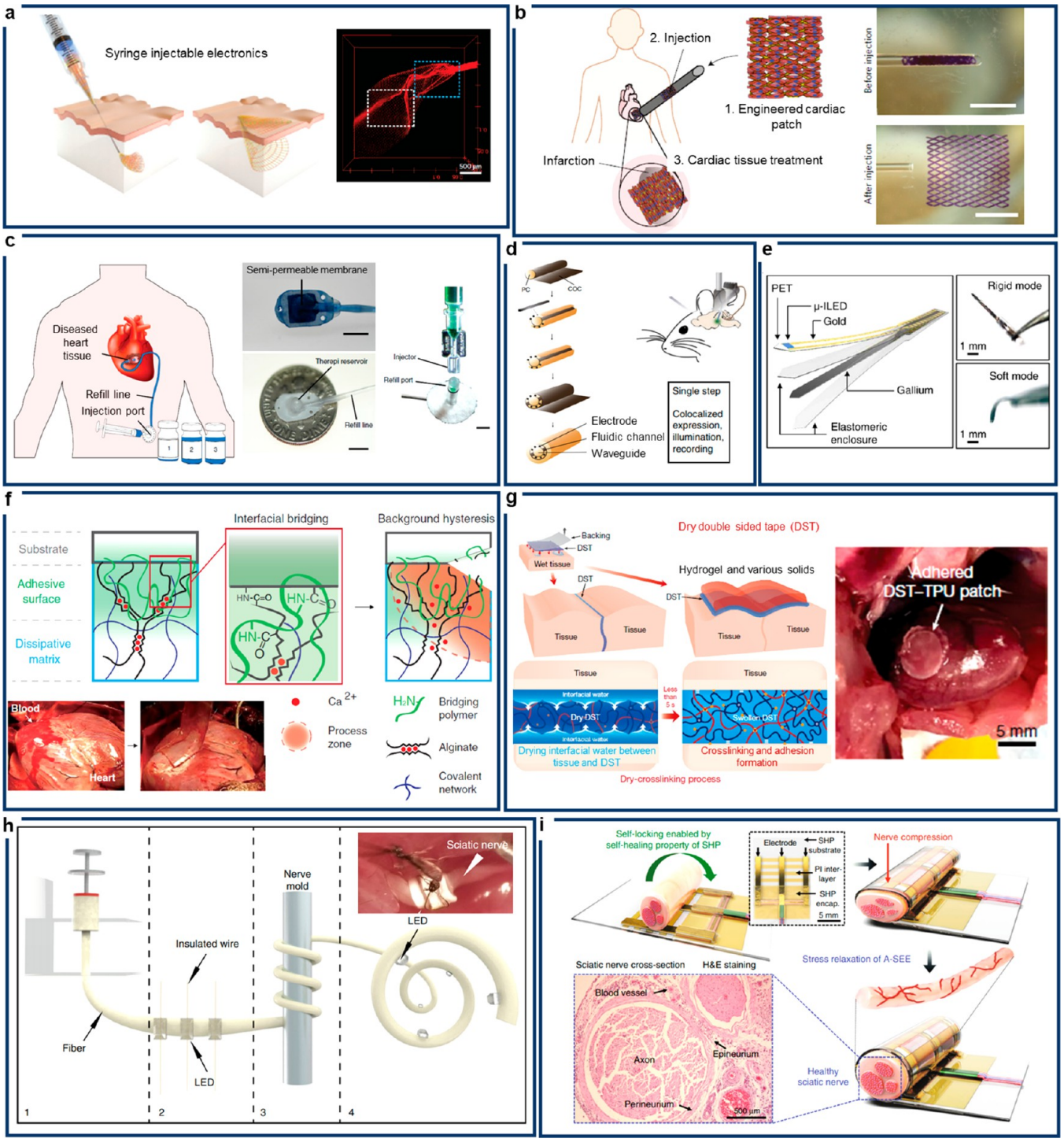

Figure 14. Minimally invasive injection and *in vivo* compatible mounting strategies. (a) Schematic illustration and confocal microscopy image of syringe-injectable electronics. Reproduced with permission from ref 386. Copyright 2020 Nature Publishing Group. (b) Schematic illustration and photograph of minimally invasive tissue delivery scaffold. Reproduced with permission from ref 387. Copyright 2020 Nature Publishing Group. (c) Schematic illustration and photograph of tube-based minimally invasive, sustainable tissue delivery system. Reproduced with permission from ref 388. Copyright 2020 Nature Publishing Group. (d) Schematic illustration of minimally invasive functional fibers for one-step optogenetics. Reproduced with permission from ref 392. Copyright 2017 Nature Publishing Group. (e) Schematic illustration and photograph of transformable electronics for an implantable device. Reproduced with permission from ref 368. Copyright 2019 the authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC) http://creativecommons.org/licenses/by-nc/4.0/. Copyright 2019. (f) Schematic illustration of tough adhesion formation on wet surface and photographs of tough adhesive hydrogel mounted on a heart. Reproduced with permission from ref 66. Copyright 2017 American Association for the Advancement of Science. (g) Schematic illustration of tough adhesion formation between tissue and dry double side tape, and photograph of dry double-sided tape mounted on a heart. Reproduced with permission from ref 67. Copyright 2019 Nature Publishing Group. (h) Schematic illustration of shape memory polymer-based optical neuromodulation device. Reproduced with permission from ref 397. Copyright 2019

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Figure 14. continued

Nature Publishing Group. (i) Schematic illustration of self-healing polymer-based electronic epineurium for neural interfaces. Reproduced with permission from ref 398. Copyright 2020 Nature Publishing Group.

internal power source. This renders them flexible in terms of materials selection (Figure 13b), enabling them to be made entirely with soft, stretchable, and functional (*i.e.*, self-healable, biodegradable, attachable) materials.[68,69] However, use of these materials currently has limited performance due to the absence of silicon-based high-performance integrated circuits. Considering these trade-offs, wireless implantable electronic devices should be carefully designed according to their use. If researchers want to demonstrate a complex system that contains multiple electrical functionalities such as a feedback system, a chip-integrated wireless device is more suitable. Otherwise, relatively simple systems such as tactile sensing and power transferring can be developed with passive components.

A typical passive wireless communication device employs an LC resonator, which is generally fabricated as electrodes or sensors (acting as a capacitor) connected *via* a 2D coil (acting as an inductor) (Figure 13c). An LC resonator stores maximum EM energy at a specific resonant frequency. At this resonant frequency ($f_{res.}$), the reflection coefficient (S_{11}) shows a dramatic decrease, as depicted in Figure 13c. The resonant frequency is related to the capacitance (C) and the inductance (L_{2Dcoil}) by eq 1.[371]

$$f_{res.} = \frac{1}{2\pi\sqrt{L_{2Dcoil}C}} \quad (1)$$

By monitoring the resonant frequency with a reader coil that is connected to a vector network analyzer (VNA), variation of capacitance or inductance due to the external stimuli can be measured. For instance, as shown in Figure 13d, if the capacitance of the LC resonator decreases, the resonant frequency of the LC resonator (sky blue curve) increases.[372] By utilizing tactile and chemical sensors that are based on changes in the capacitance, the shift in the resonance frequency can be utilized as a means to detect tactile or chemical changes in the body.[373,374]

The modulation in quality (Q)-factor can also be used as a sensing mechanism.[375] The Q-factor is related to the stored energy in the LC resonator as seen in the equation below.[371]

$$Q = 2\pi f \frac{\text{average stored energy}}{\text{energy loss/s}} \quad (2)$$

Therefore, a decrease in the stored EM energy leads to a decrease in the Q-factor, which is manifested as an increase in the magnitude of the resonance peak (red curve in Figure 13d). The Q-factor of the resonator can be adjusted in two ways. First, the increase in the resistance of the resonator reduces the quality factor.[371,375] Second, the Q-factor can be reduced by interfering EM energy stored in the resonator. Considering the fact that most electric field is stored in the gap between the electrodes (*i.e.*, capacitor, split-ring), mounting the EM shielding materials or high dielectric constant material can modulate the Q-factor.[376] Conventional VNA and near-field communication (NFC) readout circuit can monitor the variation of Q-factor.[375]

Power transfer is another critical issue in wireless implanted electronic devices. Various power transfer techniques have been demonstrated recently, such as mechanical vibration, light transmission, ultrasound transmission, and inductive coupling.[62,64,367,377,378] Among these techniques, inductive coupling has been regarded as the most reliable and practical for implantable device activation; hence, it is being applied to commercial implantable devices, and translational medical devices that have been demonstrated at the laboratory scale.[62,64,69,379] As shown in Figure 13e, inductive coupling is a phenomenon where electrical energy between two closed-circuit can be exchanged *via* magnetic field variation between a transmitter and a receiver, which is usually implemented with a 2D coil-based inductor. This remote power transfer strategy can also be utilized as a medical treatment procedure, such as RF ablation, and electrical stimulation[64,380] (Figure 13f).

Despite their promising prospects, due to the high dielectric constant of human tissues, such as skin, muscle, and fat (*i.e.*, typically >10),[381,382] the effectiveness of signal and power transfer is inevitably compromised when wireless implantable devices are inserted in the human body.[64,383] Therefore, innovations targeting this issue is urgently needed for the practical and reliable use of implantable devices in patient-friendly treatment.

Insertion Strategies for Implantable Devices. Conventional open surgeries can cause significant physical suffering, infection, long recovery time, and economic burden on patients.[384] In order to overcome these drawbacks, minimally invasive surgery such as laparoscopic surgery and catheter-based treatment have been introduced, and due to their effectiveness and minimal side effects, they have been now been adopted as standard medical procedures.[60,385] Inspired by the success of minimally invasive surgery, the concept of minimally invasive insertion of implantable devices have engendered a great deal of interest among researchers.[62,380,386−389]

Syringe-injectable implantable electronics is considered as the most ideal medical device for minimally invasive insertion of implantable devices. As shown in Figure 14a, nanoscale-tilted mesh-like electronics fabricated with SU8 photoresist was injected into a commercialized syringe.[386] The tilted mesh structure not only allows the injection of implantable devices through the small outlet hole of the syringe but also unfolds the implantable device once it is inserted into the body. Moreover, integration of the silicon nanowire-based FETs and metal electrodes on the tilted mesh structure imparted electronic device functionality while maintaining its deformability. This device was inserted into a living mouse in a minimally invasive manner and brain activity of the mouse was successfully recorded, demonstrating its potential in clinical applications. Other studies have reported that the mesh structure can be inserted into the body through small tubes. For instance, Radisic *et al.* reported a shape-memory polymer-based flexible mesh scaffold for functional tissue delivery[387] (Figure 14b). This elastic and microfabricated tissue delivery scaffold was made up of UV-cross-linkable poly(octamethylene maleate (anhydride) citrate) (POMaC), a biodegradable elastomer. The scaffold effectively delivered cardiac tissue to the heart in a minimally invasive manner.

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Moreover, after the completion of medical treatment, it can be degraded through metabolic processes in the human body.

Inflatable balloon catheters are an extremely simple yet powerful medical instrument that have been utilized in many clinical operations.[59,380] It is an effective tool in medical treatment first because it enables minimally invasive insertion into lumens or other organs of the body through small incisions, owing to its small size and shape (cylindrical form in its deflated state).[59] Second, through controlled inflation, its size and shape can be optimally configured, through which contact with surrounding tissues can occur in a soft and conformal manner.[59] Hence, it can accommodate to complex, curvilinear, and time dynamic surfaces in a completely nondestructive manner. However, the main constraint of the conventional medical balloon catheter is it offers limited utility, owing to its lack of functionality. Therefore, in order to improve the effectiveness of inflatable balloon catheters, multifunctional electronics-integrated catheters were introduced by Rogers *et al.*[380] The authors utilized the balloon catheter as a platform for heterogeneous integration of high-performance sensors, heaters, and other components. To render the electronics stretchable, electronic components such as temperature and tactile sensors and heaters were placed on rigid islands while stretchable serpentine structured interconnectors were used to connect the electronic components. Finally, a practical application of this multifunctional catheter has been demonstrated through *in vivo* electrophysiological recording, RF ablation, and tactile and temperature sensing.

Mooney *et al.* have suggested the possibility of tube-based medical treatment that can be utilized as a sustainable therapeutic material delivery platform[325] (Figure 14c). Conventional clinical regenerative therapy of a diseased heart has been hindered by poor retention and rapid collapsing of the therapeutic agent *in vivo*. Also, controlling the multiple doses of therapeutic agents is practically challenging. To solve this issue, a polymer-based reservoir connected to a medical tube was utilized as a functional therapeutic material delivery platform. The polymer-based reservoir was first mounted on the diseased cardiac tissues. To solve this issue, a polymer-based reservoir connected to a medical tube (*i.e.*, refill line) was utilized as a functional therapeutic material delivery platform. The polymer-based reservoir, which contains the therapeutic agent (*i.e.*, the cellular paracrine factors and the drug), was mounted on the diseased cardiac tissues. The interface between the reservoir and the diseased heart tissue consisted of a semipermeable membrane that facilitated the diffusion of the therapeutic agent. The reservoir can be filled with the therapeutic agent without leakage through the refill line connected to the outside body. This sustainable delivery platform enables the accurate and controllable delivery of therapeutic materials on the damaged tissues and demonstrated its medical usefulness with an animal study.

Optogenetics has been demonstrated of being able to control the function of brain and nerve system, and it has recently been spotlighted due to its promising applicability for several neuron-related diseases.[390,391] Anikeeva *et al.* reported a fiber-based one-step optogenetics system that can be implanted in a human body by minimally invasive insertion[392] (Figure 14d). This fiber-based multifunctional optogenetics system is composed of an optical waveguide with six electrodes and two microfluidic channels. This modality was implemented in hopes to replace the conventional optogenetics, which entails multiple steps, including injection of opsin and implantation of an optical waveguide. On the other hand, the combined implementation of a microfluidic channel, optical waveguide, and electrodes in the fiber-based system enabled the injection of opsin, optical stimulation, and recording of neural activity in a single step. This one-step, multifunctional operation system demonstrated the possibility of easy and cost-effective implementation of optogenetics.

One thing to consider when implementing an implantable device is the fact that each organism has different body size and shape. Therefore, for the precise and effective medical treatment, implantable device should be customized. In this regard, Jeong *et al.* reported a 3D printing-based customizable, scalable implantable optogenetic probe.[393] The probe can be fabricated with different lengths corresponding to the size of mammalian brains; therefore, precise implantation can be realized.

For the insertion of implantable devices in tough medium such as skin, both sharpness and rigidity are required. However, the rigidity of implantable device may cause inflammation in tissue and organs *in vivo*. Recently, transformable electronics was introduced as an innovative concept of implantable device insertion strategy[368] (Figure 14e). The authors demonstrated transformable electronics based on the phase changing properties of gallium. Gallium is a well-known metal for its low melting temperature (29.76 °C), which is below the normal temperature of the human body (37 °C). Due to its specific melting temperature, gallium embedded substrate is soft in or on the human body but rigid outside of the body. The authors successfully demonstrated the injection and implantation of transformable electronics in mouse. First, the rigid-phase electronics were injected into the mouse brain. After injection, the substrate became soft, which matched the mechanical properties of brain tissues *in vivo*. Therefore, the inflammation response significantly diminished.

Mounting Strategies for Implantable Devices. For clinical use of implantable devices, it is important to mount the implantable devices strongly on the targeted tissues or organs. However, since the surfaces of tissues or organs are in a wet environment surrounded by biological fluids, it is challenging to achieve strong and stable adhesion of implantable devices. Conventionally, mechanical joints such as a helix or corkscrew are used for firm fixation of implantable devices on the organ.[366] However, due to the invasive nature of this procedure and the mechanical mismatch between the joint and the organ, wound and inflammation on the organ typically occur.[366,394,395] Furthermore, severe fibrosis of the muscular layer will cover the implantable device, which may cause a malfunction of the device or render the implantable device difficult to remove.[396]

As an alternative strategy, a hydrogel-based substrate can be an ideal adhesive layer for implantable device mounting due to its ultrasoftness and abundant functional groups on its surface. Mooney *et al.* reported a strategy to enhance the adhesion of hydrogel adhesive (interfacial toughness $>10^2$ J m^{-2}) on a variety of wet surfaces, including the surface of organs[66] (Figure 14f). Furthermore, the utility of their substrate for medical applications was verified by organ surface adhesion in the presence of blood. Enhancement of the interfacial toughness is based on the synergy of strong chemical bond formation and energy dissipation within the hydrogel adhesive. Specifically, the adhesive should be positively charged in order to form a strong bond with the cells/tissues

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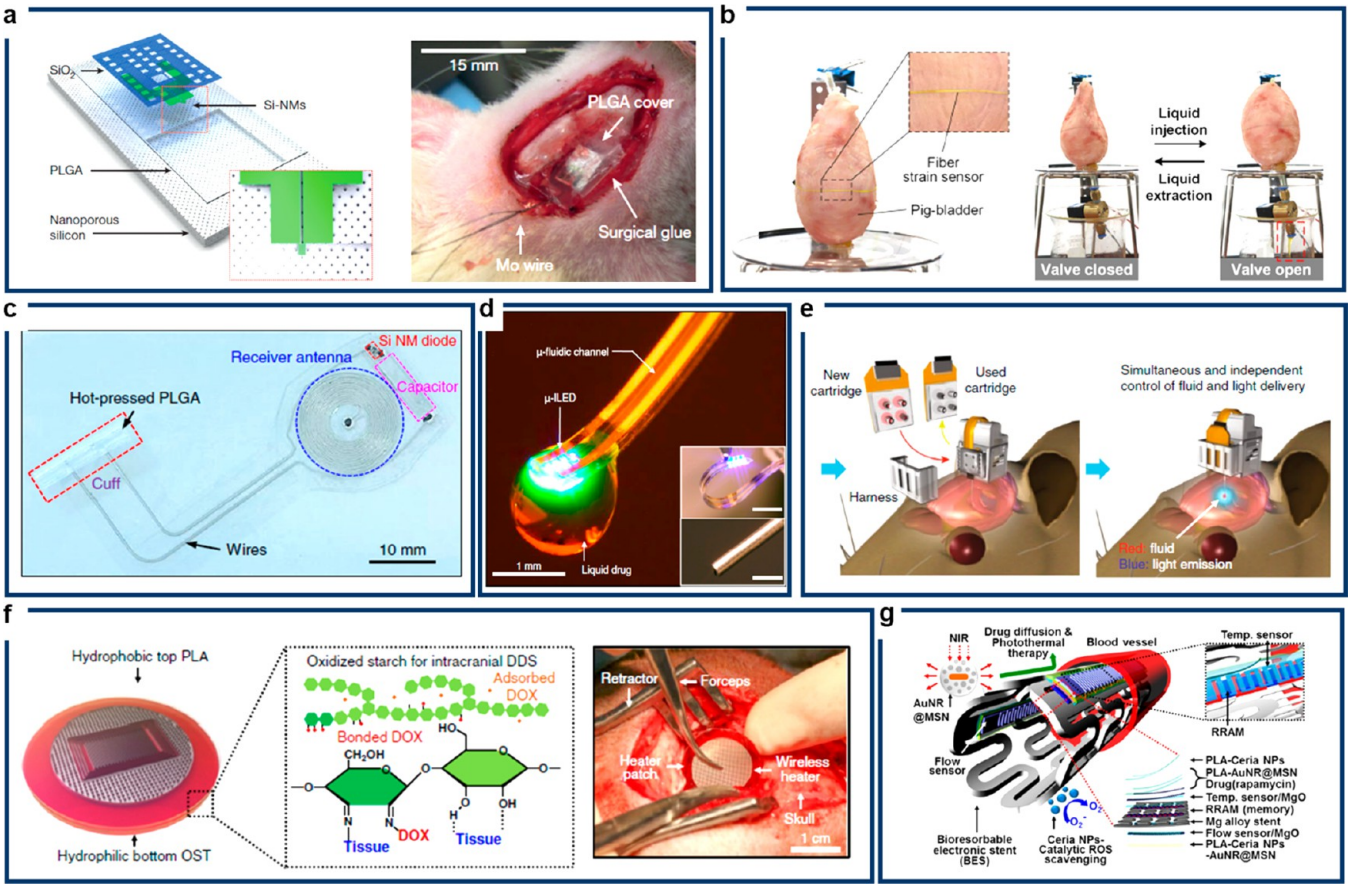

Figure 15. Implantable devices with special functionalities. (a) Schematic illustration and photograph of a biodegradable brain pressure sensor. Reproduced with permission from ref 63. Copyright 2016 Nature Publishing Group. (b) Photograph of a fiber-based ultrastretchable strain sensor for bladder volume monitoring. Reproduced from ref 400. Copyright 2018 American Chemical Society. (c) Photograph of an implantable biodegradable electrical stimulator. Reproduced with permission from ref 64. Copyright 2018 Nature Publishing Group. (d) Photograph of an optofluidic device capable of drug delivery and photostimulation. Reproduced with permission from ref 62. Copyright 2015 Cell Press. (e) Schematic illustration of a refillable, smartphone-based controllable optofluidic device. Reproduced with permission from ref 389 Copyright 2019 Nature Publishing Group. (f) Schematic illustration and photograph of a biodegradable drug delivery device for brain tumor. Reproduced with permission from ref 69. Copyright 2019 Nature Publishing Group. (g) Schematic illustration of a biodegradable multifunctional stent. Reproduced from ref 70. Copyright 2015 American Chemical Society.

that are negatively charged. Also, the hydrogel at and near the interface should consist of components that can dissipate the mechanical energy under stress. In this regard, a hydrogel composed of a combination of bridging polymer and energy dissipative matrix has superior adhesive toughness on wet surfaces compared to that of the conventional hydrogel. Furthermore, this mechanism can be adapted with a variety of materials such as chitosan, polyallylamine, polyethylenimine, collagen, and gelatin as the bridging polymer, which allow property tuning according to the targeted applications.

Adhesion techniques mentioned above is diffusion-based, which is intrinsically slow in forming the adhesion as the molecules take a considerable amount of time to form chemical bonds. To address this matter, Zhao *et al.* reported a double-sided dry tape that can form strong adhesives on various wet surfaces within 5 s with gentle pressure (less than 1 kPa)[67] (Figure 14g). This double-sided dry tape is composed of biopolymer such as gelatin or chitosan combined with a cross-linked polymer that contains carboxylic acid groups (cross-linked poly(acrylic acid) grafted with *N*-hydroxysuccinimide ester). The dehydrated hydrogel chain and negatively charged carboxyl acid groups in the tape accelerates the absorption of interfacial water between human organ and the tape, which subsequently leads to the swelling of the tape. Meanwhile, the carboxylic acid groups also form intermolecular bonds that can further enhance the adhesion.

Materials other than hydrogels can also form a tight adhesion to the surface of organs. Kim *et al.* reported an ambivalent surface chemistry patch where one side was made hydrophilic for conformal adhesion to organ surfaces while the other side was made hydrophobic to suppress drug leakage.[69] In this patch, oxidized starch was used as the adhesive due to its hydrophilicity, biocompatibility, and biodegradability. By increasing the portion of oxidized starch, adhesion between the patch and tissue was enhanced, which was verified by measuring shear stress applied on the attached patch. The authors successfully demonstrated the implantation of their device on an animal brain for *in vivo* drug delivery.

Other than the mounting of implantable devices on organ surfaces, fixing devices on nerve tissues in a safe and reliable way has been studied due to the importance of neuromodulation. Neuromodulation has been considered as a promising therapy for neurological disorders such as Parkinson's disease, pelvic disorders, and ischemic disorders. For neuromodulation, the device should be fixed on the targeted nerve tissue, which is in the form of a thin and soft

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fiber-like structure. Conventionally, a cylindrical cuff electrode has been utilized for wrapping the nerve tissue; however, its rigid and physically fixed structure can induce damage and inflammation. Furthermore, the closing mechanism for fixation, such as suturing or gluing, induces mechanical stress during implantation, which further causes a serious impairment on the tissue. To properly cope with these matters, researchers have engaged in developing neuromodulation devices with soft and functional materials. For instance, Zhang *et al.* introduced a soft optical neuromodulation device that can be implanted on a targeted nerve tissue (contralateral seventh cervical nerve) by self-wrapping without additional surgical process[397] (Figure 14h). Here, a polyurethane fiber, a well-known biocompatible shape memory polymer, was utilized as the backbone of the device. By memorizing the spiral form as an original structure, this neuromodulation device can be fixed on the nerve tissue by wrapping without any additional closing process. Multiple mini-LEDs were integrated on this shape memory polymer-based backbone substrate for optogenetic stimulation, where precise multisite optical stimulation without notable side effects was demonstrated. Successful controlling of a mouse's limb muscles demonstrated its applicability in neuroscience and translational medicine research.

Recently, the aforementioned self-healing mechanism was utilized in a cuff electrode for minimal induction of mechanical stress. Son *et al.* reported an adaptive, soft self-healing electronic epineurium for neural interfaces, which does not need to be sutured or glued for implantation[398] (Figure 14i). Tough and water insensitive self-healing polymer, which consists of PDMS, 4,4′-methylenebis(phenyl urea), and isophorone bisurea units, was utilized as a substrate and encapsulation layer. For the electrode demonstration, a Ag flake was mixed with this polymer to make a conductive composite. Unfortunately, Ag ions that leak into the *in vivo* environment from the composite may cause serious side effects. To minimize this unwanted situation, a biocompatible Au nanomembrane was coated on the Ag flake polymer composite. The validity of this strategy has been verified by confirming that only a small amount (17.03 ppm) of Ag ions have been leaked over a 32 week experiment. Using this electronic epineurium, bidirectional neural signal recording, and stimulation in an animal study was successfully demonstrated.

In summary, conventionally cumbersome and risky implantation methods can be replaced by recently developed injection and mounting strategies. These simple and *in vivo* compatible methods are expected to provide alternative approaches for next-generation medical treatment based on the soft implantable devices.

Implantable Devices with Special Functionalities. The capability of the implantable device to perform a specific function for medical treatment has become vitally important in recent decades. Herein, we discuss the advancement of implantable devices with various functions that can be utilized in clinical treatment in the future.

Tactile sensing has been regarded as an important function of implantable devices for rapid and accurate monitoring of physiological signals; thereby enabling diagnosis and treatment of certain diseases. For instance, accurate diagnosis of traumatic brain injury (TBI) requires monitoring of intracranial pressure (ICP). Conventional skull surgery requires mounting and subsequent removal of bulky and rigid pressure sensors in the human brain. However, due to the risk of skull surgery and high cost of the intensive care unit (ICU), many suspected patients hesitate to receive this monitoring treatment. In order to tackle this issue, Rogers *et al.* developed a biodegradable pressure sensor that can monitor the ICP for the diagnosis of TBI[63] (Figure 15a). This pressure sensor consists of biodegradable and biocompatible components, such as Si NM, Mg, and PLGA. Specifically, a nanoporous silicon structure with a trench has been utilized as the substrate to support the entire device. The PLGA film suspended on the trench can be deformed in response to pressure. The Si NM cantilever attached on the PLGA film acts as a piezoresistive pressure sensor. This ICP sensor shows comparable sensing performance to the commercialized ICP monitoring medical device. More importantly, it can be completely biodegraded *in vivo* through human metabolism after its medical use. Therefore, burdensome secondary surgery for removing the used medical implantable device is omitted. Furthermore, the authors demonstrated the feasibility of wireless monitoring of ICP by integrating this sensor with a remote signal transmitting unit.

Malfunction of the neurogenic lower urinary tract deterioration may cause renal failure, posing a significant threat to patients.[399] Continuous monitoring of bladder volume is necessary to prevent the further expansion of patients' bladder beyond its capacity. This requires strain sensors with a large sensing range, stretchability, conformability, and strong adhesive property, as the bladder undergoes significant lateral expansion and has a 3D curvilinear surface. To address this issue, Lee *et al.* introduced a highly stretchable multifilament fiber-based sensor[400] (Figure 15b). Multifilament fiber percolated with metal nanoparticles provided a large strain sensing range beyond its theoretical value. Additionally, the 1D geometry of this sensor made it possible to be wrapped around the 3D curvilinear surface with a conformal contact. Though wired operation and use of nonbiocompatible materials may hinder its medical applications, this sensing principle can be applied to the future development of implantable devices.

Implementing medical treatment functionalities has been considered as an essential factor of implantable devices. Electrical current, heat, and light which were exploited as promising candidates of medical therapies can be delivered to the targeted organ *via* implanted electrical devices.[56,64,401] For instance, electrical stimulation of the injured nerve tissues demonstrated its utility for enhancing and accelerating damaged nerve recovery.[57] Despite the advantages of this approach, the necessity of frequent surgical procedures hindered its clinical use. To address this issue, Rogers *et al.* introduced a wireless biodegradable electrical stimulator for nerve regeneration[64] (Figure 15c). The antenna and the electrode were made of Mg, and the capacitor was made of Mg and SiO_2. A diode composed of Si NM is integrated with the other electrical components for rectifying the current for electrical stimulation. After implanting this biodegradable wireless stimulator into a living mouse, electrical stimuli were transmitted to the damaged nerves, which subsequently accelerated the nerve regeneration. Since this wireless electrical stimulator was only composed of biodegradable components, it can be dissolved by hydrolysis reaction *in vivo* after the medical treatment and the byproducts can be removed through metabolism.

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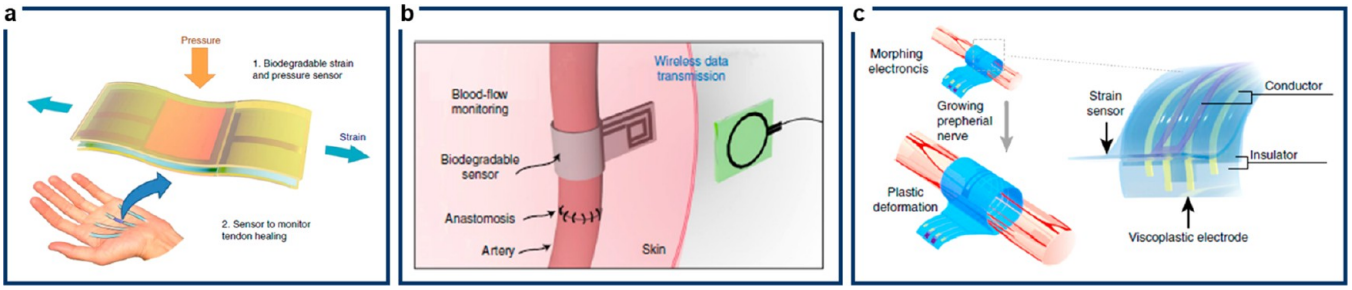

Figure 16. Functional material-based implantable devices for effective postoperation monitoring and treatment. (a) Schematic illustration of a biodegradable tactile sensor for rehabilitation monitoring of pressure and strain after orthopedic surgery. Reproduced with permission from ref 71. Copyright 2018 Nature Publishing Group. (b) Schematic illustration of a biodegradable wireless pressure sensor for monitoring blood pressure after blood vessel reconstruction surgery. Reproduced with permission from ref 68. Copyright 2019 Nature Publishing Group. (c) Schematic illustration of morphing electronics for continuous neuromodulation capable of adapting to the growth of peripheral nerve. Reproduced with permission from ref 73. Copyright 2020 Nature Publishing Group.

Direct delivery of drugs to the targeted tissue or organ plays a pivotal role in patient-friendly treatment.[402] Since drugs injected into a human body may not be delivered to the targeted spot, side effects may occur. In this regard, implantable electronics have been considered as promising candidates for targeted drug delivery *in vivo* due to their programmable and reliable drug-releasing capability that can be activated by remote control. Rogers *et al.* reported a microfluidic drug delivery platform that can be controlled *via* wireless power transmission[62] (Figure 15d). This device consisted of a microfluidic channel and reservoir for drug releasing, a micro-LED, and wireless power receiving unit. Electrical energy transferred by inductive coupling was converted to thermal energy *via* joule heating of the resistors. Thermally actuating polymer under the reservoir absorbs this thermal energy and undergoes thermal expansion, thereby pushing the bottom of the reservoir to release the stored drug. The multichannel of this microfluidic system enables the injection of different drugs in a minimally invasive manner. Furthermore, the integrated micro-LED enabled optogenetic application by combining the photostimulation functionality into the drug-delivery platform. Recently, Jeong *et al.* reported a further improved version of this device as a follow-up study[389] (Figure 15e). Their device adopted a reusable cartridge and a smartphone-based control system, which renders it more suitable for patient-friendly treatment at medical resource-limited settings.

Delivering the anticancer agent near the surgical area has been considered as a promising medical treatment method for eliminating brain tumors. Unfortunately, delicate and reliable delivery of drug has been impractical due to the lack of programmed delivery tools. Kim *et al.* demonstrated a biodegradable patch that could deliver drugs to the brain tumor accurately through wireless activation[69] (Figure 15f). In order to firmly mount the device on the intended spot of the brain, the researchers employed oxidized starch as the interfacial adhesive agent. Furthermore, in order to prevent drug leakage, the opposite side of the patch was modified with hydrophobic poly(lactic acid). A passive component-based antenna integrated into the patch allowed electrical energy transfer *via* wireless inductive coupling and this electrical energy was transformed into thermal energy by joule heating. Subsequently, this activated drug release from the reservoir to the brain tissue. After drug delivery, all of the components can be eliminated through the *in vivo* metabolism.

Passive component-based electrical devices composed of biodegradable materials can be used to make conventional medical instruments, through which desired functionalities can be imparted. Stents enable the opening of clogged anatomic duct such as blood vessel and ureter; therefore, it has been clinically utilized for peripheral diseases, cerebrovascular stenosis, and urethral stricture.[403,404] Unfortunately, a conventional stent has side effects over long-term use, such as neointimal hyperplasia, and accumulation of muscle cell near the stent implanted site. To overcome these drawbacks, Kim *et al.* introduced a biodegradable stent that can be eliminated through metabolism in human body after its medical use, therefore circumventing the potential side effects of long-term stent use[70] (Figure 15g). Furthermore, flow and temperature sensing, data storage, and wireless power transfer were utilized by integrating the biodegradable electric components into the stent.

Implantable Devices for Postoperation Monitoring and Treatment. After surgery, it may be necessary to continuously monitor the state of health of the patient so that side effects can be prevented and recovery can be ensured.[405] In this sense, implantable devices that are used for postoperation health monitoring can be effective for injury prevention. However, some long-term implantation of conventional medical devices can cause side effects, and additional removal surgery is generally necessary. In this sense, by utilizing biodegradable materials, this additional burdensome surgery can be omitted.

After the orthopedic surgery, the application of mechanical stimuli on the surgical region may cause further injury; therefore, continuous monitoring of pressure and strain is helpful for preventing relapse.[61] Since implanting multiple devices in the body is a burden to the patient, it is practical for a single implantable device to detect multiple stimuli such as pressure and strain. As presented in Figure 16a, soft and stretchable biodegradable materials such as PGS and POMaC were utilized as a multifunctional tactile sensor.[71] By laminating the pressure and strain sensors vertically on top of each other, vertical and longitudinal strain applied on the sensor can be monitored simultaneously. Lastly, since all components of this device are biodegradable, additional surgery for removing the implantable device can be negated. However, practical use of this implantable device as an implantable monitoring sensor is limited due to the wire-based operation of the monitoring system. In order to broaden the application of implantable devices, it is necessary to produce a

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wireless monitoring system in the future. In this regard, the same authors also reported a biodegradable wireless pressure sensing system for monitoring blood pressure after blood vessel reconstruction surgery[68] (Figure 16b).

There are some diseases that need to be managed for life, such as seizures. However, long-term implantation of a fixed structure (*i.e.*, implantable devices) can cause complications because they do not mechanically match with the dynamic motion or adapt to the growth of the body. Therefore, multiple surgeries are generally required after the first implantation. As a potential solution, Bao *et al.* introduced "morphing electronics" that is able to adapt to different morphologies according to the surrounding tissue growth. This device demonstrated the capability to stimulate and modulate the nervous system for treating neurological diseases over a relatively long period without additional surgeries[73] (Figure 16c). Morphing was realized by utilizing a composite of viscoplastic conductive and self-healable viscoplastic insulating polymer. The viscoplastic conductive polymer was composed of PEDOT:PSS and glycerol, and the insulating polymer was composed of a PDMS-based self-healable elastomer. Specifically, the self-healable elastomer consisted of isophorone bisurea units and PDMS that had weak dynamic bonding between them, which enabled the fast and stress-free adaptation in accordance with the change in the surrounding tissues.[370]

CHALLENGES AND FUTURE PERSPECTIVES OF PATIENT-FRIENDLY IMPLANTABLE DEVICES

Now, more than ever, researchers are focusing on developing implantable devices for effective medical treatment. Discoveries and developments of functional materials have led to the development of implantable devices with promising and exciting functionalities. In particular, the implementation of biodegradable materials, self-healing materials, and tough adhesive hydrogels have led to significant advancement of implantable devices. However, there are remaining challenges that need to be solved to further progress these implantable devices toward clinical applications. For instance, since even a small skin perforation can cause infection and inflammation, wireless communication for perforation-free operation should be implemented into implantable devices.[406] To implement wireless operation capability into implantable devices, it is necessary to develop soft, stretchable, and highly conductive materials that can effectively react with EM waves at relatively high frequencies (>10 MHz). For biodegradable implantable devices, programmable and controllable degradation strategies should be implemented, rather than passive degradation after insertion. Furthermore, for actual clinical use, implantable devices need to satisfy the regulatory guidelines set by the government. Many implantable devices are classified as Class III devices by the FDA, which are typically utilized as life-supporting, life-sustaining, or treating impairment of human health, such as drug delivery platforms or stents. For the commercialization of Class III devices, premarket approval by the FDA and ensuring the device's safety and efficacy are needed.[407] In this vein, long-term reliability and safety must be extensively studied prior to their clinical use. Also, device to device uniformity and reproducibility of functionality should be carefully examined. For instance, in RF ablation, a small difference in the resistance of the heating components may cause serious damage to tissues and organs due to excessive temperature increases. Currently, standardization to test long-term reliability, safety, and tolerable range of uniformity and reproducibility of different devices has not yet been set due to the necessity of different standards for a wide variety of devices and their related treatments, and due to the insufficient amount of animal and clinical testing. Recently developed devices, in particular, require extensive animal and clinical testing in order for them to pass regulatory restrictions.

Implantable devices require active collaboration between scientists, engineers, and medical doctors to determine which diseases are most suitable for treatment by implantable devices and how to best treat the diseases. For instance, guidelines for tuning the operation of devices to maximize the efficacy of treatment while minimizing the side effects require expertise from various disciplines. We expect that more advanced treatment strategies and ideas combined with the improvement in implantable devices will bring forth a revolution in medical treatment.

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Notes

The authors declare no competing financial interest.

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VOCABULARY

Point-of-care-testing (POCT): Simple medical testing near-patient using portable or wearable biosensors, which allow patients to self-test without visiting health care facilities; **Noninvasive diagnosis**: A diagnosis procedure which does not induce pain of patients; **Molecularly imprinted polymers (MIPs)**: A polymer that has been processed using the molecular imprinting techniques to obtain antibody mimicking bioreceptors, which has specific cavities in the polymer matric with an affinity for bio analytes; **Förster resonance energy transfer (FRET)**: FRET is the nonradiative transmission of energy from a donor molecule to an adjacent acceptor molecule; **Translational medicine**: An interdisciplinary approach to discover different types of diagnostic tools and medical treatment strategies; **Minimally invasive surgery**: A surgical technique that is only using a limited small size of incisions during operation; **Optogenetics**: A biological technique that uses light to modulate local neuron activities. For optogenetics, targeted neurons should be genetically modified to express light-sensitive ion channels

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