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PERSPECTIVE

Emerging Telemedicine Tools for Remote COVID-19 Diagnosis, Monitoring, and Management

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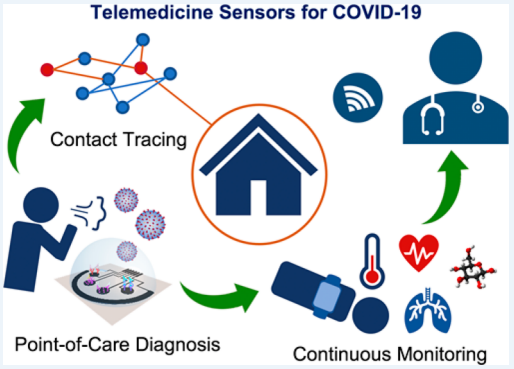
ABSTRACT: **The management of the COVID-19 pandemic has relied on cautious contact tracing, quarantine, and sterilization protocols while we await a vaccine to be made widely available. Telemedicine or mobile health (mHealth) is well-positioned during this time to reduce potential disease spread and prevent overloading of the healthcare system through at-home COVID-19 screening, diagnosis, and monitoring. With the rise of mass-fabricated electronics for wearable and portable sensors, emerging telemedicine tools have been developed to address shortcomings in COVID-19 diagnostics, monitoring, and management. In this Perspective, we summarize current implementations of mHealth sensors for COVID-19, highlight recent technological advances, and provide an overview on how these tools may be utilized to better control the COVID-19 pandemic.**



The COVID-19 pandemic has defined 2020, spreading globally to over 65 million cases in early December, with over 20% occurring in the United States (U.S.).[1] Initial efforts to mitigate the spread involved state-mandated "stay at home" orders and travel restrictions, which seemed to slow the spread temporarily but also severely impacted the global economy and disrupted daily life. However, upon reopening, even when daily cases have been dramatically reduced as in France and Spain, countries are seeing a resurgence with higher incidence rates than the initial peak in April.[1] Governments are struggling to limit the community spread of the disease while also attempting to limit the economic fallout. Without available vaccines, the U.S. gross domestic product (GDP) may suffer losses estimated upward of $45.3 billion during the pandemic.[2] While simple measures of social distancing, face coverings, and increased access to testing have been implemented to seek a return to normal daily activities, there is a clear and present need for innovative tools to intercept the spread of COVID-19, increase the efficiency and quality of care, and alleviate pressures on the global healthcare system.

Telemedicine is well-positioned to address these needs through at-home COVID-19 screening, diagnosis, and monitoring. Telemedicine has already been instituted by many U.S. health systems to see patients at home and limit the possible spread of COVID-19, since many cases have been observed to originate in hospital.[3−5] A major barrier to leveraging telemedicine for COVID-19 is the coordination of testing.[3] Not only are current testing strategies a resource intensive process, but they also cannot keep up with the demand for testing with significant delays in results, which may result in further delays in medical treatment. Once diagnosed, telemedicine treatment is the best strategy to prevent the inundation of hospitals with COVID-19 patients while also allowing patients to recover in the comfort of their own home. However, utilization of continuous monitoring tools at home is necessary for informed medical decisions such as when the patient should report to the hospital. By monitoring for biomarkers associated with COVID-19 prognosis using telemedicine sensors in home and community-based settings, early medical intervention steps and more aggressive treatment plans may prevent patient degradation and death.

In this Perspective, we aim to provide a summary of telemedicine-based tools for COVID-19 diagnosis, symptom monitoring, prognosis, and risk prevention. We highlight current rapid and remote diagnostics, wearables for symptom

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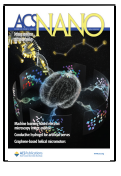

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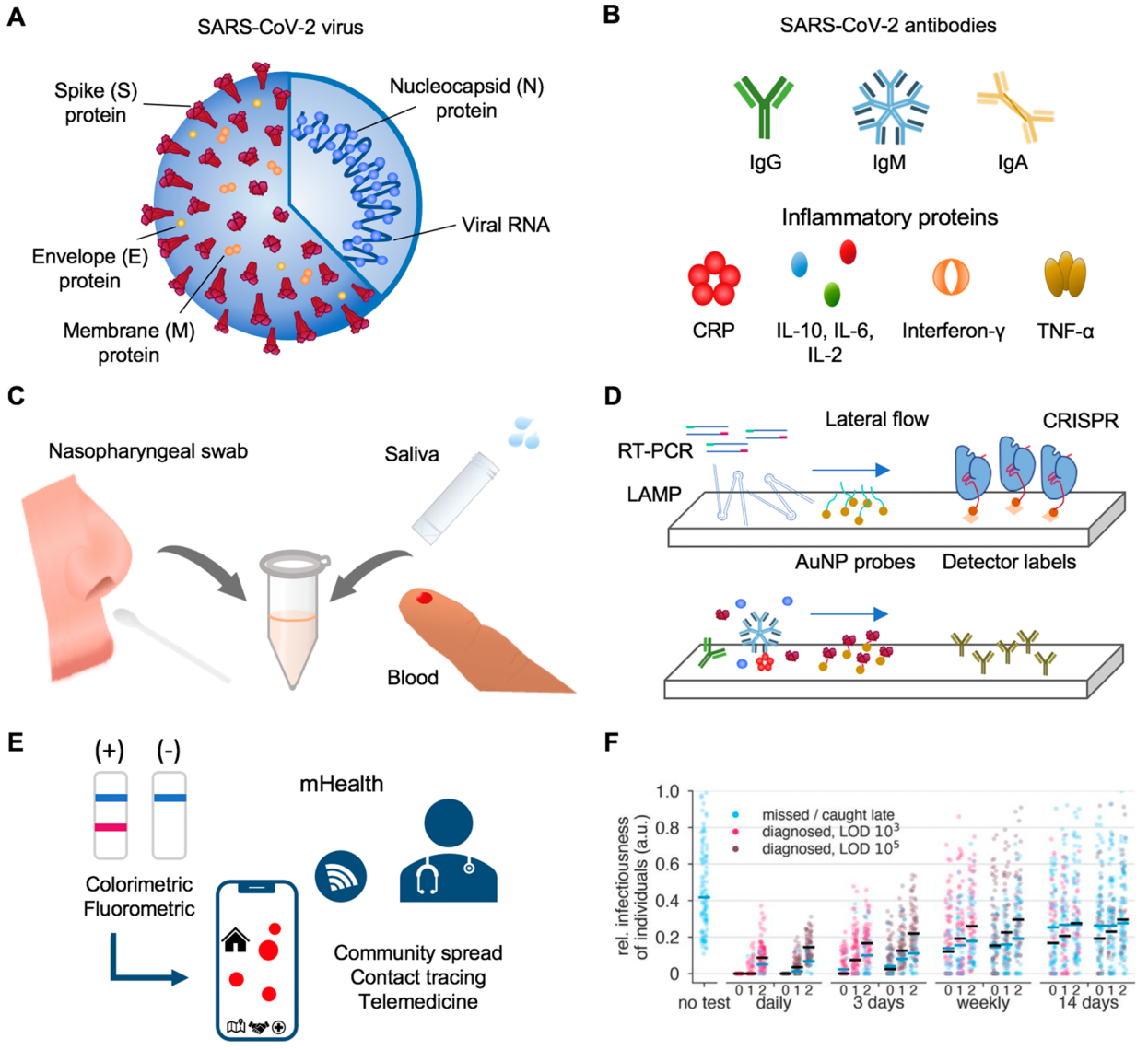

Figure 1. COVID-19 diagnosis through rapid and point-of-care biomarker detection. (A) SARS-CoV-2 viral products including antigens and RNA. (B) Antibodies and inflammatory proteins produced from the body's immune response to the SARS-CoV-2 virus. (C) Detection of COVID-19 biomarkers in nasopharyngeal swabs, saliva, and blood. (D) Lateral flow assays (LFAs) for the rapid detection of COVID-19 biomarkers. For RNA detection (top), amplified RNA through either real-time reverse transcriptase polymerase chain reaction or loop-mediated isothermal amplification is added and binds to AuNP conjugated complementary probes or CRISPR-based enzymes for colorimetric or fluorometric detection. For antibody and antigen detection (bottom), AuNP conjugated antibodies and antigens tag the associated target in solution and are then detected by the immobilized detector antibodies. (E) Results from LFAs can be captured by a portable user interface. The mHealth platforms may then facilitate case reporting, community spread mapping, contact tracing, and telemedicine treatment. (F) COVID-19 surveillance is most effective under daily testing with test sensitivity being secondary to test turnaround time in importance. Reproduced with permission from ref 41. Copyright 2020 Larremore *et al.*

monitoring, and mobile platforms for tracking community spread. We also present novel electrochemical platforms developed for biomarker sensing for rapid diagnostics, risk assessment, and on-body monitoring at home.

TELEMEDICINE-BASED COVID-19 DIAGNOSTICS

As communities seek a return to normalcy during the continued spread of COVID-19, greater emphasis has been placed on widespread access to testing, with the idea that those who become infected and exposed isolate, while others continue safe social practices. However, effectively implementing this public health strategy has proven difficult with significant backlogs in testing. The gold standard for diagnosing COVID-19 has been real-time reverse transcriptase polymerase chain reaction (RT-PCR) for the detection of SARS-CoV-2 viral nucleic acid. RT-PCR is a slow process that takes on average 2−3 h to generate results.[6] It requires expensive equipment and trained technicians, such that tests may not be able to be performed on-site.[6] RT-PCR is also known to produce false negatives, which may limit containment strategies and access to treatment. One study reported a 70% positive rate for nasal swab samples from suspected COVID-19 patients.[7] While lung computed tomography (CT) scans have been suggested as a more accurate diagnostic tool for patients with COVID-19 symptoms, it is less practical to implement and may not be specific to COVID-19.[8]

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Beyond the need for improving the accuracy of COVID-19 diagnostic tools, there is a need to make these tools compatible with point-of-care (POC) and at-home use. In public spaces, there is a need for COVID-19 screening tools. At the hospital, there is a need for patient severity information for effective triage and resource allocation. At home, there is a need for quarantined individuals to test for COVID-19 before re-entering society, and in the case of a positive test, to monitor their symptoms *via* telemedicine to reduce the strain on hospital resources. Designing these diagnostic tools requires careful selection of target COVID-19 biomarkers, sample specimens, detection mechanisms, and mHealth integration.

Biomarkers for COVID-19 Diagnosis. SARS-CoV-2 is a genus β-coronavirus, like SARS-CoV and MERS-CoV, with a crown-like, enveloped, positive-strand ribonucleic acid (RNA) (Figure 1A). The single-stranded RNA is packaged into a helical structure defined by the nucleocapsid (N) protein.[9] The viral envelope is decorated with membrane (M) proteins, envelope (E) proteins, and spike (S) proteins. While M and E proteins play more structural roles, the protruding outer S protein is involved in binding to host cell angiotensin-converting enzyme 2 receptors to facilitate viral entry.[9] Each part of the SARS-CoV-2 virus can be detected for active infection diagnosis. Previous research on SARS-CoV found that viral antigen concentrations are in agreement with RT-PCR patterns.[10] One of the greatest challenges with viral particle detection is the molecular sensitivity. A variety of RNA amplification methods, including RT-PCR, loop-mediated isothermal amplification (LAMP), and recombinase polymerase amplification (RPA), have been developed to improve RNA detection. For antigen testing, ultrasensitive immunoassays are necessary. The N protein is the most favorable for antigen detection since it is the most abundant viral protein,[11] yet it requires lysing of the virus and is similar to other coronaviruses, including being 90% identical in proteomic structure to that of SARS-CoV, potentially leading to reduced assay selectivity.[12−14]

One can also potentially diagnose COVID-19 based on the physiochemical response to infection (Figure 1B). Anti-SARS-CoV-2 antibodies provide information regarding the immune response. Antibodies appear later into the infection, as early as 4 days after symptom onset,[15] with immunoglobulin M (IgM) peaking around 12 days after symptom onset and seroconversion to immunoglobulin G (IgG) around 20 days after symptom onset.[11,16−18] Because of variable antibody concentrations, simultaneous detection of IgM, IgG, and immunoglobulin A (IgA) antibodies may improve assay performance.[19] Although antibodies are not optimal for early diagnosis and detection, they may provide important temporal information on the infection course. Also, antibody testing may provide information regarding acquired immunity and community seroprevalence. In addition to the immune response, COVID-19 is known to cause a dysregulated inflammatory response, known as the "cytokine storm". Inflammatory cytokine levels may serve as important biomarkers for symptom severity and prognosis. Increased levels of C-reactive protein (CRP) have been found to correlate with lung lesions and disease severity.[20−24] Upregulation of interleukin (IL)-6 and IL-2 at late stages of infection is well correlated to fatality.[25] Other cytokines, chemokines, and growth factors, such as interferon-γ, tumor necrosis factor alpha (TNF-α), and transforming growth factor-beta-induced protein K676Ac, have been found to be highly reliable, independent severity diagnostic biomarkers.[26−28] These symptomatic markers have been looked at as potential therapeutic targets in addition to diagnostic targets.[25,28]

Biofluids containing these markers may contain active virus, therefore at-home sample collection is desirable. Nasopharyngeal swabs have been the standard collection technique for accessing viral samples of the respiratory infection. To reduce the possibility of false negatives, high efficiency swabs have been engineered using functionalized microneedles.[29] However, this sample collection method requires assistance by a healthcare professional, placing a strain on medical and personal protective equipment (PPE) resources. In addition to nasopharyngeal swabs, COVID-19 biomarkers have been detected in blood and saliva (Figure 1C).[30−32] Both blood and saliva provide alternative specimens for self-collection.

Lateral Flow Assays for POC Detection. Lateral flow assays (LFAs) have become a standard for commercial rapid, POC testing. LFAs are typically built on nitrocellulose membranes with a sample pad, a conjugate pad, and absorption pad and operate based on a wicking-directed flow of sample fluid over the binding and testing regions of the assay (Figure 1D). LFAs can be used for detection of amplified nucleic acids, antigens, and antibodies based on specific gold nanoparticle (AuNP) conjugated probes. Upon flow, they may bind to immobilized probes at the detection strip causing aggregation of AuNPs and a color change at the test line.[6,33,34] Nucleic acid LFAs may also use immobilized CRISPR-based enzymes, which cleave a reporter-quencher pair upon binding of the target nucleic acid sequence, producing a fluorometric signal at the test line.[35] A variety of LFAs are now commercially available, including the Abbot ID Now and the Cepheid Xpert Xpress for rapid molecular testing.[36]

Advances have been made based on the lateral flow design. A portable multiplexed microfluidic-based platform has been developed to provide rapid detection of IgG, IgM, and SARS-CoV-2 antigens simultaneously *via* fluorescent detection.[37] By testing for both antibodies and antigens, one can simultaneously identify infected and convalescent individuals. The Sikes group has designed and validated methods for developing lateral flow antigen assays using binding protein scaffolds based on the reduced charge Sso7d variant (rcSso7d) rather than capture antibodies. rcSso7d-based assays have similar limits of detection as antibody-based assays and even improve sensitivity when a larger sample volume is applied.[38] Their methodology allows for high-density adsorption to unmodified cellulose within 30 s.[39] Using binding protein scaffolds for paper-based immunoassays have many benefits including inexpensive and simple manufacturing methods. 3M is now collaborating with the Sikes lab to develop a rapid, inexpensive lateral flow antigen test based on these methods.[40]

LFAs provide immediate POC results that may be easily interpreted through qualitative colorimetric or fluorometric readouts (Figure 1E). It is recommended that lateral flow assays use validated automated readings for reliable LFA deployment.[18] If readings are recorded electronically, the data can then be easily sent to an mHealth platform for community spread tracking, immediate contact tracing, and personal symptom monitoring and treatment *via* telemedicine. Viral transmission models demonstrate that frequency of testing and short sample-to-answer time should be prioritized in testing and surveillance (Figure 1F).[41] These factors prove to be even more important than test sensitivity in controlling disease

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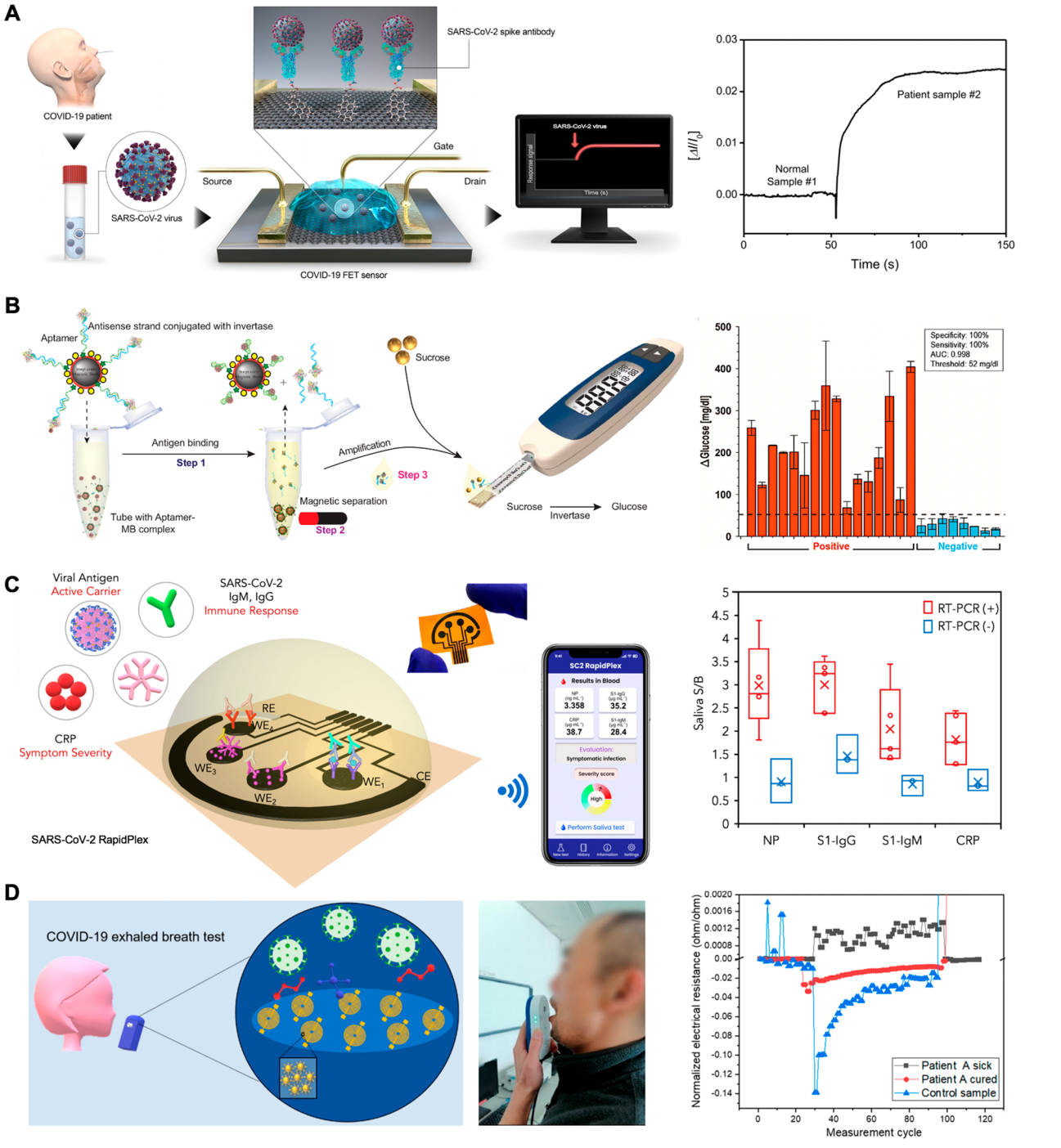

Figure 2. Nanoengineered electrochemical sensors for POC COVID-19 diagnosis. (A) Ultrasensitive and rapid detection of the SARS-CoV-2 antigen using a field-effect transistor-based biosensor. Reproduced with permission from ref 43. Copyright 2020 ACS. (B) Point-of-care aptamer-based detection of SARS-CoV-2 antigen in saliva using invertase for signal amplification *via* a commercial glucometer. Reproduced with permission from ref 44. Copyright 2020 Singh *et al.* (C) Rapid multiplexed detection of SARS-CoV-2 antigen, antibodies, and C-reactive protein using a laser-engraved graphene-based immunosensor with demonstrated use in saliva. Reproduced with permission from ref 32. Copyright 2020 Elsevier. (D) A COVID-19 breath test that uses an array of nanomaterial-based hybrid sensors for exhaled breath analysis toward machine learning assisted COVID-19 diagnosis. Reproduced with permission from ref 48. Copyright 2020 ACS.

spread. These results demonstrate the importance that rapid POC tests like LFAs have in controlling the pandemic.

Nanotechnology-Enabled Telemedicine Sensors for COVID-19 Diagnosis. Although LFAs have promise to be widely deployed as an inexpensive, rapid, at-home testing tool, they are limited to qualitative binary diagnostic results and have variable performance under independent reviews.[18,42] Highly sensitive, quantitative testing methods may allow for earlier detection and more accurate screening for asymptomatic carriers as well as a more informative tool for monitoring disease progression at home through telemedicine care. Electrochemical sensors based on novel nanomaterials are well-positioned to provide rapid, highly sensitive testing that can be easily integrated into mHealth platforms.

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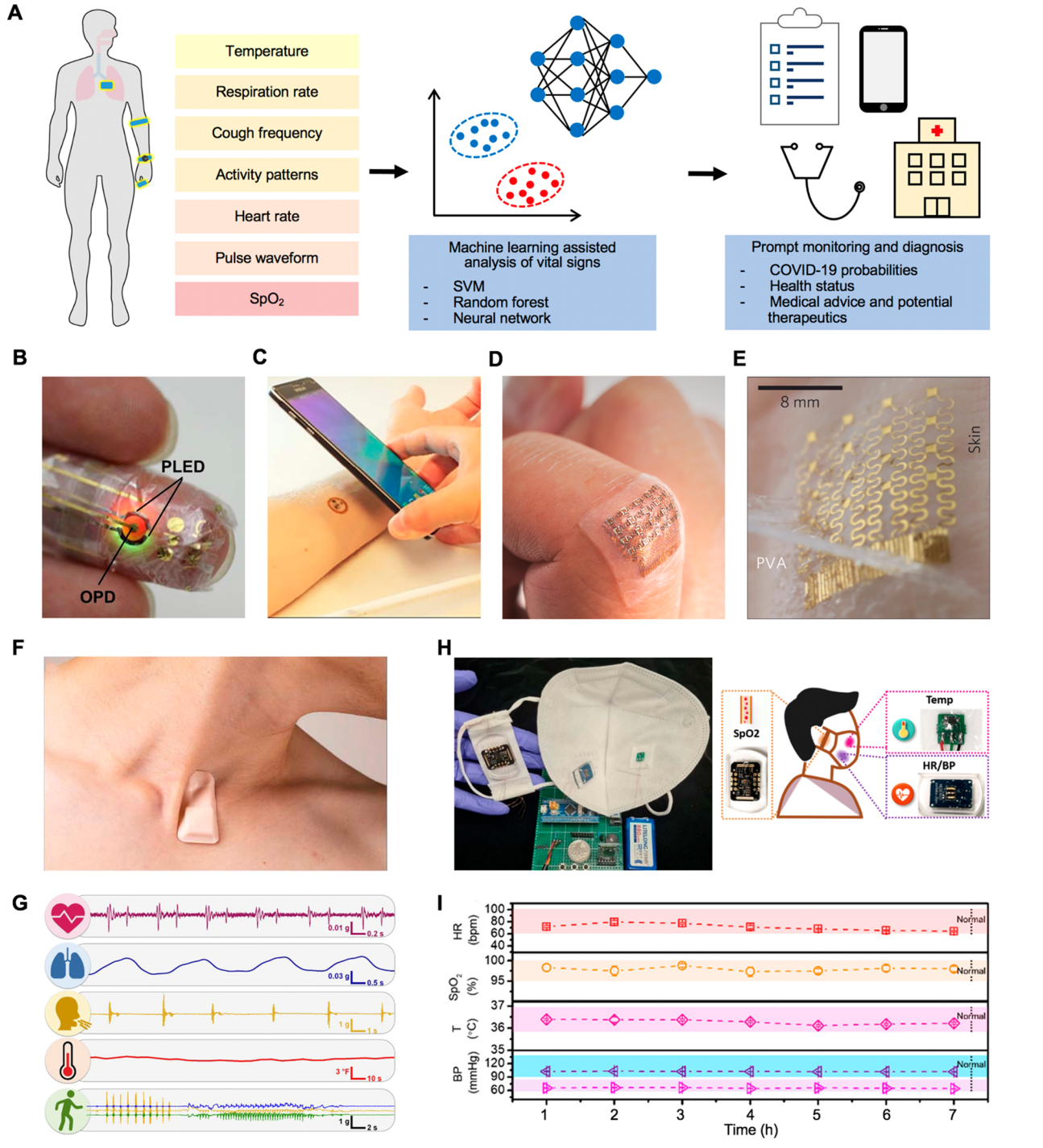

Figure 3. Skin-interfaced wearable sensors for continuous and non-invasive COVID-19 early detection and monitoring. (A) Wearable sensors for continuous monitoring of physiological biomarkers related to COVID-19 infections. Workflow of vital sign data analysis and COVID-19 predictive system. (B) A flexible pulse oximeter mounted on a subject's finger measuring oxygen saturation level. Reproduced with permission from ref 55. Copyright 2016 AAAS. (C) Wireless measurement of oxygenation with a smartphone. Reproduced with permission from ref 56. Copyright 2016 AAAS. (D) An epidermal ultrasonic device that monitors central blood pressure waveform. Reproduced with permission from ref 57. Copyright 2018 Springer Nature. (E) A skin TCR sensor array for temperature mapping. Reproduced with permission from ref 58. Copyright 2013 Springer Nature. (F) A soft skin-interfaced sensor platform designed for COVID-19 monitoring. (G) Continuous multimodal monitoring of vital signs from a COVID-19 patient. (F and G) Reproduced with permission from ref 61. Copyright 2020 AAAS. (H) A smart mask that monitors respiratory signs associated with COVID-19. (I) Remote real-time monitoring of a person wearing the mask. (H and I) Reproduced with permission from ref 77. Copyright 2020 ACS.

An ultrasensitive field-effect transistor (FET)-based biosensor was recently developed for label-free detection of the SARS-CoV-2 S protein (Figure 2A).[43] The sensor was prepared using capture antibodies bound to graphene sheets of the FET using a 1-pyrenebutyric acid (PBA) *N*-hydroxysuccinimide ester linker. Using this electrochemical technique, the device could detect spike protein at the fg/mL level, with a limit of detection of 242 copies/mL in clinical

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nasopharyngeal sample specimens. The signal response was immediately observable upon antigen-binding with stable signals and quantitative detection achieved in under a minute.

Instead of developing a highly sensitive sensor, one can also amplify the signal to a detectable range. A POC aptamer-based sensor was developed in saliva that uses invertase to amplify the signal by converting sucrose to glucose (Figure 2B).[44] Upon antigen-aptamer binding, invertase-conjugated antisense strands are released from functionalized magnetic beads and separated. Using a commercial glucometer, the glucose concentration could be effectively calibrated to the antigen concentration. Given the commercial availability of glucometers and their connectivity to mHealth networks, this diagnostic platform cleverly utilizes existing technology for ready POC deployment.

Rapid, electrochemical sensing of cytokine biomarkers has been an ongoing field of research given the diagnostic use of monitoring the body's inflammatory response in several diseases. An aptamer-based graphene FET with a HfO_2 dielectric layer was demonstrated to detect IL-6 in saliva at the picomolar level.[45] For real-time COVID-19 diagnosis based on viral-induced inflammation, an electrochemical sensor was reported to selectively detect the reactive oxygen species (ROS) levels in sputum samples.[46] During infection, mitochondrial ROS induce cytokine dysregulation in the lungs. Using functionalized multiwalled carbon nanotubes, the sensor detects ROS levels in 30 s *via* cyclic voltammetry. The test achieved 97% sensitivity and was well-correlated to chest CT scan results. This electrochemical sensor has the potential to be adapted for an easy-to-use, reliable at-home test to diagnose COVID-19 and monitor lung health over the course of the infection.

A multiplexed electrochemical platform, SARS-CoV-2 RapidPlex, was developed for at-home diagnosis and monitoring *via* simultaneous detection of SARS-CoV-2 antigen, antibodies, and CRP.[32] In a single test, the platform provides quantitative information on viral infection, immune response, and disease severity. The platform is composed of an immunosensor array based on four 1-pyrenebutyric acid (PBA)-coated laser-engraved graphene working electrodes (Figure 2C). The design allows for ultrasensitive, selective, and simultaneous amperometric detection of SARS-CoV-2 N protein, anti-S1 IgG, anti-S1 IgM, and CRP. The data are wirelessly transmitted to a user interface *via* Bluetooth, allowing for remote reporting and monitoring. The platform was applied to both serum and saliva samples with substantial differences between COVID-19 positive and negative samples for all biomarkers (Figure 2C). Taking advantage of graphene's properties and using simple and well-established surface functionalization and immunosensing techniques, the SARS-CoV-2 RapidPlex platform provides a basis for quantitative panel testing of COVID-19 biomarkers.

Artificial intelligence (AI) has been incorporated into the diagnosis of COVID-19 based on standard laboratory testing, CT scans, and clinical presentation,[47] but it is also used to identify COVID-19 signatures in exhaled breath analysis through a hand-held breathalyzer system (Figure 2D).[48] A sensor array of AuNPs functionalized with organic ligands produces changes in the electric resistance due to shrinking and swelling of the nanomaterial film based on chemical reactions upon exposure of exhaled breath composed of respiratory gases, volatile organic compounds (VOCs), and water vapor. The testing procedure was observed to be highly specific for COVID-19 in comparison to other lung infections. Such immediate and simple testing procedures would allow for mass screening in public and POC settings.

The rapid development of diagnostic tools for SARS-CoV-2 has led to creative ways to exploit viral products and the immune response to provide key diagnostic information. However, few of these tools are ready for mass deployment, and some argue that the priorities of researchers are misaligned with the priorities of clinicians.[49] In practice, robustness outweighs sensitivity. With more attention placed to clinical validation and reproducibility, these novel devices have great potential to address the challenges of current testing. Electrochemical sensors are prime for integration with mHealth platforms, allowing for immediate contact tracing and telemedicine access. Because of their rapid result turnaround, these tools may be used frequently before and ongoing during the infection to better monitor the disease progression.

TELEMEDICINE TOOLS FOR VITAL SIGN MONITORING AND CONTACT TRACING

Given the current challenges in implementing widespread testing, wearable sensors monitoring general vital signs may be used to continuously monitor for early warning signs and worsening of symptoms. Early symptoms of COVID-19 infections are nonspecific and typically present as fever, cough, shortness of breath, and fatigue.[50] Real-time and at-home monitoring of physiological signals using telemedicine devices may offer insight into the patient's health status to prompt medical treatment and prevent sudden degradation, thus reducing overall mortality rate (Figure 3A). Skin-interfaced wearable devices and mobile health (mHealth) monitors have been widely used for fitness tracking and daily life and, now, have the potential of translating toward collecting physiological signals during the pandemic to monitor and identify potential patients, and contain the COVID-19 outbreak (Figure 3B–E).[51−58] These wearable devices can be deployed to healthy individuals who have the risk of potential exposure, asymptomatic persons, and people with mild symptoms, who are suggested to stay at home and self-quarantine without further medical care under current clinical guidances.[59] Additionally, monitoring physiological signals of patients continuously may offer a deeper understanding of the development of COVID-19 infections as well as the process of recovery or potential long-term sequelae.[60,61] Population level mHealth monitoring will unveil the true incidence among communities, guide local reopening policies, and provide an early warning system to help reduce viral transmission and mortality rate. In this section, we summarize the clinical translation of physiological biomarkers that are strongly related with COVID-19 symptoms, introduce the wearable sensor platforms developed to track them, and then discuss the current progress of using these wearable vital sign monitors and the collected relevant data for COVID-19 monitoring and management.

Wearable Sensors for Continuous Vital Sign Monitoring. When a viral infection occurs, the immune system will defend against it by elevating body temperature. Temperature measurements are therefore indispensable and have been widely adopted in many countries. For example, a continuous body temperature monitoring program using the TempTraq system has been launched in University Hospitals in Ohio to monitor temperatures of caregivers who may be exposed to

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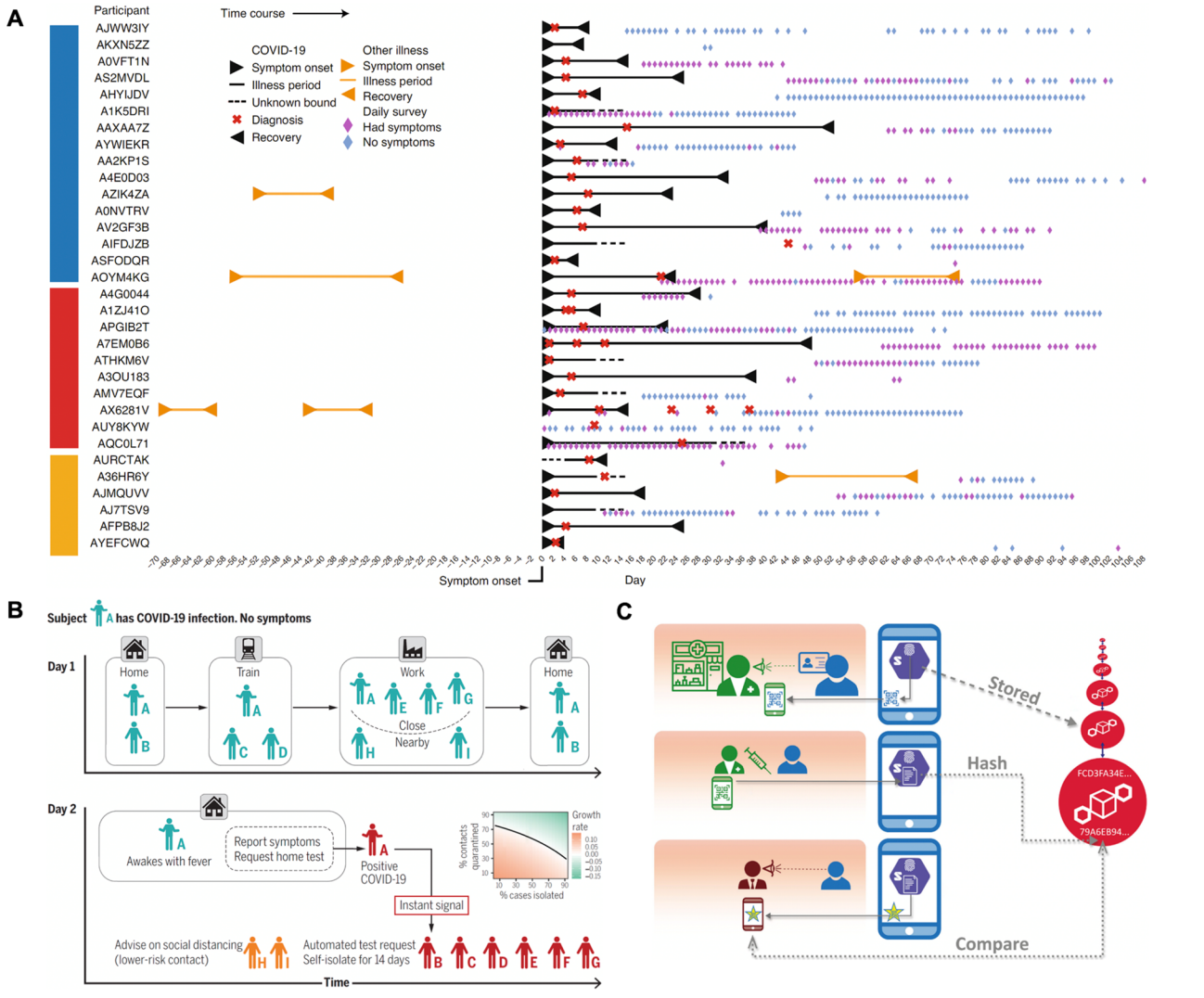

Figure 4. mHealth platforms for physiological data monitoring, analysis, and contact tracing. (A) Physiological monitoring of 31 COVID-19 positive patients using a smartwatch platform. Reproduced with permission from ref 83. Copyright 2020 Springer Nature. (B) Contact tracing and quarantine by monitoring the proximity between phones running the mHealth app. Reproduced with permission from ref 84. Copyright 2020 AAAS. (C) Schematic of testing, certification, and verification for data security using decentralized verifiable data registry. Reproduced with permission from ref 85. Copyright 2020 IEEE.

COVID-19.[62] The single use, disposable sensor patch can last up to 72 h and transmit real-time data wirelessly. When a fever is detected, the caregiver is immediately quarantined to ensure the safety of the general public. While identifying potential patients with fever may help control the spread to some degree, measuring temperature alone is neither sufficient nor accurate. Fever is also related with many other infections, such as the flu, and is not a hallmark symptom of COVID-19, as many patients are asymptomatic or do not experience a fever during infection.

Viral illness increases physiological stress leading to an increase in heart rate and blood pressure and change in pulse waveforms. One previous study reported predicting influenza-like illness by analyzing resting heart rate and sleeping duration based on commercial Fitbit and Huami devices.[63,64] Recently, researchers at Stanford and Scripps have initiated app-based monitoring programs to detect and predict viral illnesses using Fitbit and Apple watch wearables, which extract heart rate and other health data.[65,66] Studies have also shown that COVID-19 infections are associated with cardiovascular complications including myocarditis, heart failure, and venous thromboembolism.[67] Sudden cardiovascular death is highly related with COVID-19 infections and has become a major complication.[68] Thus, it is critical to monitor cardiac conditions such as heart rate variability (HRV) among COVID-19 patients using wearable electrocardiogram (ECG) sensors.

Respiration rate is of critical importance to monitor the lung functionality of COVID-19 patients. Normal respiration rates range from 12 to 20 rpm at rest, while infected lungs will cause increased respiration rates. Compared with body temperature measurements, monitoring respiration fluctuations may serve as a more specific biomarker for COVID-19 diagnosis, since most flu cases do not exhibit shortness of breath. It is worth noting that an elevated respiration rate usually requires oxygen therapy, and delayed treatment may cause the use of highly invasive procedures such as mechanical ventilation and intubation, which currently has a high mortality rate of 80%.[69] Measuring respiration rate using strain sensors can potentially monitor the coughing frequency as well, helping to

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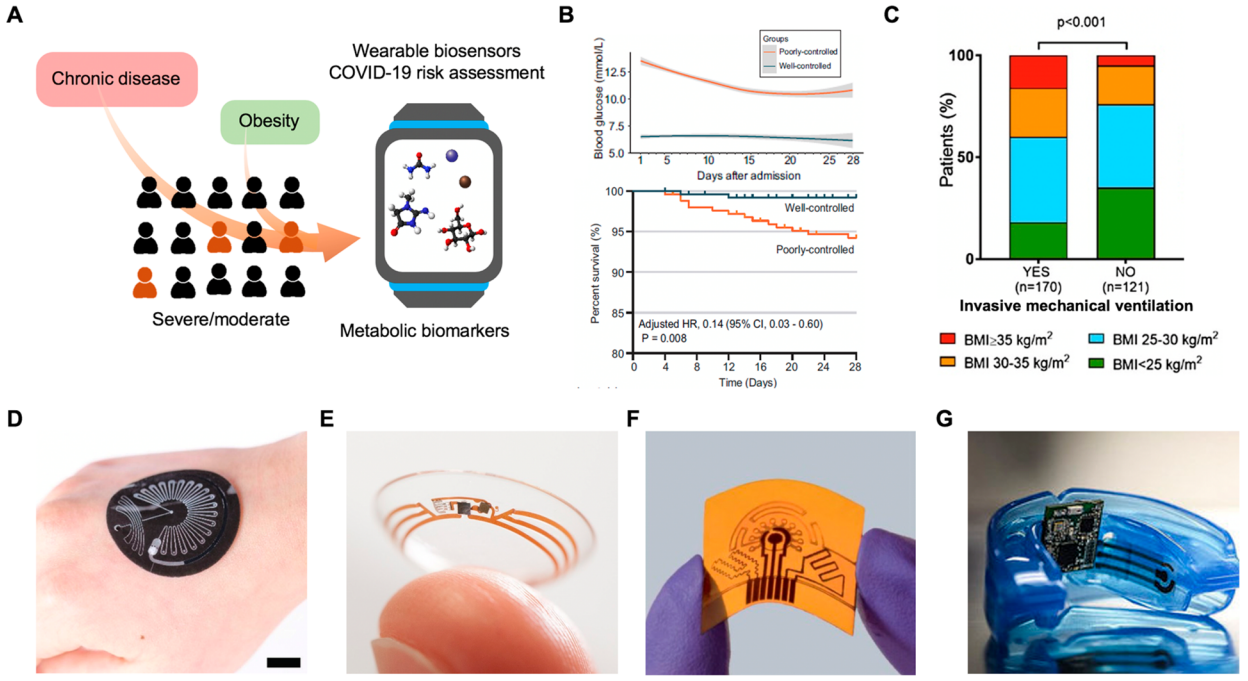

Figure 5. Wearable metabolic biosensors for COVID-19 risk assessment. (A) Schematic illustration for wearable chemical sensors for monitoring COVID-19 risk factors, severity, and prognosis. (B) Dynamics of blood glucose during the 28 day follow-up and survival rate curves of patients with poorly and well-controlled blood glucose. Reproduced with permission from ref 105. Copyright 2020 Elsevier. (C) Association between obesity and COVID-19 severity. Reproduced with permission from ref 108. Copyright 2020 The Obesity Society. (D and E) Photographs for wearable sensors for continuous and non-invasive glucose analysis in sweat (D) and tears (E). Reproduced with permission from ref 114. Copyright 2019 Springer Nature. Reproduced with permission from ref 117. Copyright 2014 Google. (F and G) Wearable chemical sensors for monitoring circulating metabolites and nutrients through *in situ* sweat (F) and saliva (G) analyses. Reproduced with permission from ref 119. Copyright 2020 Springer Nature. Reproduced with permission from ref 120. Copyright 2015 Elsevier.

assess in real-time and allow for timely medical interventions before worsening symptoms arise.

Peripheral oxygen saturation (SpO_2) measures the oxygen carrying capability of hemoglobin. Normal blood oxygen saturation level is around 94% to 100%, while breathing problems may cause life threating hypoxemia. COVID-19 attacks the lungs differently from normal pneumonia and causes oxygen deprivation that is hard to detect initially during the incubation period. By the time noticeable shortness of breath is developed, the oxygen saturation levels of the patients have usually decreased to merely 50%.[69] This makes monitoring pulse oximetry a crucial early warning factor to prevent exacerbations. Pulse oximeters, wearable devices that are mounted on the fingers of the patients to continuously and non-invasively monitor oxygen saturation levels, have been proposed to monitor symptoms at home and prevent such silent hypoxia in COVID-19 patients.[69]

Activity patterns also have the potential of reflecting the individual's health status. With current stay-at-home guidelines, a significant decline in normal activity levels measured by step counts of Fitbit users have been shown.[70] Exercise has been proven to have health benefits for both healthy individuals and patients with various diseases.[71,72] Regular physical exercise will improve cardiovascular functions,[73] increase the strength of respiratory muscles,[74] and maintain and enhance the immune system.[75,76] Some pioneering research has been conducted to study activity patterns of COVID-19 patients using skin-interfaced wearable sensors (Figure 3F–I).[61,77]

Data Analysis and Pioneering Studies of mHealth for COVID-19 Monitoring. Several COVID-19 monitoring mHealth apps have been developed to collect daily survey-based information, including whether people feel well and whether they develop COVID-19 symptoms, and to assess real-time community spread. For example, a web-based platform named CovidNearYou has been designed to visualize COVID-19 current and potential hotspots.[78] The platform has captured more than 1 million self-reports based on voluntary crowdsourced data. These apps can be used not only for the general public but also for screening health workers to implement effective containment strategies.[79] One challenge is that many infectious patients are not aware during the incubation period, which makes self-reporting a lagged measure in terms of prompt epidemiologic studies.

Given the highly diversified user health data, mHealth platforms such as smartphone apps may be combined with wearable sensors to automatically analyze and manage the data as an elementary screening tool and reduce unnecessary hospital consultations.[80] Machine learning models along with predictive algorithms that can generalize among different populations can be built to understand inconspicuous health status and predict exacerbations.[81,82] Some pioneering studies include early detection of COVID-19 using both commercial wearable products and customized wearable platforms. For example, researchers were able to distinguish cases based on changes in heart rate, steps, and sleep in 80% of COVID-19 infections by analyzing smartwatch data from 31 infected patients out of 5000 participants (Figure 4A).[83] These physiological alterations were detected before symptom onset

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in over 85% of the positive cases, which could be used to predict asymptomatic and presymptomatic COVID-19 infections and better meet surges in medical demand.

Anonymous data containing geographic information can further enable contact tracing by monitoring the proximity between phones running the app (Figure 4B).[84] With approaches that ensure data security,[85] these population-wide platforms also identify potential regions at risk and new "hot spots" in the absence of widespread population testing (Figure 4C).[86] Some representative social-media platforms including WhatsApp, Facebook, and Twitter have also been used to broadcast instant information or updates to the public, which supplement public communication and health education.[87−89]

TELEMEDICINE METABOLIC BIOSENSORS FOR COVID-19 RISK ASSESSMENTS

Many studies have revealed that the risk of COVID-19 severity and death is extremely higher among individuals with chronic diseases and metabolic disorders such as obesity, diabetes, fatty liver disease, and alcoholism.[90−95] Understanding the risk of severe COVID-19 outcomes for these patient populations, it is important that individuals take preventative steps to lower their risk for severe COVID-19. Monitoring of metabolic biomarkers may better track patient progress under physician-guided lifestyle changes, such as diet and exercise. If infected, quantitative metabolic information may be used to screen for high-risk patients and better inform treatment decisions. Once patients exhibit clinical manifestations requiring inpatient interventions, they may have already progressed to a severe phase associated with other complications, such as heart failure, liver failure, or kidney failure. Therefore, this necessitates moving toward small and inexpensive telemedicine tools that may monitor general metabolic biomarkers continuously and alert clinicians in advance of patient degradation, allowing for early intervention in high-risk patients with severe prognoses (Figure 5A). In this section, we report metabolic biomarkers that are well-correlated with COVID-19 severity and outcome. We then discuss how these biomarkers may be monitored using wearable electrochemical sensors prior to infection for preventative measures and during infection to triage and monitor vital organ function.

Metabolic Biomarkers and COVID-19 Severity. Metabolic biomarkers have been proven as an effective tool to evaluate the etiology of diseases and assess the effects of pathologies.[96] A wealth of metabolic biomarkers have recently been detected from nonsevere and severe COVID-19 patient serum, such as urea, creatinine, uric acid, ions (potassium, sodium, iron, calcium, bicarbonate, chloride), glucose, and lactic acid.[97] Some of these metabolic biomarkers have attracted attention for their direct correlation with COVID-19 severity.[98,99] As shown in Table 1, glomerular filtration biomarkers, urea and creatinine, increased by 5-fold in severe COVID-19 patients, indicating that severe infection may reduce kidney function or that patients with chronic kidney disease are at a higher risk for severe presentation of COVID-19. There was no significant difference for uric acid between COVID-19 patients and healthy reference values. Ions play an important role in blood to maintain osmotic balance, pH balance, and proper cellular function; therefore, variation in plasma ion concentrations may be indicative of metabolic disorders. The kidney regulates the levels of plasma ion concentrations including sodium, potassium, calcium, magnesium bicarbonate, and chloride. As described, COVID-19 may disrupt kidney function, changing ion concentrations in the process. Potassium showed higher concentrations of around 1 mM in severe cases.[100] Other ions like sodium, chloride, and bicarbonate showed no significant difference between the nonsevere and severe patients.[101] Iron, which is an essential element for nucleic acid replication, is an attractive biomarker for severe prognosis.[102] When the immune response is activated and the cytokine cascade starts, serum iron decreases and is converted to ferritin, leading to an observed decrease in concentration after infection when compared to normal reference values. In severe cases, serum iron concentration decreased significantly to 25.5 μg/dL due to lymphopenia, and ferritin increased correspondingly. The serum iron recovered after a median of 7−9 days of treatment in the intensive care unit. As a key biomarker for health, blood glucose increased after infection among COVID-19 patients and was well-correlated to disease severity.[103,104] Well-controlled blood glucose concentrations significantly reduced complications, adverse outcomes, and death (Figure 5B).[105] Blood glucose provides novel insight into patients with severe COVID-19 and possible avenues aimed at improving their disease outcomes. Similar with glucose, lactic acid in serum increased after infection. In addition to diabetes mellitus and chronic kidney disease, obesity, another health condition in the metabolic syndrome cluster, has been linked to a high risk of severe COVID-19 illness and death.[106,107] There is a clear relationship between increasing values of BMI and the proportion of patients with severe COVID-19 (Figure 5C).[108] These metabolic biomarkers paint an overall picture of the course and severity of COVID-19 infection. Identifying declined metabolic health may be of great importance in the early diagnosis and treatment, potentially reducing hospitalization for severe patients. However, it should be clarified that the reported results are limited by small sample sizes and monitoring of metabolic biomarkers during treatment, which may have had an unknown influence on the serology results. Additionally, these biomarkers are not as specific to COVID-19 as viral products.

Table 1. Exemplar Small-Molecule Biomarkers in Mild and Severe Patients with COVID-19

metabolic biomarkers	reference range	range in mild cases	range in severe cases	ref
creatinine	60−120 μM	40−60 μM	50−160 μM	99
urea	2.5−7.1 mM	2−5 mM	5−25 mM	99
potassium	3.6−5.2 mM	3.8−4.6 mM	4.0−5.0 mM	100
iron	60−170 μg/dL	55−58 μg/L	median 25.5 μg/L	102
glucose	4.4−6.1 mM	4−20 mM	6−25 mM	104

Wearable Chemical Sensors. Wearable biosensors could play an important role for metabolic monitoring and infection risk assessment during the COVID-19 pandemic through real-time and continuous analysis of accessible body fluids like interstitial fluid, sweat, saliva, and tears (Figure 5D−G).[109−111] Through low-cost, commercially available wearable biosensors such as continuous glucose monitoring (CGM) devices to monitor blood glucose level in real-time, it is possible for clinicians to evaluate and treat patients more efficiently based on the observed increase in blood glucose after COVID-19 infection. Glycemic control through wearable CGM devices has been advocated for in-hospital use to monitor COVID-19 patients, especially those with diabetes, since hyperglycemia

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brought on by changes in medication and infrequent glucose monitoring during COVID-19 hospitalization is a poor prognostic indicator.[112,113] More recently, wearable sensors with an enzymatic glucose sensor can non-invasively monitor external body fluids (sweat,[114−116] tears,[117] saliva[118]) and reflect the relative blood glucose levels (Figure 5D,E). The wearable biosensing technique can be applied to other biomarkers in sweat and saliva toward non-invasive personalized metabolic monitoring. For example, sweat electroactive metabolites and nutrients (*e.g.*, uric acid, tyrosine) can be monitored by a laser-engraved microfluidic wearable sensor patch (Figure 5F),[119] and metabolites in saliva (*e.g.*, uric acid and lactate) can also be monitored with a wireless mouthguard biosensor (Figure 5G).[120] Urea in sweat has been monitored using a urease-modified enzymatic ammonium-ion-selective electrode to track protein intake in the daily diet.[121] Besides the triage of severe cases, metabolic wearable biosensors could be used for lifestyle monitoring and diet personalization for preventative healthcare and lowering the risk of severe COVID-19 outcomes prior to infection.

These continuous chemical sensors may be combined with physical sensors described previously to create a multimodal platform for health monitoring. Through continuous data processing, machine learning, and mHealth incorporation of medical records, a multimodal health platform could provide key predictive information regarding COVID-19 risk and advanced warning of COVID-19 infection. It should also be noted that these telemedicine sensors could potentially allow non-invasive monitoring of stress and mental health monitoring which has become a crucial societal issue during the pandemic.[122−124] The future of personalized medicine will incorporate continuous and mHealth connected multimodal wearable platforms in preventative treatment plans, early infection prognosis, and telemedicine monitoring.

CONCLUSIONS AND OUTLOOK

Based on recent global trends, it is clear that the battle against COVID-19 is not a passive one. While sheltering in place is the most effective method for stopping the spread of COVID-19, it is not compatible with the global economy and communal society we live in. Thus, in addition to face coverings and social distancing measures, how we approach COVID-19 screening, diagnosis, and treatment must be re-imagined. The ability to immediately isolate infected individuals and limit their contacts through telemedicine monitoring and prognosis is imperative to containing COVID-19.

COVID-19 testing has been one of the largest challenges during the pandemic. Widespread and frequent testing with rapid turnaround time is necessary since presymptomatic and asymptomatic carriers may contribute the most to spreading the disease. LFAs are being bet on as a cheap, mass-producible, simple, and rapid diagnostic tool. However, there are concerns that LFAs are not as accurate as the standard RT-PCR. Moving toward inexpensive telemedicine electrochemical sensors may solve this problem with accurate and quantitative results which may better inform physicians. Additionally, diagnostic platforms may be advanced to multiplexed designs to provide information regarding not only infection status but also the immune response, inflammatory markers, and metabolic markers to better understand the time course and severity of the infection. A key for telemedicine implementation though is that diagnostic tools must be self-administered using accessible samples including blood, saliva, or exhaled breath.

Once diagnosed, at-home isolation and monitoring of symptoms is necessary to prevent overwhelming healthcare systems. By pairing continuous wearables that monitor physiological markers and telemedicine platforms, physicians can track patient health statuses in real-time and determine when to change treatment courses. Through mHealth platforms, these data may be automatically analyzed for early warning signs of patient degradation. At-home monitoring of metabolic markers associated with prognosis may also allow for forward triage of COVID-19 patients. These tools may allow for earlier intervention in serious cases and efficient allocation of hospital resources to improve positive patient outcomes. Additionally, continued telemedicine monitoring of chronic metabolic disorders may allow for preventative steps to be taken by changes in diet and lifestyle and treatments that would help to lower their risk of severe COVID-19 outcomes.

Considering the large infected population and high transmission rate, manual contact tracing and identification have become infeasible. Contact tracing and quarantine, case isolation and monitoring, hygiene, and decontamination will be the new normal until a vaccine is widely available.[84] With the widespread availability of commercial wearable devices and smartphone-based platforms, they can be used for continuous monitoring of individuals as well as autonomous tracing of disease activity. Machine learning and predictive algorithms of the user data will play a role in disease identification and assessment. At a population level, these algorithms combined with geographic app data may form more accurate models of the spread that may guide quarantine strategies and reopening policies.

In conclusion, with new advances in remote diagnostics and wearable sensors, telemedicine may be effectively leveraged for COVID-19. Through widespread, rapid screening and at-home testing, mHealth reporting, and integrated wearable technologies for symptom monitoring and prognosis, we may control future surges of COVID-19 infections and optimize patient outcomes.

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Notes

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