ACS APPLIED BIO MATERIALS

www.acsabm.org Review

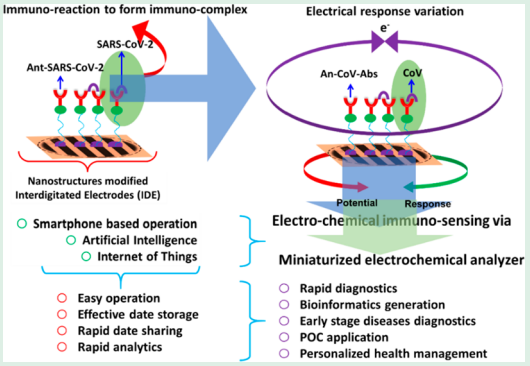
Electrochemical SARS-CoV-2 Sensing at Point-of-Care and Artificial Intelligence for Intelligent COVID-19 Management

Ajeet Kumar Kaushik,* Jaspreet Singh Dhau, Hardik Gohel, Yogendra Kumar Mishra, Babak Kateb, Nam-Young Kim, and Dharendra Yogi Goswami

Cite This: https://dx.doi.org/10.1021/acsabm.0c01004 Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: To manage the COVID-19 pandemic, development of rapid, selective, sensitive diagnostic systems for early stage β-coronavirus severe acute respiratory syndrome (SARS-CoV-2) virus protein detection is emerging as a necessary response to generate the bioinformatics needed for efficient smart diagnostics, optimization of therapy, and investigation of therapies of higher efficacy. The urgent need for such diagnostic systems is recommended by experts in order to achieve the mass and targeted SARS-CoV-2 detection required to manage the COVID-19 pandemic through the understanding of infection progression and timely therapy decisions. To achieve these tasks, there is a scope for developing smart sensors to rapidly and selectively detect SARS-CoV-2 protein at the picomolar level. COVID-19 infection, due to human-to-human transmission, demands diagnostics at the point-of-care (POC) without the need of experienced labor and sophisticated laboratories. Keeping the above-mentioned considerations, we propose to explore the compartmentalization approach by designing and developing nanoenabled miniaturized electrochemical biosensors to detect SARS-CoV-2 virus at the site of the epidemic as the best way to manage the pandemic. Such COVID-19 diagnostics approach based on a POC sensing technology can be interfaced with the Internet of things and artificial intelligence (AI) techniques (such as machine learning and deep learning for diagnostics) for investigating useful informatics via data storage, sharing, and analytics. Keeping COVID-19 management related challenges and aspects under consideration, our work in this review presents a collective approach involving electrochemical SARS-CoV-2 biosensing supported by AI to generate the bioinformatics needed for early stage COVID-19 diagnosis, correlation of viral load with pathogenesis, understanding of pandemic progression, therapy optimization, POC diagnostics, and diseases management in a personalized manner.



KEYWORDS: *COVID-19 pandemic, infectious diseases, smart diagnostics, smart sensing, artificial intelligence, Internet of things, point-of-care, diseases management*

1. INTRODUCTION

Since the first case was reported by Chinese physicians in late 2019, the β-coronavirus severe acute respiratory syndrome (SARS-CoV-2) has resulted in a life-threatening respiratory infectious disease (COVID-19)[1−4] which is continuously affecting socio-economic aspects along with national financial policies.[5,6] Medical health experts and the medical administration of Wuhan municipal health committee observed unexpected pneumonia emerging by unknown causes and unknown ways for dealing and handling it.[3,4] The number of affected patients started growing rapidly, and the actual reason was unknown to prescribe a suitable therapy. The early investigation ruled out seasonal flu, and medical officials started making efforts to figure out the actual reason.[7] Several investigations confirmed that these respiratory syndrome related symptoms are emerging drastically due to the coronavirus infection.[8,9] This virus has crown-like spikes on their surface (Figure 1A,B) and is categorized in seven groups as (1) 229E (α coronavirus), (2) NL 63 (α coronavirus), (3) OC43 (β human coronavirus), (4) HKU1 (β human coronavirus), (5) MERS-CoV (β human coronavirus that causes the middle east respiratory syndrome, or MERS), (6) SARS-CoV-1 (β human coronavirus that causes the severe acute respiratory syndrome, or SARS), and (7) novel coronavirus (SARS-CoV-2), a new strain, confirmed by the World Health Organization (WHO), which caused the COVID-19 pandemic. People generally get infected with α

Received: August 11, 2020
Accepted: October 10, 2020

ACS Publications © XXXX American Chemical Society

https://dx.doi.org/10.1021/acsabm.0c01004
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

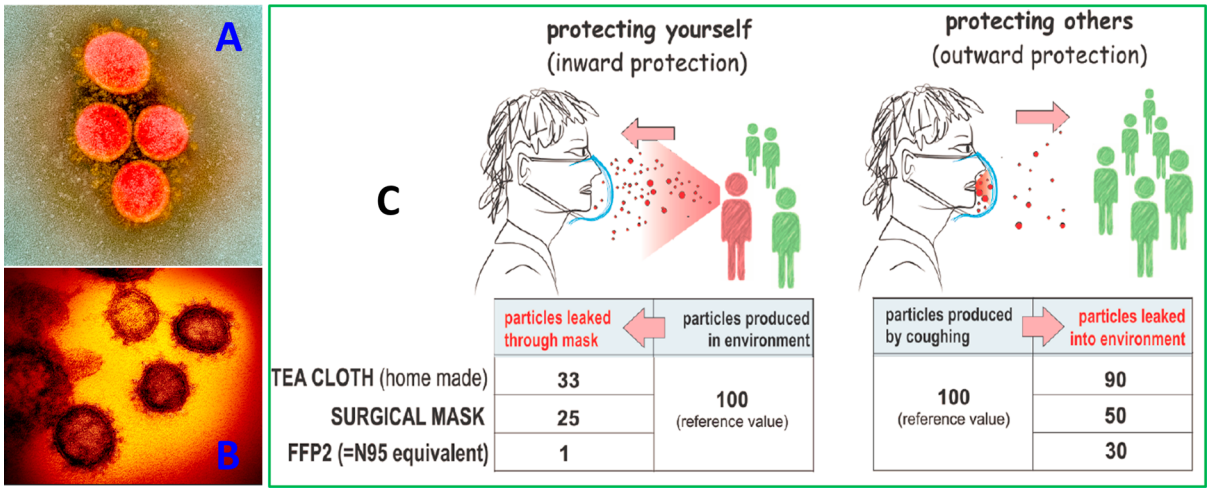


Figure 1. (A) Microscopic image of SARS-CoV-2 [Courtesy: National Institute of Allergy and Infectious Diseases, U.S. National Institutes of Health (NIAID-NIH)], (B) color enhanced transmission electron microscopic image of SARS-CoV-2 virus isolated from a patient [Courtesy; National Institute of Allergy and Infectious Diseases, U.S. National Institutes of Health (NIAID-NIH)], and (C) illustration of aerosolization of SARS-CoV-2 virus protein. Reprinted with permission from ref 10. Copyright 2020 Author Sui Huang.

and β coronavirus, but in certain circumstances that can evolve into a new strain leading to new disease patterns. SARS-CoV-2 is an example of this such evolution.

In the unprecedented present situation and considering the severity of a rapidly increasing respiratory disorder associated with the SARS-CoV-2 virus, efforts were made to release advisories and guidelines mainly based on self-protection or protecting each other (Figure 1C) to avoid human-to-human (H2H) transmission through the use of an appropriate mask-based effort for social and profession involvements.[10−13] The association of SARS-CoV-2 virus spreading through aerosolization and droplet methods has been proven, and using a very simple mask, made of simple cloth (cotton, silk, and so on) or of disposal surgical purpose, can reduce infection risk significantly.[14−16] Besides, having a careful practice of sanitization and social/physical distance is also among the top recommendations of experts.[17] The COVID-19 disease became an epidemic as a declared international health emergency in a short period of time because of its immediate adverse effect on the respiratory system, especially in the immune-compromised population.[8] SARS-CoV-2 virus, which easily transmits H2H,[18] via contact and aerosol droplets, has a novel strain more active site (S1 protein) to bind with host cells' receptors, i.e., angiotensin-converting enzyme 2 (ACE2).[19] COVID-19 infection was declared as a pandemic by WHO[20] because it has affected more than 30.0 million people in 227 countries and approximately 30% of cases belong to the United States of America (USA). Since then, efforts are being made to investigate virus structure profiling, virus life cycle, infection pathways, functional sites useful for therapeutics discovery, and pathogenesis.[9]

Due to several unanswered encounters such as asymptomatic carriers (silent carriers),[21] unknown virus strain categories, and unpredicted virus mutation,[22] the investigation of therapeutics and diagnostics to manage COVID-19 have emerged as very challenging.[23] Keeping these aspects in view, this report explores the potential of a timely investigation of affordable, sensitive, and selective detection and diagnostics of SARS-CoV-2 virus infection.[24] In a combination of artificial intelligence (AI), such a SARS-CoV-2 sensor can be managed to perform personalized COVID-19 diagnostics in desired conditions and locations. Before describing COVID-19 diagnostics aspects, trends in the fundamentals of SARS-CoV-2, recommended advisories, and nanoenabled strategies to manage COVID-19 are also discussed briefly.[6]

2. TOWARD EXPLORING SARS-COV-2 TO UNDERSTAND COVID-19

After preliminary advisories, efforts were being made to understand the SARS-CoV-2 categories, mutations, strains, and structure. Such bioinformatics is very useful to explore pathogenesis, mechanism on infection progression, and identification of functional sites and to design therapeutics. In this direction, the phylogenetic network of SARS-CoV-2 genome was analyzed by Forster et al. and they claimed the existence of three variants (types A, B, and C, as illustrated in Figure 2), differentiated on the basis of amino acid changes.[25] In this research, 160 complete human SARS-CoV-2 genomes were analyzed, and outcomes confirmed that type B is significant in East Asia, and both types A and C are associated with COVID-19 in Europe and the USA. The outcomes of this

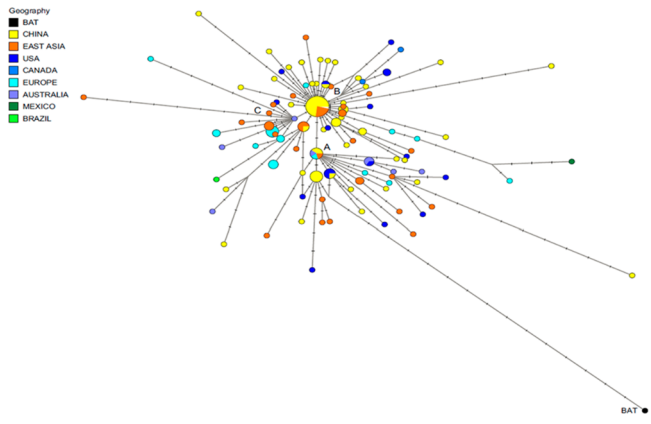


Figure 2. Phylogenetic expression of SARS-CoV-2 virus analyzed using 160 genomes. Reprinted with permission from ref 25. Copyright 2020 The Authors under Creative Commons Attribution License 4.0, published by PNAS.

https://dx.doi.org/10.1021/acsabm.0c01004
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

research are useful to understand the evaluation and mutation of SARS-CoV-2 in humans.[25]

In order to develop an effective vaccine, diagnostics, and therapeutics antibodies, Wrapp et al. have investigated cryo-EM structures of the CoV spike (S) glycoprotein.[26] The authors utilized 3.5 Å resolution cryo-EM to investigate SARS-CoV-2 S trimer in the perfusion conformation (Figure 3A).

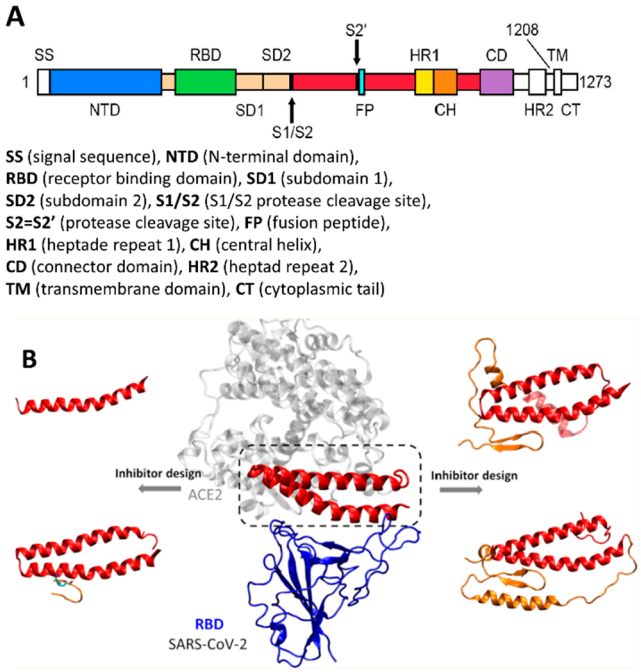


Figure 3. (A) Cryo-EM structure of SARS-CoV-2 S in the perfusion conformation. Presentation of SARS-CoV-2 primary structure showing color domains that were excluded from ectodomain contract or unable to visualize. (B) Computational-based approach for the designing of ACE2-based peptide selective as SARS-CoV-2 inhibitors Reprinted with permission from ref 28. Copyright 2020 American Chemical Society.

The outcomes of this research based on biophysical and structural evidence suggested that SARS-CoV-2 S form binds with ACE2 with higher affinity in comparison to SARS-CoV-2 S form. These claims were validated using available monoclonal antibodies specific to SARS-CoV-2 receptor-binding domain (RBD) proteins. This newly investigated SARS-CoV-2 S structure will be useful to develop medical countermeasures (MCMs) to fight against the COVID-19 epidemic.[26] Further, Yan et al. explored the cryo-EM high-resolution structure of full-length human ACE2. In this research, docking was performed in the presence of a neutral amino acid transporter with or without the RBD of SARS-CoV-2 S protein. The outcome of this research confirms that RBD is recognized by the extracellular peptidase domain of ACE2 through polar residues. This investigation is useful to explore the molecular basis for coronavirus recognition and infection.[27] These findings were useful to introduce a computational approach for exploring the function site of the virus. Han and Kral explored a computational approach to investigate possible ACE2-based peptide inhibitor (Figure 3B).[28] These inhibitors were suggested as a potential therapeutic to manage COVID-19 diseases.[28]

To develop effective and efficient COVID-19 therapeutics, it becomes very essential to have the best understanding of the SARS-CoV-2 entry pathway, virus lifecycle, and therapeutic site to be targeted.[29] The SARS-CoV-2 has enveloped virions (virus particles) that measure approximately 120 nm in diameter.[8] It has been investigated that both SARS-CoV-1 and SARS-CoV-2 are very much similar on a structural level, sharing 77.5% of their amino acid sequence,[30] with reference to coronavirus genomic profiling. For transmission and infection, SARS-CoV 2 spike (S) protein binds with ACE2 enzyme and TMPRSS2 protein of the host cell in humans, as described by Hoffmann et al. as illustrated in Figure 4A.[31] This recent investigation suggests that the S protein of SARS-CoV 2 can be a key target site to develop monoclonal antibodies and therapies. Targeting/blocking SARS-CoV 2 S protein-ACE2 enzyme/or both TMPRSS2 proteomes interaction can also be useful to inhibit virus progression and when developing vaccines and drugs.[30]

Further, efforts were made to explore the life cycle of SARS-CoV-2 to define the cell-uptake mechanism and process of viral replication, as shown in Figure 4A,[31] on the basis of the investigation of Kim et al.[32] The research explained the mechanism of the SARS-CoV-2 life cycle involving the following steps: (1) S1 protein SARS-CoV-2, a single-stranded RNA-enveloped virus, binds with host cell receptors and then after the envelope of the virus peeled off integrates with genomic RNA present in the cytoplasm. (2) In this process, ORF1a and ORF1b of genomic RNA translated into pp1a and pp1ab proteins, respectively. (3) Protease takes place, wherein pp1a and ppa1b proteins make nonstructural proteins, such that a total of 16 forms formed a (+) strand genomic RNA template based replication/transcription complex, i.e., RNA polymerase (RdRp). (4) these (+) strand genomics served as genomes of the new virus particle wherein subgenomic RNAs translated into structural protein units (S, envelope, membrane, and nucleocapsid protein) of a viral particle. (5) These protein units merge with an endoplasmic reticulum to form a nucleoprotein complex via combination of nucleocapsid protein with (+) strand genomic RNA. (6) Finally nucleoprotein complexes merge together to form complete virus particle in the endoplasmic reticulum-Golgi apparatus region, which further expelled to the extracellular region of vesicle. This nanopore-based high-resolution gene mapping research of SARS-CoV-2 involved a functional investigation of the unknown transcripts and RNA modifications.[32] The outcomes of this research successfully explored gene and associated mechanisms of viral gene fusion. Such informatics which explained the life cycle and pathogenicity of SARS-CoV-2 were needed to design and develop diagnostics and therapeutics to combat against the COVID-12 pandemic.[32]

Exploring the SARS-CoV-2 virus structure, virus entry mechanism, and genomic profile become essential for designing new therapeutics and optimizing a therapy based on the available drugs.[4,33] The schematic of SARS-CoV-2 potential drug targeting concerning the viral life cycle is illustrated in Figure 4B, well-explained by Sanders et al.[34] and supported scientific evidence.[35,36] It was well-understood that developing an appropriate therapy for managing COVID-19 would be a time-consuming procedure, so WHO and other agencies recommended the exploration of available antiviral drugs such as remdesivir (for Ebola), chloroquine (or its derivative as hydroxychloroquine, developed for malaria), and a combination of anti-HIV drugs (lopinavir and ritonavir) in combination

https://dx.doi.org/10.1021/acsabm.0c01004
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

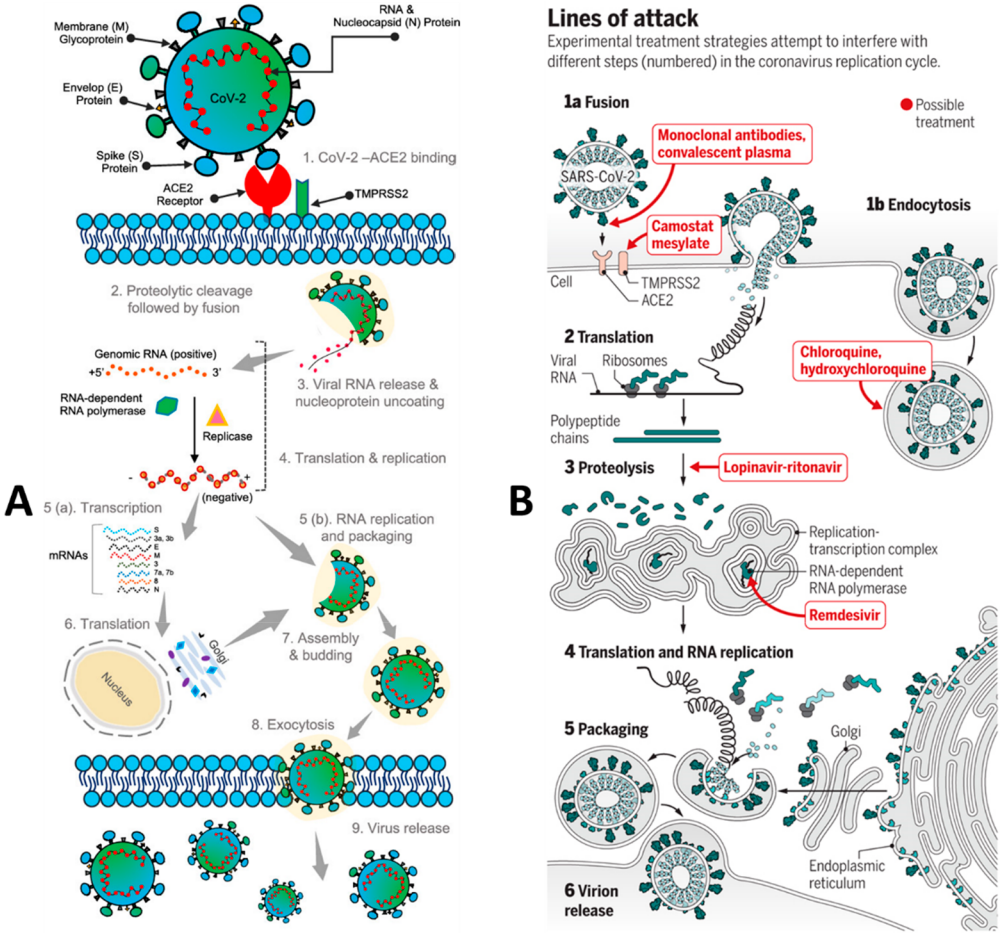


Figure 4. (A) Illustration of SARS-CoV-2 virus binding with ACE2 and TMPRSS2 receptor justifying virus entry in human *and further* presentation of coronavirus life cycle confirmed using nanopore-based high-resolution gene mapping of SARS-CoV-2. Reprinted with permission from ref 31, Copyright 2020 American Chemical Society. (B) Treatment strategies investigated by WHO based on clinical trials to explore possible steps (numbered) in the coronavirus replication cycle. Reprinted with permission from ref 36. Copyright 2020 American Association for the Advancement of Science.

with interferon β (an immune system messenger and useful for virus crippling). None of these drugs emerged as a potential therapeutic solution but were acceptable up to an extent. Every in-practice drug has side effects as well, and the studies later confirmed that ingestion emerged more dangerous than SARS-CoV-2-related effects. Adverse effect of anti-COVID-19 drugs on the lungs, heart, and eyes have been reported. In addition, the following three alternative therapies—(1) corticosteroids (decreases host inflammatory response but causes lung injury and ARD), (2) immunomodulatory or anticytokine (monoclonal antibody-based approach to knock down SARS-CoV-2 and to boost up immune systems), and (3) immunoglobulin therapy (convalescent plasma or hyperimmune immunoglobulins collected from recovered patient found useful to clear virus)—were also recommended as potential alternatives.[34] These approaches have shown good results at initial stages; however, experts suggested extensive and elaborate studies to optimize therapeutic agents of purity in scaling up a facility to promote them for COVID-19 management.

Along with exploring effective drug and alternative therapies based on investigated SARS-CoV-2 genomic profiling, parallel efforts are also developing vaccines against SARS-CoV-2 to manage COVID-19.[33,37] Keeping this in view, the development of around 90 vaccines using various approaches is under process and some of them are in line for FDA approval. Around seven groups have started exploring the efficacy of vaccine formulation into human volunteers or animals to explore safety, efficacy, and selectivity.

State-of-the-art vaccines developed against SARS-CoV-2, categories of vaccines, therapeutics mechanisms, and aspects to promote them for COVID-19 management are summarized by Callaway[35] and Amanat along with Krammer.[38] The outcomes of studies conducted by Callaway,[35] based on the finding of Le et al.,[33] proposed an array of vaccines (Figure 5) and confirmed eight investigated ways associated with vaccines to provide immunity to SARS-CoV-2. It suggested having vaccines as a therapy due to long-term effects which certainly will reduce morbidity and mortality if SARS-CoV-2 integrates with the human genome to stay permanently in the system.[33,38]

3. TRENDS IN COVID-19 PANDEMIC MANAGEMENT

Managing COVID-19 is not only a respiratory-related challenge but the severity of SARS-CoV-2-associated infection is emerging in a different scenario that affects organ functions, including injury, which leads to damage and failure as well. Studies have demonstrated that SARS-CoV-2 can attack anything in the body and cause devastating consequences including death.[39] To suggest appropriate diagnostics, therapy, and monitoring, presently efforts are being made to understand

https://dx.doi.org/10.1021/acsabm.0c01004
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

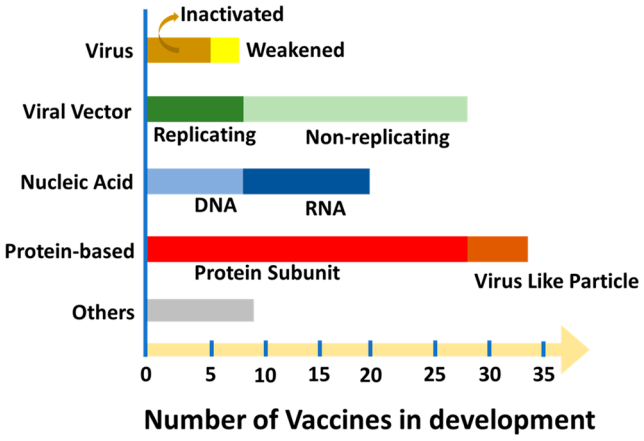


Figure 5. Roadmap of vaccine development against SARS-CoV-2: Array of vaccines proposed on the basis of WHO−COVID-19 vaccines landscape.

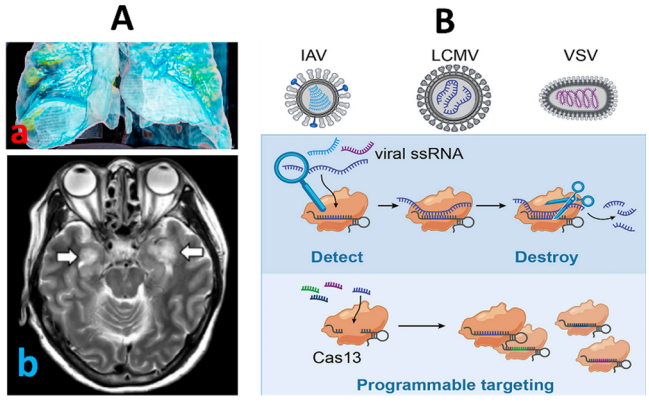


Figure 6. (A) Lung and brain damage from SARS-CoV-2 [SARS-CoV-2 caused extensive damage (yellow, as predicted 3D modeling using a computerized tomography scans) on the lungs of a 59-year-old man who died due to diseases severity (a) and MRI images analysis of a 58-year-old woman with COVID-19 showed encephalitis which causes brain tissue damage (b)]. Reprinted with permission from ref 39. Copyright 2020 American Association for the Advancement of Science. (B) CRISPR Cas9-based gene-edited strategy proposed to recognize and eradicate mutated genome. This approach can be useful for selective detection and diagnostics of COVID-19. Reprinted with permission from ref 45. Copyright 2020 Elsevier.

how the virus kills, i.e., the ferocious rampage through the body (from the brain to toe)? When inhaled via nose or throat, SARS-CoV-2 interacts with receptor ACE2, an enzyme known to regulate blood pressure. Once it enters in cells, SARS-CoV-2 hijacks functional machinery to replicate and expedite viral infection. As virus is replicating, the symptoms such as fever, dry cough, sore throat, loss of smell, and head/body ache appear within a week. This is a situation where the immune system needs to attack back to eradicate SARS-CoV-2; otherwise, the virus can move down to the lungs, where it can turn deadly as the lungs' respiratory tree, rich in ACE2 receptors, which keep feeding SARS-CoV-2. Over time, SARS-CoV-2 keeps replicating by consuming the blood oxygen, even though battling with immune cells, and causes respiratory-related syndromes. As COVID-19 infection progresses, the oxygen concentration in blood keeps decreasing and the patient develops a condition of acute respiratory distress syndrome (ARDS), a condition where breathing becomes very difficult.[39]

Moreover, SARS-CoV-2 has shown various adverse effects regarding various organs as follows: (1) lung (a cross-section of the lung showed that immune cells crowded in an inflamed alveolus, or air sac, whose walls break down from the SARS-CoV-2 attack and diminishing oxygen uptake (Figure 6A(a,b)), (2) health and blood vessels SARS-CoV-2 enters those cells lining blood vessels through binding with ACE2 receptors and as a result, viral infection promoted blood clots, heart attacks, and cardiac inflammation), (3) brain (SARS-CoV-2 can transmigrate to the brain through the nasal route and COVID-19 infected patients exhibited strokes, seizures, confusion, and brain inflammation; therefore, efforts are being made to establish a correlation between SARS-CoV-2 level and brain tissues function, injury, and damage (Figure 4A(c)); (4) eyes (COVID-19 patients have exhibited conjunctivitis; (5) nose (COVID-19 infected patients lose their sense of smell because SARS-CoV-2 can move up through the nasal route to damage cells); 6) liver (almost 50% of COVID-19 patients have shown serious liver problems due to combating against SARS-CoV-2 and ingestion of drugs in excessive doses; (7) kidney (a very common and serious issue among COVID-19 patients which may cause death; SARS-CoV-2 virus attacks kidneys directly and results in kidney failure due to a whole-body event with plummeting blood pressure); (8) intestines (biopsy of COVID-19 patients suggested that SARS-CoV-2 infects the lower gastrointestinal tract, as it is rich in ACE2 receptors, to cause diarrhea).[39]

On the basis of the above outcomes, experts suggested that the lungs are ground zero for SARS-CoV-2 but COVID-19 affects organ systems from the brain to blood vessels.[39] Thus, managing COVID-19 needs a lot of testing (decided based on patient symptoms), careful symptoms analysis (because SARS-CoV-2 is affecting several organs at the same time), and optimization of therapy-based available therapeutics options. Developing COVID-19 specific therapy is now a futuristic approach, but exploring biotechnology and nanotechnology to manage SARS-CoV infection becomes the focus, as briefly discussed in this section.

In the clinical setup, there are several molecular bioassay based diagnostics tools, mainly PCR and ELISA, to detect MERS and SARS virus protein.[40] Considering the possibilities of the SARS-CoV-2 virus spreading via travel, thermal-based screening is in practice at airports. Thus, very efficient thermal cameras have been installed at public places and are also recommended as a very rough and preliminary qualitative screening method. However, as of now, there is no available diagnostics tool for COVID-19 diagnostics for SARS-CoV-2 detection at a specified and public place. Considering pandemic management aspects in view, presently efforts are being made to achieve the followings tasks: (1) developing novel therapeutics of desired efficacy, (2) exploring new strategies to recognize and eradicate the virus, (3) exploring nanoscience and nanotechnology to design and develop protective units such as nanoenabled masks, and (4) miniaturized diagnostics tools to manage targeted and mass detection, contact tracing, and big data analytics to introduce AI for optimization and selection of management-related parameters.[41]

International health agencies including WHO and the Center for Disease Control (CDC) have requested experts of universities, research institutes, electronics and biomedical companies, and the pharma sector to accelerate efforts to

https://dx.doi.org/10.1021/acsabm.0c01004
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

investigate new biomarkers to early stage COVID-19 diagnostics. However, molecular bioassays, mainly RT-PCR, are in present practice for SARS-CoV-2 detection at the initial stage and imaging technology, mainly CT-scan for conformation of COVID-19 infection. Recently WHO and CDC have issued guidelines to collect biological samples of COVID-19 infected patients for diagnostics application and patient protocols, especially with the symptoms of other diseases such as pneumonia, asthma, tuberculosis, and heart, etc. These approved safety and precaution guidelines are globally accepted for both patients and helping health workers.[42,43] As a result, the patient got better testing along with an appropriate follow-up. Besides, these guidelines will minimize the possibilities of COVID-19 spreading among health workers who are front line warriors and need a very safe working environment.

To manage an infectious disease-related pandemic that involves millions of people, who may be in big cities, towns, and urban areas, there exists a cost-effective need for therapeutics of higher efficacy and protective component, rapid, and sensitive diagnostics systems. Such efficient diagnostics tools are also suggested to perform at the site of the location, which requires special attention and focus. Shen et al. have summarized the prospects of nucleic acids-based prototypes and possible strategies for COVID-19 diagnostics.[44] The authors suggested paying attention for developing a real-time (RT), loop-mediated isothermal amplification (LAMPS)—vertical flow (VF)- and CRISPR-associated enzyme Cas 13/12-based platform, namely, specific high-sensitivity enzymatic reporter unlocking (SHERLOCK),[45] to detect RNA and DNA[44] (Figure 6B).[45]

Parallelly, several efforts are also being made to explore the mechanism of virus pathogenesis which required accelerated efforts to design and develop biomarker and selective recognition of SARS-CoV-2 virus protein. Such biomarkers can be used to develop analytical for selective and rapid detection of SARS-CoV-2 virus protein. The continuous monitoring of COVID-19 emerged as essential because the RT-PCR test was surprisingly positive for three out of four patients who recovered from COVID-19.[46] The scope of developing analytical tools, such as an efficient biosensor, and related possible strategies is discussed in the next section.

Besides molecular biology, sincere efforts are also being made to explore functional nanomaterials, micro-/nano-electronics, numerical simulations, and algorithms to predict or optimize strategies for COVIS-19 management. One such approach is to explore nanomaterials for trapping and eradication of SARS-CoV-2 virus via using masks,[16] fabricated specifically with N95 requirements and a very normal version for everyday use. Making an efficient mask to avoid or minimize H2H transmission is presently the focus at fundamental and translational aspects.[48] However, the selection of a fabric which can trap the virus is crucial due to a lack of fundamental knowledge. Thus, assessment of filtration efficiencies of suitable fabrics such as cotton or cloth, the choice of nanomaterials-embedded membranes is essential if the targeted application concerns SARS-CoV-2 aerosolized at varying 10 nm to 10 μm particulates sizes. Konda et al.[47] fabricated an efficient three layers mask alone or in a combination of cotton, silk, chiffon, and flannel fabrics to trap a particulate of <300 nm (efficiency varies from 5 to 85%) to >300 μm (efficiency varies from 5 to 90%) (Figure 7A). The outcomes of this research suggested that an optimized

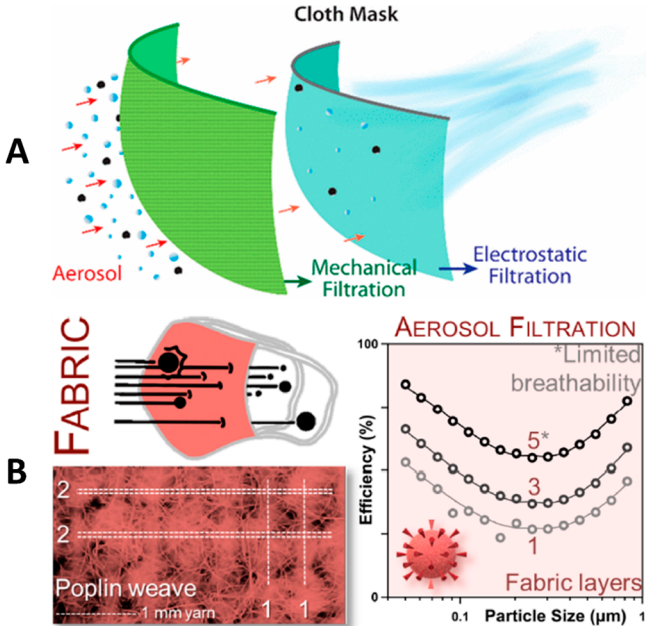


Figure 7. (A) Designing of a nanoenabled mask to avoid the SARS-CoV-2 spreading via aerosolization. Reprinted with permission from ref 47. Copyright 2020 American Chemical Society. (B) Illustration of cloth-based mask to trap the SARS-CoV-2 virus protein. Reprinted from ref 11. Copyright 2020 American Chemical Society.

combination of layers can exhibit filtration efficiency of 80–90% due to mechanical and electrostatic-assisted filtration. Herein selected materials are biocompatible, easily available, and of tunable membrane size via managing thread size.[47] Thus, required scaling up is possible as per requirement and desired filtration efficiency. However, the use of three layers may cause some sensation of suffocation which needs to be optimized before recommending for managing respiratory-related diseases such as COVID-19. In this direction, various masks made of cloth (cotton, wool, synthetic, synthetic blend, and synthetic/cotton blend) were developed to evaluate their efficiency to filter nanoscale aerosol (50–825 nm). Such cloths masks (Figure 7B) have successfully slowed down the spread of SARS-CoV-2 virus considering the case of virus transmission through the aerosol process.[11] The results of this study suggest that the charge on the cloth material does not affect the filtration efficiency. However, the quality of yarn, i.e., fabrication process, yarn count, and so on, affects the filtration efficiency. Thus, significant research is still required to investigate efficient masks which can trap the SARS-CoV-2 virus protein without causing any notable breathing problems.

Eradication of SARS-CoV-2 virus on the surfaces via a trapping and killing approach also suggested exploration Having this as a focus, Van Doremalen et al. evaluated the stability of SARS-CoV-2 and SARS-CoV-1, isolated from various strains, in aerosols of various particle sizes onto plastic, cardboard, stainless steel, and copper surfaces via assessing decay rates.[49] In a humanized environment SARS-CoV-2 aerosol (size < 5 μm) were incubated in a 50% tissue culture infectious dose. The results of this research confirmed that SARS-CoV-2 exhibit stability 3 SARS-CoV-1 but showed noticeable high viral loads in the upper respiratory tract. This means that a person may be an infection shelter for SARS-CoV-2 and can transmit this after being asymptomatic.[21] In addition, after 72 h incubation the SARS-CoV-2 was found to

https://dx.doi.org/10.1021/acsabm.0c01004
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

be less viable on Cu surface (no viability after 4 h) and more stable on plastic and stainless steel (no viability after 24 h). This is the first research to confirm the aerosolization of SARS-CoV-2, viability on various substrates, and possibilities of H2H transmission via nosocomial spread.[49]

Another approach to managing the COVID-19 epidemic is to eradicate this virus from the air because this virus can stick to tiny air particulates and has the possibility to be inhaled. A recent study reported that SARS-CoV-2 virus spread from hospitals and was transmitted through the air and close contact. Experts suggested that close contact can be avoided via careful acts but the cleaning of air at huge places such as hospitals is a remaining challenge. To manage this serious issue, efforts have suggested the design and development of centralized air purifiers which can recognize and eradicate virus particulates. One such approach could be air purifiers as developed by Molecule Inc., where cleaning of air in big facilities works on nanoenabled photosensitized degradation of air pollutants. On the basis of a well-demonstrated and proven mechanism, the photodegradation of bacteria in the presence of TiO_2 nanoparticle.[50] An approach of nanosystem-assisted photodegradation of a living micro-organizm is illustrated in Figure 8A. Nanosystems of TiO_2 have been engineered as a

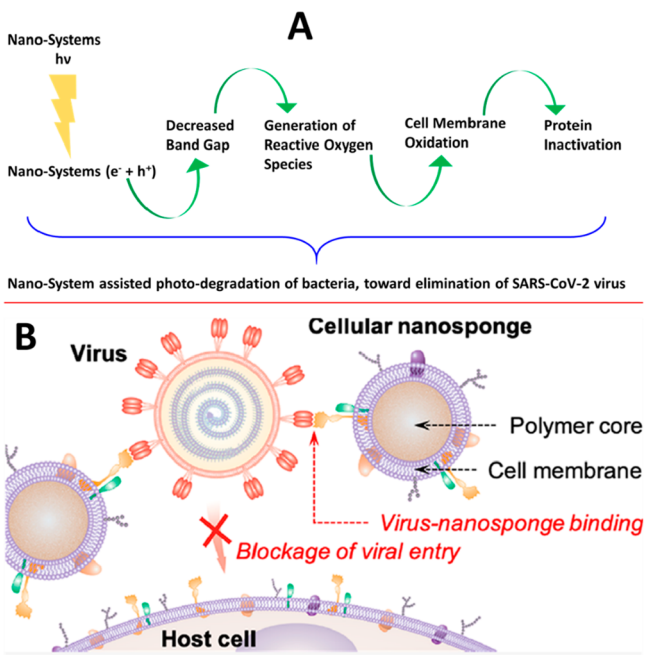


Figure 8. (A) Presentation of a nanoassisted photosensitive degradation of bacteria, a possible approach that can be scaled-up to remove virus particles from the air. (B) Development of cellular nanocage, wrapped by polymeric nanoparticle, for inhibiting SARS-CoV-2 infectivity. Reprinted from ref 54. Copyright 2020 American Chemical Society.

potential candidate for various photocatalytic applications. On photostimulation, nano-TiO_2 generates photocouple electrons which produce enough energy required to attack the weak sites of microorganism cells, enough to degrade them as a function of exposure time. Presently, sincere efforts are being made to investigate novel cost-effective and scalable TiO_2 nanosystems, via doping or generating functionality, to enhance photocatalytic efficiency with reference to a targeted field of applications.[50] These smart TiO_2 nanosystem can serve as a suitable coating material to eradicate biowarfare agents, weather they are indoor or outdoor. A similar working principle is demonstrated by Molecule Inc., with a claim that SARS-CoV-2 can be removed, degraded, or eradicate from indoor air. In addition, several other functional nanosystems have been investigated and are in the process of development for eradicating microorganisms on applying an optimized stimulation.[51−53]

Along with eradicating SARS-CoV-2 virus protein, another approach is to inhibit the entry of this virus via using an appropriate inhibitor, protein receptor, or receptor-/inhibitor-like nanosystems.[54] Such a nanosystem, namely, cellular nanosponges, has recently been fabricated using human microphages to inhibit the cellular entry of SARS-CoV-2 virus (Figure 8B). The result of a systematic study demonstrated the cellular nanosponges are agnostic to viral mutation and over time neutralize the SARS-CoV-2 protein to inhibit viral entry though the host cell. Besides inhibiting SARS-CoV-2 virus entry, the beneficial role of cellular nanosponges to treat inflammatory diseases were also claimed in this research.

The above-discussed advancements are very motivating to direct present and future research to investigate technologies needed to manage the COVID-19 pandemic. Significant efforts have been made to explore nanoscience technology in all of the possible directions to investigate novel approaches for recognizing and eradicating SARS-CoV-2 virus protein.[31,54−56] Among them, investigating sensitive, selective, and affordable analytical COVID-19 tools to detect SARS-CoV-2 are in demand to perform targeted and mass COVID-19 diagnostics.[41,57] The aspects and advancements in the field of developing sensing strategies to detected SARS-CoV-2 are discussed in the next section.

4. URGENCY OF EARLY STAGE COVID-19 DIAGNOSTICS

The COVID-19 pandemic is getting more serious due to the new continuously varying strain of SARS-CoV-2. Recent studies confirmed that SARS-CoV-2 virus infection is not only affecting the respiratory system but damaging major organs, mainly the lungs, brain, heart, kidney, and gut, along with effecting pregnancy,[58] child growth,[59,60] and the neurological system.[61,62] COVID-19 is transmitting mainly through H2H and aerosol and well-supported via traveling and social gathering. Thus, qualitative and quantitative detecting of SARS-CoV-2 becomes essential with the focus on mass and targeted testing.[41] Such a manageable COVID-19 diagnosis will help health experts to know how SARS-CoV-2 is progressing and varying under several conditions, for example—under the influence of weather, prescribed drugs (such as chloroquine, hydroxyquinol, and so on), and other diseases (such as tuberculosis, asthma, and heart problems, etc.) and in the setting of drug abuse and alcohol consumption. Keeping the above discussion in consideration, novel biomarkers for selective detection,[29] SARS-CoV-2 virus recognizing agents,[63] and miniaturized biomolecular assays can be factors for efficient diagnostics of the COVID-19 pandemic.[64]

When such multiparameters dependent COVID-19 diagnostics are present, timely, well-managed, and well-planned strategies to collect personalized bioinformatics for performing artificial intelligence to optimize therapy will be required. On the other hand, selective detection of SARS-CoV-2 is also

https://dx.doi.org/10.1021/acsabm.0c01004
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

required to establish a correlation between disease progression with the SARS-CoV-2 virus level for exploring pathogenesis. The main objective for this kind of bioinformatics collection and analysis using state-of-the-art technology is required for evaluating the efficacy of the developing drug against SARS-CoV-2 virus in order to investigate therapies that recognize, eradicate, and progress inhibition via blocking active sites.

It has been suggested that sometimes therapy does not exhibit efficacy due to a sudden increment in viral load. Taking this into consideration, real-time monitoring of SARS-CoV-2 virus level variation is recommended. In addition, it has also been observed that sometimes virus infection varies at a very low level which is undetectable using conventional diagnostics systems. Thus, to optimize therapy and estimating SARS-CoV-2 level variation, the development of an efficient sensor that can detect SARS-CoV-2 at a very low level is also one of the requirements while designing an analytical diagnostics system to manage the COVID-19 pandemic. Such analytical systems are urgently required to produce bioinformatics while keeping various categories such as gender, age, race, and georegion in mind. Such informatics can be used to implement AI-supported deep learning, machine learning, and the Internet of things/medical things (IoT and/or IoMT) in order to understand the pattern of the disease. Intelligent SARS-CoV-2 detection for early stage COVID-2 diagnostics is of high significance to explore patterning associated with genomic and strain variability as well. The best knowledge of the SARS-CoV-2 concentration correlation with population-based variabilities will certainly be useful to better understand this disease and optimize therapeutics in a personalized manner. The trends in COVID-19 diagnostics using state-of-the-art sensing technology are discussed in the next section.

5. STATE-OF-THE-ART COVID-19 DIAGNOSTICS STRATEGIES

According to WHO, RT-PCR is the only available method for COVID-19 diagnostics. Once the patient is screened out as COVID-19 positive regardless of the presence of a conventional respiratory pathogen, WHO and Chinese medical authorities are suggesting performing another test to monitor disease progression.[29] The RT-PCR is an effective procedure, but the requirement of a well-equipped laboratory and expert operator limits its application to manage the epidemic.[29] In several cases, health experts recommended a combinational approach, for example, RT-PCR in combination with CT-Scan/MRI to evaluate SARS-CoV-2 presence in human systems. Such approaches were useful to differentiate COVID-19 from pneumonia and dengue viral fever.[24] However, the executions of these recommended approaches are not possible in the case of pandemic management. Some of the approaches adopted to diagnose COVID-19 are discussed in this section.

At the beginning of the COVID-19 outbreak, it was very difficult to diagnose coronavirus-related respiratory infection due to its close similarity with pneumonia and other symptoms such as fever (98%), cough (76%), and myalgia or fatigue (44%). Due to the severity of the increasing effect, more precise techniques were introduced to investigate the reasoning. Chest radiographs were recorded (at days 3 and 8, from the onset of symptoms) of patients and showed bilateral lung consolidation due to SARS-CoV-2 infection.[65] To explore SARS-CoV-2 detection, the long-term CT-scan studies were recommended for COVID-19 epidemic understanding.[65] Chung et al. recorded the chest CT scans of 21 COVID-19 infected patients to evaluate the common and variable factors.[66] This analysis is required for the radiologist to identify early detection of SARS-CoV-2 for COVID-19 diagnostics. The finding of this study suggest that 57% of patients showed ground-glass opacities, 33% showed opacities with rounded morphology, 33% showed a peripheral distribution of disease, 29% exhibited consolidation with ground-glass opacities, and 19% showed noticeable crazy-paving pattern.[66] Li and Xia conducted a study based on chest CT scans to evaluate the effectiveness of the chest CT-scan approach for COVID-19 diagnosis (51 patients), in comparison to 2 patients affected by adenovirus.[67] The outcomes of this research suggest that CT scans exhibit more selectivity (missed diagnostics around 3.9%) and can successfully be adopted for rapid COVID-19 diagnostics and management. However, this approach is qualitative as it does not identify virus types and categories.[67] Thus, exploring other options which can perform rapid quantitative detection are also suggested to explore for COVID-19 diagnostic.

Besides the accomplishments of a CT scan, parallel efforts were also made to explore non-invasive bioassays for selective quantitative detection of SARS-CoV-2 virus protein. In this direction, the optimization is relevant and a biosample is crucial, and with the help of RT-PCR, saliva emerged as a real sample of choice to perform diagnostics. To et al. researched ways to detect SARS-CoV-2 using RT-PCR in the self-collected saliva of 12 patients.[68] The outcomes of this research confirmed that SARS-CoV-2 infected epithelial cells in the salivary gland, although further studies were recommended to evaluate the role of saliva secretion pathways and viral load. Overall, saliva-based testing would be preferable to manage COVID-19 because it can be collected easily in enough quantity, without risk of nosocomial transmission to perform the desired testing.[68] Ai et al. explored a combinational approach to analyze RT-PCR assay and chest CT imaging of 1014 COVID-19 positive cases in China.[69] The findings of this research concerning RT-PCR show that CT imaging exhibited sensitivity of 97% (580/601). Several other findings are showing RT-PCR negative but chest CT scans positive (n = 308 patients). As an outcome, 48% of patients were reconsidered to re-examine and 33% of patients were probable cases as evaluated through a comprehensive evaluation. Chest CT scanning exhibited higher sensitivity than initial RT-PCR for COVID-19, diagnostics performed with swab samples, but it is a time-consuming procedure and requires expertise and an equipped laboratory and therefore is limited in its ability to manage a pandemic. However, this technique is very useful in high risks in COVID-19 areas.[69]

6. FDA APPROVED MINIATURIZED COVID-19 DIAGNOSTICS SYSTEM

The Food and Drug Administration (FDA) of the USA and other international health agencies understood the urgent need for developing the COVID-19 diagnostic system and revised their approval policies to expedite the development and clinical applications. The Becton, Dickinson, and Co. and a global leading biomedical technology company (BioGX Inc.) developed a molecular COVID-19 diagnostic system (with results within 3 h) that received FDA and Emergency Use Authorization (EUA) to manage the pandemic. This BioGX molecular diagnostics system, a kind of real-time PCR detection method, targets viral RNA sequences (present in

https://dx.doi.org/10.1021/acsabm.0c01004
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

SARS-CoV-2) for selective diagnostics of COVID-19. Such a miniaturized system has the potential for hospital use as it is fully automated and can process 24 samples at the same time.[70] A POC system developed by Cepheid's GeneXpert received FDA and EUA approval for COVID-19 diagnostics. This device has a cartridge-based design which contains all the necessary reagent to perform rapid detection of SRAS-oV-2 within 45 min. This company is working closely according to the norms of the FDA to improve performance, validation, and translation for clinical and hospital use.[71]

Healgen Scientific developed a COVID-19 diagnostics kit based on the COVID-19 IgG/IgM working principle and is getting FDA and EUA approval to detect the DNA of SARS-CoV-2 present in the bloodstream in 15 min. This diagnostics kit is selective and in practical use in China, Singapore, and Taiwan. This testing is serological and confirms the presence of antibodies (developed by SARS-CoV-2 virus) in the patient's blood. However, its global clinical application will take a significantly long time due to a multistep testing procedure with the need for some big caveats. Although this device is performing well, its emergency use has been approved by FDA and the device performance outcomes are under FDA assessment criteria.[72] FDA approved a POC diagnostics system developed by Abbot, a healthcare technology producer, which produces the Abbott ID NOW COVID-19 test. This lab-in-a-box is portable and detects the virus RNA of COVID-19 infected patients in 5 min without using the sophisticated laboratory to perform COVID-19 testing. However, this POC system is not commercially available yet and the company is exploring translational and marketing aspects to promote this technology for clinical application.[73]

Recently, the Indian Council of Medical Research (ICMR) also approved a confirmatory diagnostic system for COVID-19 diagnostics via detecting the N Gene of SARS-CoV-2 using reverse transcriptase loop-mediated amplification of viral nucleic acid (RT-LAMP) within 2 h.[74] This RT-LAMP kit, developed by the Sree Chitra Tirunal Institute for Medical Sciences and Technology and supported by the Department of Science and Technology (DST), Government of India, is specific to two regions of the gene present in the SARS-CoV-2 virus structure. Such two-sites-based detection introduced selectivity in diagnostics, especially when SARS-CoV-2 is showing mutation and train variation. The Chitra Gene LAMP-N gene-based COVID-19 kit is affordable, enables rapid diagnostics (detection time as 10 min and RNA extraction along with testing within 2 h), and performs confirmative testing without a screening test cost. This system was tested on 30 samples in a batch at the same time, and the observed results were acceptable.[74] The Indian government is making efforts for scaling up and promotion of this kit for clinical application.

Despite the significant outcomes mentioned above, FDA approved COVID-19 diagnostics systems are not capable enough to manage a pandemic due to a lot of variabilities in virus structure, disease systems, and the need for big bioinformatics to understand and manage the disease. Thus, health experts suggested mass and targeted sensing of SARS-CoV-2 at a site of interest. Such diagnostics can be achieved using nanotechnology and a smart-technology-assisted approach, which are discussed in the next section.

7. NANOENABLED BIOSENSING FOR MANAGING CORONAVIRUS INFECTION DISEASES

7.1. Nanoenabled Detection of SARS and MARS. Since 2002, the coronavirus has stricken mankind several times and caused loss of lives and added economic burden to individuals and governments. To manage the coronavirus epidemic, the design and development of a smart sensor were recommended. These sensors appeared as one of the potential solutions to provide cost-effective and rapid diagnostics of SARS and MERS infection. Over time systematic efforts were made to make such sensors more effective via introducing miniaturization and nanotechnology. The introduction of nanotechnology enables sensing of SARS and MERS at a very low level. In addition, miniaturization makes these sensors suitable for on-site diagnostics application.[75]

A microcantilever array technology-based sensor was fabricated by Velanki and Ji to detect SARS-CoV-1. This system detected feline coronavirus (FIP) type I virus using a very specific feline coronavirus (FIP) type I antiviral antiserum.[76] In this sensing approach, a type I virus-positive sample was injected into the fluid cell holding a microcantilever. The target analyte produced microcantilever bends due to the recognition of the virus by the antiserum available on the microcantilever surface. To confirm sensing, a few samples which do not contain a virus were also used as a negative control. As a result, no microcantilever bends were obtained in this situation. This sensor exhibited a detection limit as 0.1 μg/mL, and the detection time was observed as <1 h. This sensor exhibited the potential to be used as an analytical tool for detecting SARS but needs more study related to the translational approach for clinical application.[76]

Zuo et al. utilized horse polyclonal antibody to fabricate a piezoelectric immunosensor to detect SARS-CoV-1 in sputum in the gas phase.[77] In this research, antibodies selective to SARS-CoV-1 was immobilized onto a PZ crystal surface. The target analyte of SARS-CoV-1 was atomized into an aerosol by an ultrasonator. In this process, the antibody on the crystal absorbed SARS antigen specifically which changed the mass of the crystal and eventually led a frequency shift. Such a developed piezoelectric sensor detected SARS with a linear range that varies from 0.6 to 4 μg/mL. This was reproducible 100 times without losing sensing ability and stable for 60 days at 4−6 °C, and detection time > 2 min. Despite the remarkable performance, the authors suggested focusing more on stability and precision before promoting it for clinical application.

To improve the sensing performance, the role of nanoscience and nanotechnology was emerging as one of the best solutions to manage COVID-19 via selective detection of the virus protein. Keeping these aspects in mind, various electroactive smart nanostructures were investigated to fabricate a biosensor.[78] Ishikawa et al. fabricated a nanowire-based label-free electrochemical sensing of the N-virus protein of SARS Virus N-Protein using an antibody mimic protein (AMP) approach (Figure 9A).[78] In this research, In_2O_3 nanowire was utilized as an antibody immobilizing platform to design nano-biosensors. The AMP (Fibronectin, Fn) was used for selective detection of nucleocapsid (N) protein of SARS at nM concentration. The authors recommend testing this developed sensor using real samples and biological complex systems involving antibodies, antigen, protein, ligand, and oligonucleotides, etc. Over time, it was also reported that developing fluorescent and colorimetric assays could be one

https://dx.doi.org/10.1021/acsabm.0c01004
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

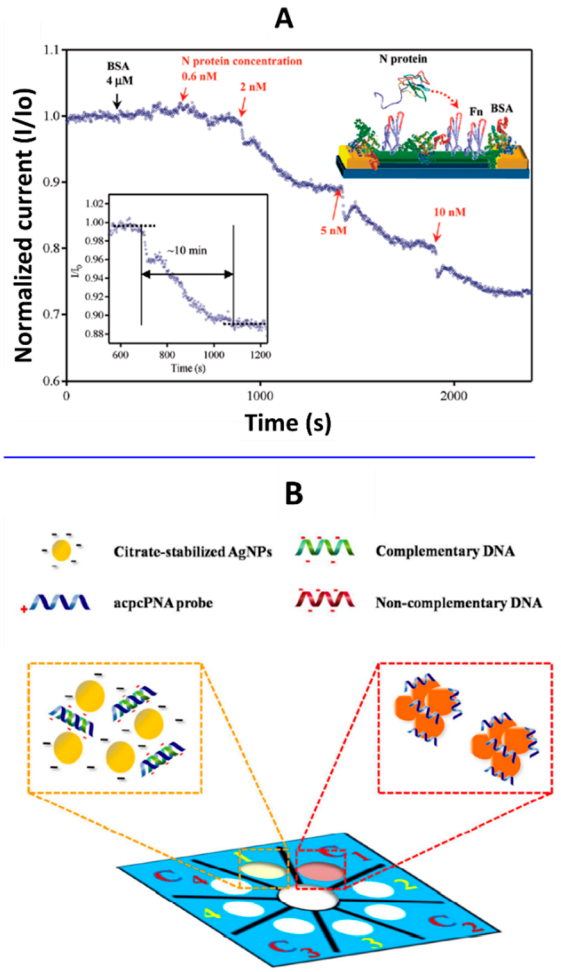


Figure 9. (A) Label-free sensing of SARS using In_2O_3 nanowire-based biosensor. The variation in electric response was observed as a function SARS virus level. The sensing principle was based on AMPs and BSA was used to block nonspecific binding Reprinted from ref 78. Copyright 2009 American Chemical Society. (B) Illustration paper-based multiplex sensing chip fabrication process using acpcPNA-induced AgNP aggregation in the presence 201 of DNA complementary and DNA noncomplementary. Reprinted with permission from ref 79. Copyright 2017 American Chemical Society.

such approach to detect DNA and RNA for point-of-care applications. Teengam et al. developed a paper-based colorimetric assay for detecting DNA associated with MERS-CoV, *Mycobacterium tuberculosis* (MTB), and human papillomavirus (HPV), as illustrated in Figure 9B.[79] In this research, the authors used a positively charged pyrrolidinyl peptide nucleic acid (acpcPNA) due to attachment with the C-terminal of lycin as a probe and silver (Ag) nanoparticle and as a calorimetric sensing reagent. The variation in Ag nanoparticle dispersion in the presence/absence of target DNA led to the color change. Such fabricated paper-based colorimetric DNA sensors exhibited selectivity against a single-base mismatch, two-base mismatch, and noncomplementary target DNA. This sensor exhibited a low detection of limit as 1.53, 1.27, and 1.03 nM concerning MERS-CoV, MTB, and HPV, respectively. The author claimed this developed system as one of the potential alternates of available state-of-the-art technology due to low cost and multiplex detection, but said this sensor would be more effective if multiplex detection were optimized to detect viruses of the same category as Ebola, Zika, and other coronaviruses, etc.[79]

A 2D nanosheet of molybdenum disulfide (MoS_2) was utilized to develop a fluorescent biosensor to the detection of the infectious bronchitis virus (IBV).[80] The IBV is an avian coronavirus that is known to affect the performance of egg-laying and meat-type birds causing substantial economic loss in the poultry industry. A MoS_2 nanostructure based fluorescent immunosensor was fabricated using a selective antibody for IBV detection (Figure 10A). This flexible optical sensor, fabricated on the low-cost cotton-thread-based microfluidic manifold, performed on the bases of fluorescence resonance energy transfer (FRET) between the nanosystem and fluorescence dye during the formation of Ab−antigen immune−complex formation. The authors optimized operational conditions of IBV sensing, and the sensor exhibited a sensitivity as 4.6×10^2 EID50/mL, with the detection range varying from 10^2 to 10^6 EID50/mL. Further, this sensor was tested using a real sample of chicken serum which proves its application in the field of poultry farming. However, this sensor was not designed to detect coronavirus considering the application for diseases and diagnostics in humans.

7.2. Nanoenabled Biosensor for SARS-CoV-2 Detection. It has been demonstrated that the SARS-CoV-2 virus has mutated and shown numerous strains under categories regarding country, region, race, and age, etc. Thus, exploring aspects of nanobiotechnology to investigate miniaturized diagnostics systems of selective SARS-CoV-2 detection is a key component to manage COVID-19. In this direction, Broughton et al. designed a lateral flow assay using the CRISPR−Cas12 gene to detect SARS-CoV-2 virus protein selectively within 40 min.[81] This miniaturized bioassay detected known SARS-CoV-2 protein concentrations (1−5 fM) and further validated using respiratory RNA extracts swabs of 36 COVID-19 infected and 42 other virus-infected patients. The CRISPR-based test exhibited sensing at a low level (10 copies/μL input) faster SARS-CoV-2 detection than FDA approved real-time RT−PCR assay with 95% selectivity (regarding E and N genes) and 100% negative with reference to non-COVID-19 infected patients. CRISPR-based design of the Cas-12 gene provides selectivity and portability seems useful for POC applications.[81] However, with significant efforts toward device packaging, the introduction of the microfluidic unit for automated sampling and testing based a greater recommended number of patient investigators of this research promoted a CRISPER-Cas-12-based approach for COVID-19 diagnostics for clinical application.

Well-supported by outcomes with nanotechnology-assisted SARS and MERS sensing, efforts are seriously being made to develop efficient and effective nanoenabled optical and electrical SARS-CoV-2 biosensors. In this direction, Qui et al. developed a dual-functional plasmonic SARS-CoV-2 gene sensor which functions on the basis of combined features of plasmonic photothermal (PPT) effect and localized surface plasmon resonance (LSPR) based transduction (Figure 11A).[82] Such a combinational sensing approach was useful to achieve selectivity which is desired for diagnostics of COVID-19 at clinical application. In this research, the 2D nanostructure of gold (Au), utilized as a plasmonic platform, functionalized with a complementary DNA to detect a specific sequence of SARS-CoV-2 based on the concept of gene hybridization. During sensing, the thermoplasmonic heat generated by Au, on illumination at an optimized frequency

https://dx.doi.org/10.1021/acsabm.0c01004
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

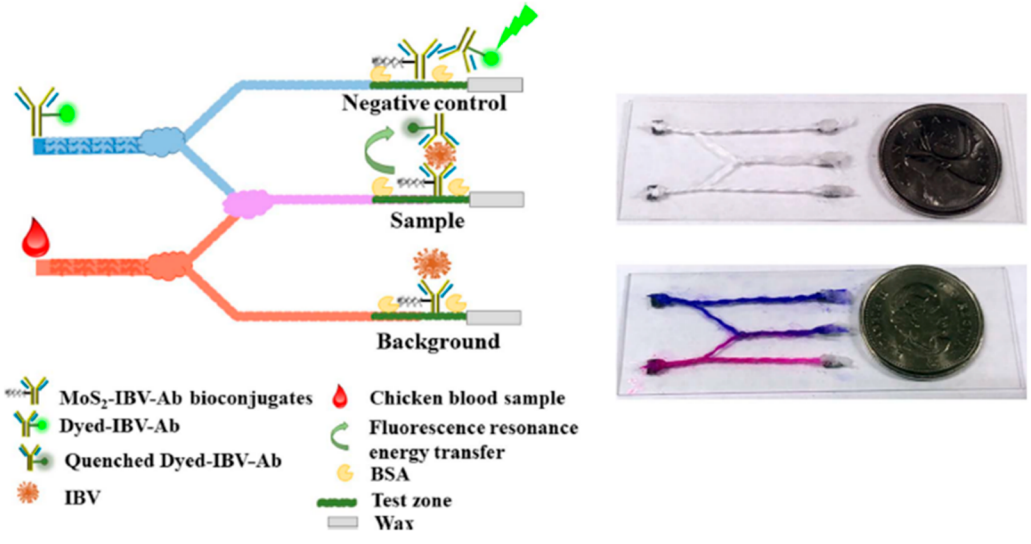


Figure 10. Schematic presentation immunosensor fabrication and cotton thread microfluidic. On integration, this sensor detected IBV selectively at 4.6×10^2 EID50/mL. Adapted with permission from ref 80. Copyright 2018 The Authors under Creative Commons Attribution 4.0, published by IEEE.

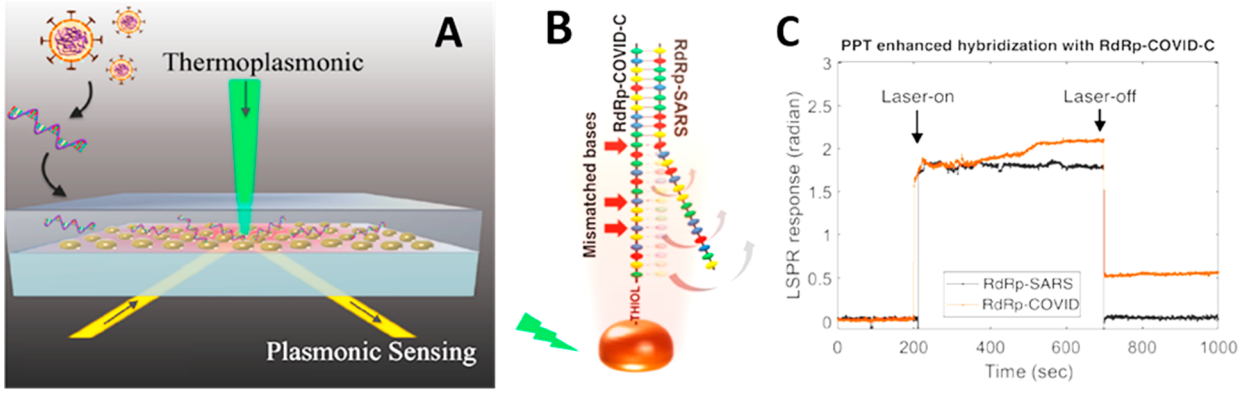


Figure 11. (A) Plasmo-photothermal-based biosensor for selected viral sequences for SARS-CoV-2 detection. (B) 2D nanoisland of Au serving as an immobilizing platform to formulate a thiol-cDNA ligand. (C) Real-time monitoring of AuNI response on adding 0.1 nmol of cDNA and ability to demonstrate discrimination between two related and almost similar sequences. Reprinted with permission from ref 82. Copyright 2020 American Chemical Society.

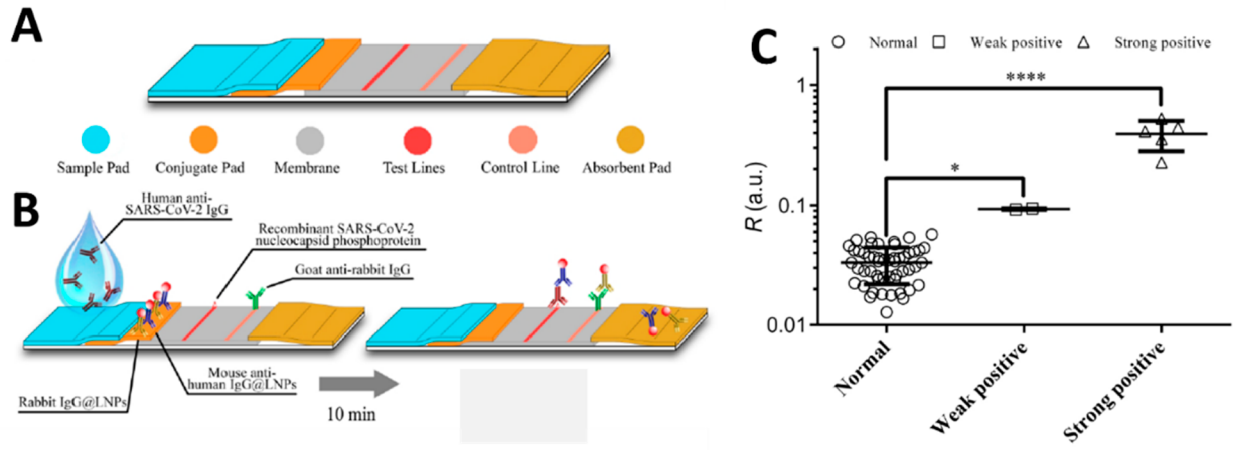


Figure 12. Representations of LTR flow-based bioassay for selective detection of SARS-CoV-2 detection (A, B). For testing 58 serum samples (51 normal and 7 infected) bioassays utilized and developed successfully differentiating the samples (C). Reprinted from ref 83. Copyright 2020 American Chemical Society.

https://dx.doi.org/10.1021/acsabm.0c01004
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

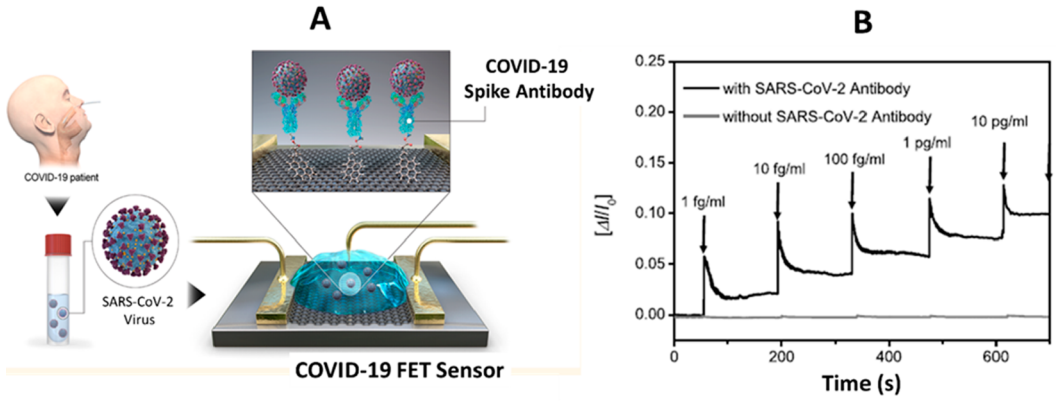


Figure 13. Schematic presentation of FET-based SARS-CoV-2 biosensor, wherein graphene was utilized as gate material (A). Specific monoclonal anti-SARS-CoV-2 antibody selected for sensing ranging from 1 fg/mL to 10 pg/mL (B). Reprinted with permission from ref 84. Copyright 2020 American Chemical Society.

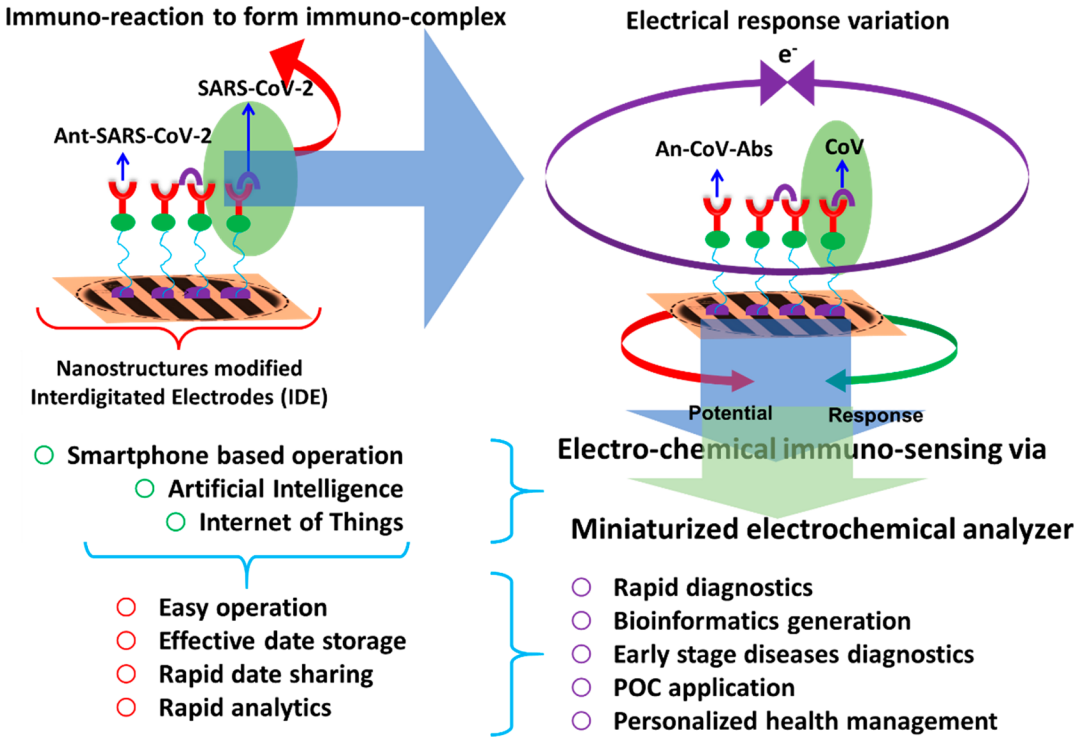


Figure 14. Schematic presentation of electrochemical SARS-CoV-2 immunosensing in the physiological range. Such sensitive smart SARS-CoV-2 sensing platforms can be interfaced with microelectronic and AI-supported IoT for rapid and selective COVID-19 diagnostics required for pandemic management, having personalized and intelligent health care as the focus.

facilitates an in situ hybridization required for accurate discrimination between gene sequences. This sensor exhibited a very low detection limit as 0.22 pM and selective SARS-CoV-2 detection even in the multigene mixture.[82] Such systems are new and need supportive studies and validations before suggesting their application as potential COVID-19 diagnostics tools.

A lateral flow immunoassay (LFIA) fabricated using a lanthanide-doped polystyrene nanosystem based rapid (10 min) and sensitive bioassay was developed by Chen et al. to detect anti-SARS-CoV-2 IgG for COVID-19 diagnostics in human serum (Figure 12).[83] A nitrocellulose membrane was utilized for IgG A capturing through recombinant nucleocapsid phosphoprotein of SARS-CoV-2 and self-assembled nanosystem labeled with mouse antihuman IgG antibody worked as a fluorescent readout. To promote clinical application, this sensor was validated using real samples (1:1000 dilution) of COVID-19 infected 12 patients. The sensing performance of this sensor was also tested involving 51 normal samples. The testing performance of this device was validated using RT-PCR, and outcomes of both techniques were in a good match. This COVID-19 diagnostic platform meets the clinical challenges and can be part of COVID-2 infection disease management due to selectivity, cost effectiveness, and portability.[83] However, its testing using a greater number of COVID-19 infected patients is also recommended. Seo et al. developed a field-effect-transistor (FET)-based biosensor for rapid detection of SARS-CoV-2 protein in nasopharyngeal swab specimens of COVID-19 infected patients (Figure 13).[84] In this research, graphene sheen was fabricated as gate

https://dx.doi.org/10.1021/acsabm.0c01004
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

materials to design a FET and a specific monoclonal antibody against the SARS-CoV-2 spike protein was utilized for selective diagnostics of COVID-19. Such a FET-based electrical SARS-CoV-2 sensor exhibited a detection limit as 1 fg/mL in the presence of phosphate-buffered saline (100 fg/mL) and ion transport mediator. Moreover, this sensor exhibited a limit of detection of 1.6 × 101 pfu/mL using a known concentration of virus protein and 2.42 × 10^2 copies/mL in the case of clinical samples. As one of the major advantages, COVID-19 diagnostics using this system will not require any pretreatment and labeling.[84] However, validation of this sensor based on a great number of COVID-19 infected patients is recommended prior to adopting this at a clinical facility.

The nanoenabled miniaturized biosensor mentioned above had shown significant contribution in the field of developing smart and desired diagnostics of COVID-19 via sensitive and selective detection of SARS-CoV-2. These developments also expressed the approach of POC application with high significance. So far available biosensors are multicomponent systems which make optimization and validation of a developed system very challenging. Thus, it has been recommended by biomedical engineers that a diagnostics biosensor should be the least component unit for effective and interfering with less sensing. Among various types of sensors, electrochemical sensors are emerging as a diagnostics tool of choice.[75,85−87] These systems can perform sensing at POC as well.[87] Due to advancements in smart materials science microfluidic systems, electrochemical biosensors can detect a target analyte at picomolar levels to manage an infectious disease caused by the epidemic.[88]

With these aspects being kept in mind and on the basis of our expertise in developing an electrochemical zika virus sensor,[88,89] we purposed the development of nanoenabled biosensors which can detect SARS-CoV-2 at the picomolar level even at POC application (Figure 14). To develop an electrochemical SARS-CoV-2 biosensor, it is recommended to adopt and optimize an immunosensing approach. The ongoing efforts to develop a biomarker to optimize pathogenesis and recognition of SARS-CoV-2 protein also required the development of monoclonal antibodies for selective performance. Such developed antibodies can be useful to develop an electrochemical immunosensor for selective detection of SARS-CoV-2 in the real samples. Considering scaled-up production, it also recommended investigating a disposable immunosensing chip which is cost effective and does not require sophisticated equipment for storage. To make such a sensor more efficient, nanoparticles modified substrate or interdigitated electrodes are also recommended to amplify signals to achieve low detection limits and a wide sensing range. Such a SARS-CoV-2 sensing chip can be integrated with a miniaturized potentiostat interfaced with a smartphone to perform on-site COVID-19 diagnostics. The smartphone-based sensing will be very much useful for performing diagnostics at the site of infection, i.e., POC application. This approach is also very useful for rapid data analysis, safe data storage, and remote data sharing with health experts. The Internet of things (IoT) will expedite diagnostics and therapy optimization. Introduction of IoT will manage the generation and securing of bioinformatics that will need AI to analyze the several optimized relationships between SARS-CoV-2 protein level with individual pathogenesis. These outcomes will certainly be useful for exploring the best therapy as per the patient genomic profile.

8. ARTIFICIAL INTELLIGENCE-ASSISTED APPROACHES FOR COVID-19 PANDEMIC MANAGEMENT

It has been suggested by experts that if there is a vast bioinformatics collection related to the COVID-19 pandemic and its rapid analysis, then it is crucial to investigate AI for intelligent healthcare. There are some AI-based systems designed and developed to predict which Covid-19 patients will become critically ill, even as many are struggling to validate the tool's effectiveness on those with the new disease. The effects of SARS-CoV-2 are associated with socioregional aspects such as country, region, race, gender, and age, etc. Smart technology is required which can perform in all of these aspects to optimize diagnostics, therapeutics agents, and optimization of prediction. To manage the COVID-19 pandemic, AI-supported deep learning, machine learning algorithms, and IoT approaches have emerged collectively to combat against SARS-CoV-2. Taiwan is using this technology at the front line to explore big data analysis, new technologies, and proactive testing, as reported by Wang et al.[90] The outcomes of this research were useful to recognize pandemic zones, optimization of resources, and understanding of emergency and timely diagnosis decisions. Such smart use of technology was sensitive population oriented and helped the government for making necessary decisions to decide the plan of action and policies. Taiwan set up an example to manage the COVID pandemic with a combinational approach, using both the smartphone-based technologies and the support of people. Some of the recent developments in AI-based COVID-19 pandemic are discussed below.

Song et al. reported that IoT-based combinational approaches to involve sensors, sharing informatics, AI, and dynamic networking devices was very useful to health workers to evaluate COVID-19 full spectrum perception, reliable transmission, and intelligent processing.[91] These IoMT devices have demonstrated several advantages as follows: (i) rapid leaning and certifying a high-quality guideline application; (ii) systematic and desired management of suspected patients; (iii) management of a sensitive population who may need medical consultations to improve success rates; and (iv) control over aspects. Prior to recommending them for medical application, several recommendations are suggested to resolve the following tasks as follows: (i) improved and adoptable interoperability (this is required to establish good communication between numerous open standards and products of different manufacturers); (ii) ensuring no leakage; and (iii) enhancement in the istribution network, specially sensors-based services which are urgently required for remote health workers. Presently, sincere efforts are being made to resolve these challenges for developing advanced IoMT systems which can be useful to improve current telemedicine. These devices are can be coupled with smartphones and programmed concerning a targeted disease, and yes COVID-19 pandemic can be one example. COVID-19-related IoM seems a smart platform designed to achieve easy to prevent/diagnose/treat diseases/communicate with experienced doctors.[91] Keeping easy and real-time operation in view, IoM technology can be a part of the medical center cloud system for COVID-19 management.

Experts suggested that anti-COVID-19 therapy development will certainly take time; thus monitoring of this pandemic has made using AI-assisted smart technology essential. To

https://dx.doi.org/10.1021/acsabm.0c01004
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

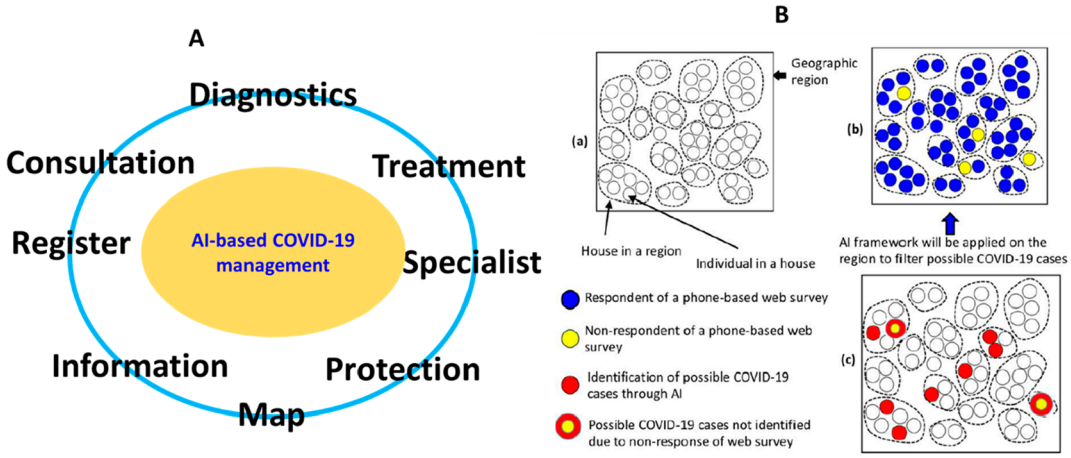


Figure 15. Various AI-supported approaches investigated for COVID-19 management. (A) Illustration of nCapp, a cloud-based terminal, supported diagnostics, tracing, and treatment, etc., needed for COVID-19 management. (B) Presentation of a conceptual framework developed for various data collection and COVID-19 identification considering geographical region-based approach including city, county, town, village, or households (a); respondents- and nonrespondents-based cloud-assisted survey (b); and probable identification of COVID-19 infection people regarding respondents and nonrespondents-based survey outcomes (c). Reprinted with permission from ref 95. Copyright 2020 The Society for Healthcare Epidemiology of America under Creative Commons License 4.0.

understand disease spreading patterns, the smartphone is emerging as one of the best technology platforms to collect bioinformatics, which is also required for diagnostics and diagnosis points of view. This seems an executable approach, especially in the case of a lockdown, because most of the population carry a smartphone. For example, Allam and Jones presented the concept of Smart City Network which is useful to monitor the COVID-19 pandemic in the case of a lockdown. This AI-assisted contact tracing-based approach is useful to share national policies, educate people, standardize national protocols, and share health data, leading to better global understanding and management of COVID-19.[92] As the COVID-19 outbreak emerged as a serious pandemic, besides exploring specific diagnostics and therapeutics, health experts suggested social distancing, staying at home, and being quarantined in suspected cases, to cut the human-to-human transmission. Keeping this in view, Dandekar explored machine learning to quantify the effect of quarantine control in COVID-19 infectious spread.[93] In this research, a neural network augmented model was developed to interpret and extrapolate public health data available at Wuhan, China; Italy; South Korea; and the USA. The outcomes of the data analysis were compared with the parameters associated with quarantine and isolation measures, i.e., the reproduction number R_t of the virus. The outcomes of this research suggested that countries that executed rapid interventions and strict public health measures such as testing and reporting for quarantine and isolation were able to significantly control the virus spreading.

Bai et al. proposed a COVID-19 intelligent diagnosis and treatment assistant program (nCapp) based on IoT-assisted intelligent diagnostics along with treatments to manage COVID-19.[94] This team explored automated analysis based on real-time communication to manage data, questionnaires, analysis, and diagnosis-related bioinformatics. The outcomes of this programming were useful for knowing whether someone suspected to have infection did or for concerns that a COIVD-19 infected patient has a mild, moderate, severe, or critical pneumonia scenario. The nCapp enables real-time database update and predicting the appropriate diagnosis model of best accuracy (Figure 15A). Such systems are useful for front-line health workers for rapid diagnostics and long-term follow-up needed for better understanding of disease progression, to evaluate the effects of therapy and physicians and to examine the postinfection effects.[94] Besides, smartphone-assisted implementation of nCapp can be useful to avoid COVID-19 spreading via blocking human-to-human transmission. In this way, we can block disease transmission, avoid physician infection, and epidemic prevention and control as soon as possible. Srinivasa Rao developed machine learning-based algorithms, for a person under investigation (PUI), for quicker identifications of COVID-19.[95] This approach is smartphone based and involves a web-based survey based on basic information such as travel history. The outcome of this approach can successfully reduce the diseases spreading in sensitive populations. Thousands of data points collected using this method can be processed through AI for the early stage screening and identification of COVID-19 infected patients (Figure 15B). The outcomes of this approach, recommended during quarantine, are useful to predict all kinds of risks factor, for example, no/minimal/moderate/high risk associated with COVID-19 pandemic.[95]

It is confirmed that available anti-COVID-19 drugs have limited therapeutic properties and exhibit some adverse effects to lung and heart. In the present scenario, these drugs are in practice and have raised the demand of smart technology for the design and development of effective and efficient drugs which target only SARS-CoV-2 specifically with side effect. In this direction, a deep-learning-based approach was investigated by Zhang et al. for screening available drugs for effective treatment of COVID-19.[96] In this model (DFCNN), RNA sequences were collected from the GISAID database to explore related 3D protein sequences modeling using homology modeling. The DFCNN explores possible protein−ligand interactions of high accuracy to perform drug screening without using docking or molecular dynamics. This protease-based modeling successfully identified 4 chemical compound databases and confirmed that peptides-based drugs exhibited good stability, the desired bioavailability, and negligible immune responses.[96]

https://dx.doi.org/10.1021/acsabm.0c01004
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

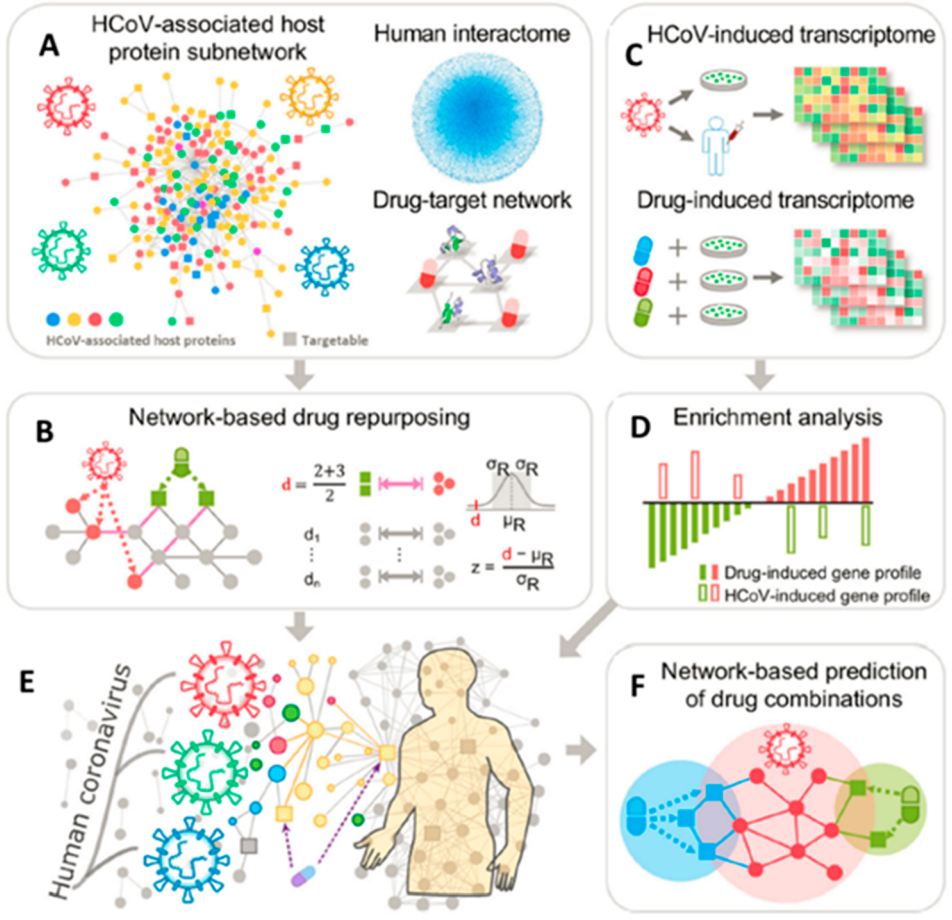


Figure 16. Network-based methodology based on a protein−protein network involving (A) HCoV-associated host protein collected from literature and pooled to generate a pan-HCoV protein subnetwork, (B) screening of potential repurposable candidates via analyzing network proximity between targeted drugs and proteins associated with HCoV, (C, D) validation of network-based predictions using gene set enrichment analysis, (E) network-based prediction of optimized drug combination using complementary exposure pattern, and (F) hypothesis illustration of the network-based methodology to explore PPI based on human interactome. Reprinted with permission from ref 97. Copyright 2020 The Authors via Creative Commons License 4.0, published by Springer Nature.

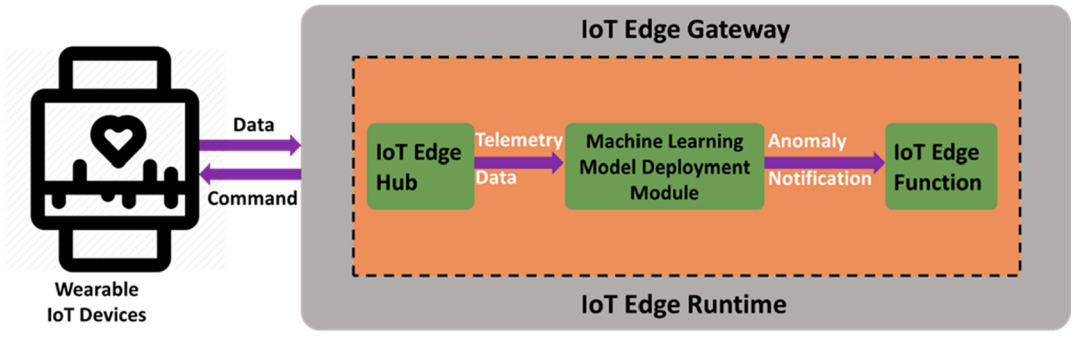


Figure 17. Deployment of the machine learning model on IoT Edge Gateway.

In this unprecedented situation, sincere efforts are being made to explore drug repurposing, an effective drug discovery approach using existing drugs. This approach is very cost effective and recommended to optimize timely therapy. In this direction, Zhou et al. developed a network-based approach to identify an optimized drug combination to combat against the COVID-19 pandemic.[97] This approach developed a pharmacology-based network medicine which quantifies the interplay between human coronavirus/SARS-CoV-2-host molecular interactions interactome and possible drug targeting sites in a protein−protein interaction network (Figure 16).[97] In this research, detailed phylogenetic-based analyses of 15 human coronavirus genomes confirmed that COVID-19/SARS-CoV-2 exhibit a major nucleotide sequence with reference to SARS-CoV-2 as 79.7%. Using this model, 16 potential anti-COVID-19/SARS-CoV-2 repurposable drugs were recommended which were further validated using enrichment analyses based on drug−gene signatures and virus-induced transcriptomics. Besides, three potential drug combinations as follows, (i) sirolimus plus dactinomycin, (ii) mercaptopurine

https://dx.doi.org/10.1021/acsabm.0c01004
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

plus melatonin, and (iii) toremifene plus emodin, were identified using complementary exposure pattern.[97] The outcomes of this research project were suitable for the rapid identification of a therapeutic drug/or drugs needed for perfect targeting of COVID-19/SARS-CoV-2.

The current healthcare industry is rapidly adopting IoT- and AI-based new technology for intelligent healthcare management. As illustrated in Figure 17, technological integration of IoT, Edge, and machine learning, a branch of AI, can demonstrate predictive capabilities, the deployment of a predictive model on the cloud or edge. This system tries to avoid or mitigate the impact of unexpected changes happening on the IoT device and observes the anomalies, using machine learning, occurring on the device. In addition, this system is capable of identifying anomalies at the IoT Edge instead of the IoT Cloud and will notify one about the necessary action. This is to reduce or avoid communication latency to the cloud so that critical decisions can be implemented right away at the edge by deploying AI models. Efforts are sincerely made to explore these devises for COVID-19 management via predicting diseases' patterns, assessing therapy, spatial impact, personalized assessment, and easy connection with health centers, optimizing timely therapy, and many others.

9. VIEWPOINT

Health agencies and experts have confirmed that adverse effects, mainly loss of lives, related to the COVID-19 pandemic maybe got worse than yesterday.[29] This is because of the new SARS-CoV-2 strain and unavailability of therapy along with lacking effective diagnostics tool.[6] The COVID-19 respiratory diseases are spreading faster than the productive efforts made by health agencies and governments.[1] This virus spread via H2H and traveling, also another factor of the rapid spreading of viruses from big cities to a small village. This situation makes COVID-19 pandemic management very difficult because small villages do not have well-equipped laboratories for timely diagnostics.[57,83,98−100] These challenges have raised the demand for investigating novel nanoenabled sensing approaches for rapid and selective SARS-CoV-2 detection at the site of infection.[101] Scientists of various expertise are requested to work together to design and develop a miniaturized sensing system which can perform POC diagnostics. These systems should be cost effective, selective, and able to detect SARS-CoV-2 at the picomolar level. The low-level detection of SARS-CoV-2 is also required to understand the COVID-19 progression while a patient is under prescribed therapy.

It is also known that smartphone-based operation made operation and application of a biosensor more in accord with a patient's requirements. Such a user-friendly approach made multiple times testing very easy in a day.[89,102,103] In this approach, more data, such as bioinformatics, can be collected which can be managed using IoT technology for better understanding and analysis of COVID-19 progression and control. Besides, AI including deep learning and machine learning approaches is required to investigate the algorithm for big data analysis.[87] The outcomes of such analysis are required to explore the correlation between the SARS-CoV-2 level and patient pathogenesis. This correlation will be useful to design and develop new therapeutics according to race, location, gender, and age. Besides, IoT-AI-assisted bioinformatics analysis is required to optimize the best appropriate biomarkers for developing novel and smart COVID-19 diagnostics tools.[1] On having the best combination of sensing prototype, device engineering, IoT, and AI, such a COVID-19 diagnostics system will be capable of early stage diagnostics, disease progression under therapy, and epidemic management according to patient profile (Figure 18).

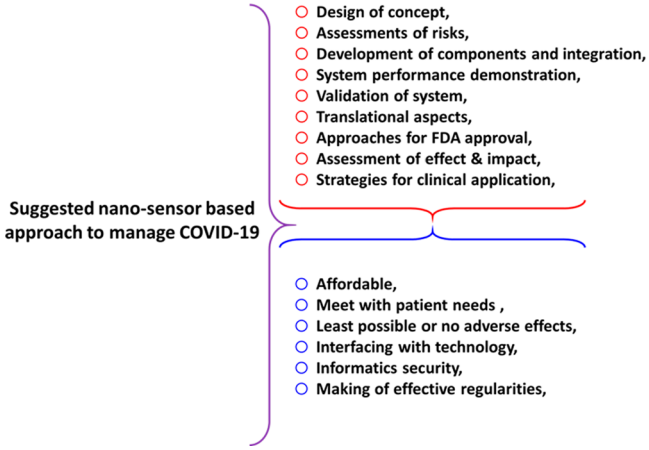


Figure 18. Systematic planning and execution of steps suggested by developing a nanosensor for early stage COVID-2 diagnostics.

However, optimization of the operation parameter, integrating a sensing chip with micro-/nanoelectronics, and interfacing of the sensing platform with a smartphone, optimizing sensing system performance at POC applications, data-related aspects (collection, sharing, storage, and safety), big data analytics, correlation of SARC-CoV-2 levels with pathogenesis, therapy optimization, and timely therapy decisions are the very challenging aspects to consider in developing a smart sensing platform for COVID-19 pandemic management. However, AI-assisted predictions related to COVID-19 pandemic have been found to be inaccurate or nonreliable due to too much outlier data and noisy social media, big data hubris, and algorithmic dynamics. This is the reason experts avoid AI-based modeling and prefer established epidemiological models, namely, SIR models standing for the population sensitive to SARS-CoV-2 infection. Developing such as smart sensing system is a multidisciplinary approach and requires public−private involvement. Stepwise planning and execution of every aspect, as illustrated in Figure 18, associated with developing a SARS-CoV-19 sensor is crucial for the timely development of COVID-19 diagnostics for clinical and POC applications.

10. CONCLUSIONS

This review summarizes the seriousness, demand, and high significance of developing a nanoenabled electrochemical biosensor for COVID-19 diagnostics at POC application. Overall, the smart sensor for SARS-CoV-2 virus protein detection, as discussed carefully and critically in this report, is a required technology for managing the COVID-19 pandemic and analyzing consequences via collecting and analyzing bioinformatics to investigate therapeutics, even in a personalized manner. Having multimodel approaches for consideration, AI-supported nanoenabled biosensing strategies assisted by IoT designed and developed for application can successfully be adopted for expedite diagnostics and bioinformatics-based big data analysis needed for timely decisions. With such intelligent healthcare approaches being recommended by health experts on an urgent basis, therefore significant efforts, supported by

https://dx.doi.org/10.1021/acsabm.0c01004
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

public−private cooperation, are required to promote advanced research in the direction of developing a nanoenabled electrochemical SARS-CoV-2 sensing system optimized using AI and IoT to perform at POC intelligent COVID-19 management in a personalized manner.

AUTHOR INFORMATION

Corresponding Author

Ajeet Kumar Kaushik − *NanoBioTech Laboratory, Department of Natural Sciences, Division of Sciences, Art, & Mathematics, Florida Polytechnic University, Lakeland, Florida 33805, United States;* orcid.org/0000-0003-4206-1541; Email: akaushik@floridapoly.edu, ajeet.npl@gmail.com

Authors

Jaspreet Singh Dhau − *Molecule Inc., Tampa, Florida 33612, United States;* orcid.org/0000-0002-3894-4301

Hardik Gohel − *Applied AI Research Lab, University of Houston Victoria, Victoria, Texas 77901, United State*

Yogendra Kumar Mishra − *Mads Clausen Institute, NanoSYD, University of Southern Denmark, 6400 Sønderborg, Denmark;* orcid.org/0000-0002-8786-9379

Babak Kateb − *National Center for NanoBioElectronics, Brain Mapping Foundation, Brain Technology and Innovation Park, Society for Brain Mapping and Therapeutics, Pacific Palisades, California 90272, United States*

Nam-Young Kim − *RFIC Bio Center, Department of Electronics Engineering, Kwangwoon University, Seoul 01897, South Korea*

Dharendra Yogi Goswami − *Clean Energy Research Center, University of South Florida, Tampa, Florida 33620, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsabm.0c01004

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We acknowledge our respective departments and institutions for providing support and facilities. A.K. acknowledges a research grant, namely, GR-2000024, funded by Florida Polytechnic University, Lakeland, FL, USA.

REFERENCES

(1) Mujawar, M. A.; Gohel, H.; Bhardwaj, S. K.; Srinivasan, S.; Hickman, N.; Kaushik, A. Aspects of Nano-Enabling Biosensing Systems for Intelligent Healthcare; towards COVID-19 Management. *Materials Today Chemistry* **2020**, *17*, 100306.

(2) Jalandra, R.; Yadav, A. K.; Verma, D.; Dalal, N.; Sharma, M.; Singh, R.; Kumar, A.; Solanki, P. R. Strategies and Perspectives to Develop SARS-CoV-2 Detection Methods and Diagnostics. *Biomed. Pharmacother.* **2020**, *129*, 110446.

(3) Zhou, F.; Yu, T.; Du, R.; Fan, G.; Liu, Y.; Liu, Z.; Xiang, J.; Wang, Y.; Song, B.; Gu, X.; Guan, L.; Wei, Y.; Li, H.; Wu, X.; Xu, J.; Tu, S.; Zhang, Y.; Chen, H.; Cao, B. Clinical Course and Risk Factors for Mortality of Adult Inpatients with COVID-19 in Wuhan, China: A Retrospective Cohort Study. *Lancet* **2020**, *395* (10229), 1054−1062.

(4) Li, G.; De Clercq, E. Therapeutic Options for the 2019 Novel Coronavirus (2019-NCoV). *Nat. Rev. Drug Discovery* **2020**, *19* (3), 149−150.

(5) Glied, S.; Levy, H. The Potential Effects of Coronavirus on National Health Expenditures. *JAMA* **2020**, *323* (20), 2001−2002.

(6) Paliwal, P.; Sargolzaei, S.; Bhardwaj, S. K.; Bhardwaj, V.; Dixit, C.; Kaushik, A. Grand Challenges in Bio-Nanotechnology to Manage COVID-19 Pandemic. *Front. Nanotechnol.* **2020**, *2*, DOI: 10.3389/fnano.2020.571284.

(7) Ahmadivand, A.; Gerislioglu, B.; Ramezani, Z.; Kaushik, A.; Manickam, P.; Ghoreishi, S. A. Femtomolar-Level Detection of SARS-CoV-2 Spike Proteins Using Toroidal Plasmonic Metasensors. *arXiv (Physics)*, Jun. 15, 2020, 2006.08536. [note; first/last information is available], https://arxiv.org/abs/2006.08536

(8) Shereen, M. A.; Khan, S.; Kazmi, A.; Bashir, N.; Siddique, R. COVID-19 Infection: Origin, Transmission, and Characteristics of Human Coronaviruses. *Journal of Advanced Research* **2020**, *24*, 91−98.

(9) Rothan, H. A.; Byrareddy, S. N. The Epidemiology and Pathogenesis of Coronavirus Disease (COVID-19) Outbreak. *J. Autoimmun.* **2020**, *109*, 102433.

(10) Huang, S. COVID-19: Why We Should All Wear Masks—There Is New Scientific Rationale. *Medium.com*, Mar. 26, 2020; https://medium.com/@Cancerwarrior/covid-19-why-we-should-all-wear-masks-there-is-new-scientific-rationale-280e08ceee71 (accessed 2020-05-14).

(11) Zangmeister, C. D.; Radney, J. G.; Vicenzi, E. P.; Weaver, J. L. Filtration Efficiencies of Nanoscale Aerosol by Cloth Mask Materials Used to Slow the Spread of SARS-CoV-2. *ACS Nano* **2020**, *14* (7), 9188−9200.

(12) Ullah, S.; Ullah, A.; Lee, J.; Jeong, Y.; Hashmi, M.; Zhu, C.; Joo, K. I.; Cha, H. J.; Kim, I. S. Reusability Comparison of Melt-Blown vs Nanofiber Face Mask Filters for Use in the Coronavirus Pandemic. *ACS Appl. Nano Mater.* **2020**, *3* (7), 7231−7241.

(13) Lustig, S. R.; Biswakarma, J. J. H.; Rana, D.; Tilford, S. H.; Hu, W.; Su, M.; Rosenblatt, M. S. Effectiveness of Common Fabrics to Block Aqueous Aerosols of Virus-like Nanoparticles. *ACS Nano* **2020**, *14* (6), 7651−7658.

(14) Bae, S.; Kim, M.-C.; Kim, J. Y.; Cha, H.-H.; Lim, J. S.; Jung, J.; Kim, M.-J.; Oh, D. K.; Lee, M.-K.; Choi, S.-H.; Sung, M.; Hong, S.-B.; Chung, J.-W.; Kim, S.-H. Effectiveness of Surgical and Cotton Masks in Blocking SARS−CoV-2: A Controlled Comparison in 4 Patients. *Ann. Intern. Med.* **2020**, *173* (1), W22−W23.

(15) Leung, N. H. L.; Chu, D. K. W.; Shiu, E. Y. C.; Chan, K.-H.; McDevitt, J. J.; Hau, B. J. P.; Yen, H.-L.; Li, Y.; Ip, D. K. M.; Peiris, J. S. M.; Seto, W.-H.; Leung, G. M.; Milton, D. K.; Cowling, B. J. Respiratory Virus Shedding in Exhaled Breath and Efficacy of Face Masks. *Nat. Med.* **2020**, *26* (5), 676−680.

(16) Klompas, M.; Morris, C. A.; Sinclair, J.; Pearson, M.; Shenoy, E. S. Universal Masking in Hospitals in the Covid-19 Era. *N. Engl. J. Med.* **2020**, *382* (21), e63.

(17) Parmet, W. E.; Sinha, M. S. Covid-19 — The Law and Limits of Quarantine. *N. Engl. J. Med.* **2020**, *382* (15), e28.

(18) Chan, J. F.-W.; Yuan, S.; Kok, K.-H.; To, K. K.-W.; Chu, H.; Yang, J.; Xing, F.; Liu, J.; Yip, C. C.-Y.; Poon, R. W.-S.; Tsoi, H.-W.; Lo, S. K.-F.; Chan, K.-H.; Poon, V. K.-M.; Chan, W.-M.; Ip, J. D.; Cai, J.-P.; Cheng, V. C.-C.; Chen, H.; Hui, C. K.-M.; Yuen, K.-Y. A Familial Cluster of Pneumonia Associated with the 2019 Novel Coronavirus Indicating Person-to-Person Transmission: A Study of a Family Cluster. *Lancet* **2020**, *395* (10223), 514−523.

(19) Andersen, K. G.; Rambaut, A.; Lipkin, W. I.; Holmes, E. C.; Garry, R. F. The Proximal Origin of SARS-CoV-2. *Nat. Med.* **2020**, *26* (4), 450−452.

(20) Gates, B. Responding to Covid-19 — A Once-in-a-Century Pandemic? *N. Engl. J. Med.* **2020**, *382* (18), 1677−1679.

(21) Gandhi, M.; Yokoe, D. S.; Havlir, D. V. Asymptomatic Transmission, the Achilles' Heel of Current Strategies to Control Covid-19. *N. Engl. J. Med.* **2020**, *382* (22), 2158−2160.

(22) Grubaugh, N. D.; Petrone, M. E.; Holmes, E. C. We Shouldn't Worry When a Virus Mutates during Disease Outbreaks. *Nature Microbiology* **2020**, *5* (4), 529−530.

(23) Morales-Narváez, E.; Dincer, C. The Impact of Biosensing in a Pandemic Outbreak: COVID-19. *Biosens. Bioelectron.* **2020**, *163*, 112274.

(24) Udugama, B.; Kadhiresan, P.; Kozlowski, H. N.; Malekjahani, A.; Osborne, M.; Li, V. Y. C.; Chen, H.; Mubareka, S.; Gubbay, J. B.;

Chan, W. C. W. Diagnosing COVID-19: The Disease and Tools for Detection. *ACS Nano* **2020**, *14* (4), 3822−3835.
(25) Forster, P.; Forster, L.; Renfrew, C.; Forster, M. Phylogenetic Network Analysis of SARS-CoV-2 Genomes. *Proc. Natl. Acad. Sci. U. S. A.* **2020**, *117* (17), 9241−9243.
(26) Wrapp, D.; Wang, N.; Corbett, K. S.; Goldsmith, J. A.; Hsieh, C.-L.; Abiona, O.; Graham, B. S.; McLellan, J. S. Cryo-EM Structure of the 2019-NCoV Spike in the Prefusion Conformation. *Science* **2020**, *367* (6483), 1260−1263.
(27) Yan, R.; Zhang, Y.; Li, Y.; Xia, L.; Guo, Y.; Zhou, Q. Structural Basis for the Recognition of the SARS-CoV-2 by Full-Length Human ACE2. *Science* **2020**, *367* (6485), 1444−1448.
(28) Han, Y.; Král, P. Computational Design of ACE2-Based Peptide Inhibitors of SARS-CoV-2. *ACS Nano* **2020**, *14* (4), 5143−5147.
(29) Yamamoto, V.; Bolanos, J. F.; Fiallos, J.; Strand, S. E.; Morris, K.; Shahrokhinia, S.; Cushing, T. R.; Hopp, L.; Tiwari, A.; Hariri, R.; Sokolov, R.; Wheeler, C.; Kaushik, A.; Elsayegh, A.; Eliashiv, D.; Hedrick, R.; Jafari, B.; Johnson, J. P.; Khorsandi, M.; Gonzalez, N.; Balakhani, G.; Lahiri, S.; Ghavidel, K.; Amaya, M.; Kloor, H.; Hussain, N.; Huang, E.; Cormier, J.; Wesson Ashford, J.; Wang, J. C.; Yaghobian, S.; Khorrami, P.; Shamloo, B.; Moon, C.; Shadi, P.; Kateb, B. COVID-19: Review of a 21st Century Pandemic from Etiology to Neuro-Psychiatric Implications. *J. Alzheimer's Dis.* **2020**, *77* (2), 459−504.
(30) Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Krüger, N.; Herrler, T.; Erichsen, S.; Schiergens, T. S.; Herrler, G.; Wu, N.-H.; Nitsche, A.; Müller, M. A.; Drosten, C.; Pöhlmann, S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* **2020**, *181* (2), 271−280.e8.
(31) Chauhan, G.; Madou, M. J.; Kalra, S.; Chopra, V.; Ghosh, D.; Martinez-Chapa, S. O. Nanotechnology for COVID-19: Therapeutics and Vaccine Research. *ACS Nano* **2020**, *14* (7), 7760−7782.
(32) Kim, D.; Lee, J.-Y.; Yang, J.-S.; Kim, J. W.; Kim, V. N.; Chang, H. The Architecture of SARS-CoV-2 Transcriptome. *Cell* **2020**, *181* (4), 914−921.e10.
(33) Thanh Le, T.; Andreadakis, Z.; Kumar, A.; Gómez Román, R.; Tollefsen, S.; Saville, M.; Mayhew, S. The COVID-19 Vaccine Development Landscape. *Nat. Rev. Drug Discovery* **2020**, *19* (5), 305−306.
(34) Sanders, J. M.; Monogue, M. L.; Jodlowski, T. Z.; Cutrell, J. B. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA* **2020**, *323* (18), 1824−1836.
(35) Callaway, E. The Race for Coronavirus Vaccines: A Graphical Guide. *Nature* **2020**, *580* (7805), 576−577.
(36) Kupferschmidt, K.; Cohen, J. Race to Find COVID-19 Treatments Accelerates. *Science* **2020**, *367* (6485), 1412−1413.
(37) Panda, P. K.; Arul, M. N.; Patel, P.; Verma, S. K.; Luo, W.; Rubahn, H.-G.; Mishra, Y. K.; Suar, M.; Ahuja, R. Structure-Based Drug Designing and Immunoinformatics Approach for SARS-CoV-2. *Science Advances* **2020**, *6* (28), eabb8097.
(38) Amanat, F.; Krammer, F. SARS-CoV-2 Vaccines: Status Report. *Immunity* **2020**, *52* (4), 583−589.
(39) Wadman, M.; Couzin-Frankel, J.; Kaiser, J.; Matacic, C. A Rampage through the Body. *Science* **2020**, *368* (6489), 356−360.
(40) del Rio, C.; Malani, P. N. COVID-19-New Insights on a Rapidly Changing Epidemic. *JAMA* **2020**, *323* (14), 1339−1340.
(41) Cheng, H.-Y.; Jian, S.-W.; Liu, D.-P.; Ng, T.-C.; Huang, W.-T.; Lin, H.-H. Contact Tracing Assessment of COVID-19 Transmission Dynamics in Taiwan and Risk at Different Exposure Periods Before and After Symptom Onset. *JAMA Intern. Med.* **2020**, *180* (9), 1156−1163.
(42) Rosenbaum, L. Facing Covid-19 in Italy — Ethics, Logistics, and Therapeutics on the Epidemic's Front Line. *N. Engl. J. Med.* **2020**, *382* (20), 1873−1875.
(43) Chang, D.; Xu, H.; Rebaza, A.; Sharma, L.; Dela Cruz, C. S. Protecting Health-Care Workers from Subclinical Coronavirus Infection. *Lancet Respir. Med.* **2020**, *8* (3), e13.
(44) Shen, M.; Zhou, Y.; Ye, J.; Abdullah AL-maskri, A. A.; Kang, Y.; Zeng, S.; Cai, S. Recent Advances and Perspectives of Nucleic Acid Detection for Coronavirus. *J. Pharm. Anal.* **2020**, *10* (2), 97−101.
(45) Freije, C. A.; Myhrvold, C.; Boehm, C. K.; Lin, A. E.; Welch, N. L.; Carter, A.; Metsky, H. C.; Luo, C. Y.; Abudayyeh, O. O.; Gootenberg, J. S.; Yozwiak, N. L.; Zhang, F.; Sabeti, P. C. Programmable Inhibition and Detection of RNA Viruses Using Cas13. *Mol. Cell* **2019**, *76* (5), 826−837.e11.
(46) Lan, L.; Xu, D.; Ye, G.; Xia, C.; Wang, S.; Li, Y.; Xu, H. Positive RT-PCR Test Results in Patients Recovered From COVID-19. *JAMA* **2020**, *323* (15), 1502−1503.
(47) Konda, A.; Prakash, A.; Moss, G. A.; Schmoldt, M.; Grant, G. D.; Guha, S. Aerosol Filtration Efficiency of Common Fabrics Used in Respiratory Cloth Masks. *ACS Nano* **2020**, *14* (5), 6339−6347.
(48) Chu, D. K.; Akl, E. A.; Duda, S.; Solo, K.; Yaacoub, S.; Schünemann, H. J.; Chu, D. K.; Akl, E. A.; El-harakeh, A.; Bognanni, A.; Lotfi, T.; Loeb, M.; Hajizadeh, A.; Bak, A.; Izcovich, A.; Cuello-Garcia, C. A.; Chen, C.; Harris, D. J.; Borowiack, E.; Chamseddine, F.; Schünemann, F.; Morgano, G. P.; Muti Schünemann, G. E. U.; Chen, G.; Zhao, H.; Neumann, I.; Chan, J.; Khabsa, J.; Hneiny, L.; Harrison, L.; Smith, M.; Rizk, N.; Giorgi Rossi, P.; AbiHanna, P.; El-khoury, R.; Stalteri, R.; Baldeh, T.; Piggott, T.; Zhang, Y.; Saad, Z.; Khamis, A.; Reinap, M.; Duda, S.; Solo, K.; Yaacoub, S.; Schünemann, H. J. Physical Distancing, Face Masks, and Eye Protection to Prevent Person-to-Person Transmission of SARS-CoV-2 and COVID-19: A Systematic Review and Meta-Analysis. *Lancet* **2020**, *395* (10242), 1973−1987.
(49) van Doremalen, N.; Bushmaker, T.; Morris, D. H.; Holbrook, M. G.; Gamble, A.; Williamson, B. N.; Tamin, A.; Harcourt, J. L.; Thornburg, N. J.; Gerber, S. I.; Lloyd-Smith, J. O.; de Wit, E.; Munster, V. J. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. *N. Engl. J. Med.* **2020**, *382* (16), 1564−1567.
(50) Vatansever, F.; Ferraresi, C.; de Sousa, M. V. P.; Yin, R.; Rineh, A.; Sharma, S. K.; Hamblin, M. R. Can Biowarfare Agents Be Defeated with Light? *Virulence* **2013**, *4* (8), 796−825.
(51) Rai, P. K.; Usmani, Z.; Thakur, V. K.; Gupta, V. K.; Mishra, Y. K. Tackling COVID-19 Pandemic through Nanocoatings: Confront and Exactitude. *Current Research in Green and Sustainable Chemistry* **2020**, *3*, 100011.
(52) Goel, S.; Hawi, S.; Goel, G.; Thakur, V. K.; Agrawal, A.; Hoskins, C.; Pearce, O.; Hussain, T.; Upadhyaya, H. M.; Cross, G.; Barber, A. H. Resilient and Agile Engineering Solutions to Address Societal Challenges Such as Coronavirus Pandemic. *Materials Today Chemistry* **2020**, *17*, 100300.
(53) Ates, B.; Koytepe, S.; Ulu, A.; Gurses, C.; Thakur, V. K. Chemistry, Structures, and Advanced Applications of Nanocomposites from Biorenewable Resources. *Chem. Rev.* **2020**, *120* (17), 9304−9362.
(54) Zhang, Q.; Honko, A.; Zhou, J.; Gong, H.; Downs, S. N.; Vasquez, J. H.; Fang, R. H.; Gao, W.; Griffiths, A.; Zhang, L. Cellular Nanosponges Inhibit SARS-CoV-2 Infectivity. *Nano Lett.* **2020**, *20* (7), 5570−5574.
(55) Weiss, C.; Carriere, M.; Fusco, L.; Capua, I.; Regla-Nava, J. A.; Pasquali, M.; Scott, J. A.; Vitale, F.; Unal, M. A.; Mattevi, C.; Bedognetti, D.; Merkoçi, A.; Tasciotti, E.; Yilmazer, A.; Gogotsi, Y.; Stellacci, F.; Delogu, L. G. Toward Nanotechnology-Enabled Approaches against the COVID-19 Pandemic. *ACS Nano* **2020**, *14* (6), 6383−6406.
(56) Talebian, S.; Wallace, G. G.; Schroeder, A.; Stellacci, F.; Conde, J. Nanotechnology-Based Disinfectants and Sensors for SARS-CoV-2. *Nat. Nanotechnol.* **2020**, *15* (8), 618−621.
(57) Russell, S. M.; Alba-Patiño, A.; Barón, E.; Borges, M.; Gonzalez-Freire, M.; de la Rica, R. Biosensors for Managing the COVID-19 Cytokine Storm: Challenges Ahead. *ACS Sens.* **2020**, *5* (6), 1506−1513.
(58) Robertson, C. A.; Lowther, S. A.; Birch, T.; Tan, C.; Sorhage, F.; Stockman, L.; McDonald, L. C.; Lingappa, J. R.; Bresnitz, E. SARS

https://dx.doi.org/10.1021/acsabm.0c01004
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

and Pregnancy: A Case Report. *Emerging Infect. Dis.* **2004**, *10* (2), 345−348.
(59) Ann Yeh, E.; Collins, A.; Cohen, M. E.; Duffner, P. K.; Faden, H. Detection of Coronavirus in the Central Nervous System of a Child With Acute Disseminated Encephalomyelitis. *Pediatrics* **2004**, *113* (1), e73−e76.
(60) Principi, N.; Bosis, S.; Esposito, S. Effects of Coronavirus Infections in Children. *Emerging Infect. Dis.* **2010**, *16* (2), 183−188.
(61) Morfopoulou, S.; Brown, J. R.; Davies, E. G.; Anderson, G.; Virasami, A.; Qasim, W.; Chong, W. K.; Hubank, M.; Plagnol, V.; Desforges, M.; Jacques, T. S.; Talbot, P. J.; Breuer, J. Human Coronavirus OC43 Associated with Fatal Encephalitis. *N. Engl. J. Med.* **2016**, *375* (5), 497−498.
(62) Netland, J.; Meyerholz, D. K.; Moore, S.; Cassell, M.; Perlman, S. Severe Acute Respiratory Syndrome Coronavirus Infection Causes Neuronal Death in the Absence of Encephalitis in Mice Transgenic for Human ACE2. *J. Virol.* **2008**, *82* (15), 7264−7275.
(63) Puoci, F. Monoclonal-Type" Plastic Antibodies for COVID-19 Treatment: What Is the Idea? *J. Funct. Biomater.* **2020**, *11* (2), 43.
(64) Wen, T.; Huang, C.; Shi, F.-J.; Zeng, X.-Y.; Lu, T.; Ding, S.-N.; Jiao, Y.-J. Development of a Lateral Flow Immunoassay Strip for Rapid Detection of IgG Antibody against SARS-CoV-2 Virus. *Analyst* **2020**, *145* (15), 5345−5352.
(65) Kanne, J. P. Chest CT Findings in 2019 Novel Coronavirus (2019-NCoV) Infections from Wuhan, China: Key Points for the Radiologist. *Radiology* **2020**, *295* (1), 16−17.
(66) Chung, M.; Bernheim, A.; Mei, X.; Zhang, N.; Huang, M.; Zeng, X.; Cui, J.; Xu, W.; Yang, Y.; Fayad, Z. A.; Jacobi, A.; Li, K.; Li, S.; Shan, H. CT Imaging Features of 2019 Novel Coronavirus (2019-NCoV). *Radiology* **2020**, *295* (1), 202−207.
(67) Li, Y.; Xia, L. Coronavirus Disease 2019 (COVID-19): Role of Chest CT in Diagnosis and Management. *AJR, Am. J. Roentgenol.* **2020**, *214* (6), 1280−1286.
(68) To, K. K.-W.; Tsang, O. T.-Y.; Yip, C. C.-Y.; Chan, K.-H.; Wu, T.-C.; Chan, J. M.-C.; Leung, W.-S.; Chik, T. S.-H.; Choi, C. Y.-C.; Kandamby, D. H.; Lung, D. C.; Tam, A. R.; Poon, R. W.-S.; Fung, A. Y.-F.; Hung, I. F.-N.; Cheng, V. C.-C.; Chan, J. F.-W.; Yuen, K.-Y. Consistent Detection of 2019 Novel Coronavirus in Saliva. *Clin. Infect. Dis.* **2020**, *71* (15), 841−843.
(69) Ai, T.; Yang, Z.; Hou, H.; Zhan, C.; Chen, C.; Lv, W.; Tao, Q.; Sun, Z.; Xia, L. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology* **2020**, *296* (2), E32.
(70) BD, BioGX Announce FDA Emergency Use Authorization for New COVID-19 Diagnostic for Use in U.S.. *BD Press Release*; Becton, Dickinson and Co., Franklin Lakes, NJ, USA, Apr. 3, 2020; https://investors.bd.com/news-releases/news-release-details/bd-biogx-announce-fda-emergency-use-authorization-new-covid-19 (accessed 2020-05-14).
(71) Coronavirus (COVID-19) Update: FDA Issues first Emergency Use Authorization for Point of Care Diagnostic. *FDA News Release*; U.S. Food and Drug Administration (FDA), Silver Spring, MD, USA, Mar. 21, 2020; https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-first-emergency-use-authorization-point-care-diagnostic (accessed 2020-05-14).
(72) Etherington, D. The FDA Just Okayed Multiple 15-minute Blood Tests to Screen for Coronavirus, but There Are Caveats. *TechCrunch*, Mar. 27, 2020; https://techcrunch.com/2020/03/27/the-fda-just-okayed-multiple-15-minute-blood-tests-to-screen-for-coronavirus-but-there-are-caveats/.
(73) Etherington, D. A New FDA-Authorized COVID-19 Test Doesn't Need a Lab and Can Produce Results in Just 5 minutes. *TechCrunch*, Mar. 27, 2020; https://techcrunch.com/2020/03/27/a-new-fda-authorized-covid-19-test-doesnt-need-a-lab-and-can-produce-results-in-just-5-minutes/.
(74) Chitra GeneLAMP-N makes confirmatory tests results of COVID 19 possible in 2 h. Department of Science & Technology, Government of India, https://dst.gov.in/chitra-genelamp-n-makes-confirmatory-tests-results-covid-19-possible-2-hours (accessed 2020-05-14).
(75) Kaushik, A.; Vasudev, A.; Arya, S. K.; Pasha, S. K.; Bhansali, S. Recent Advances in Cortisol Sensing Technologies for Point-of-Care Application. *Biosens. Bioelectron.* **2014**, *53*, 499−512.
(76) Velanki, S.; Ji, H.-F. Detection of Feline Coronavirus Using Microcantilever Sensors. *Meas. Sci. Technol.* **2006**, *17* (11), 2964−2968.
(77) Zuo, B.; Li, S.; Guo, Z.; Zhang, J.; Chen, C. Piezoelectric Immunosensor for SARS-Associated Coronavirus in Sputum. *Anal. Chem.* **2004**, *76* (13), 3536−3540.
(78) Ishikawa, F. N.; Chang, H.-K.; Curreli, M.; Liao, H.-I.; Olson, C. A.; Chen, P.-C.; Zhang, R.; Roberts, R. W.; Sun, R.; Cote, R. J.; Thompson, M. E.; Zhou, C. Label-Free, Electrical Detection of the SARS Virus N-Protein with Nanowire Biosensors Utilizing Antibody Mimics as Capture Probes. *ACS Nano* **2009**, *3* (5), 1219−1224.
(79) Teengam, P.; Siangproh, W.; Tuantranont, A.; Vilaivan, T.; Chailapakul, O.; Henry, C. S. Multiplex Paper-Based Colorimetric DNA Sensor Using Pyrrolidinyl Peptide Nucleic Acid-Induced AgNPs Aggregation for Detecting MERS-CoV, MTB, and HPV Oligonucleotides. *Anal. Chem.* **2017**, *89* (10), 5428−5435.
(80) Weng, X.; Neethirajan, S. Immunosensor Based on Antibody-Functionalized MoS_2 for Rapid Detection of Avian Coronavirus on Cotton Thread. *IEEE Sens. J.* **2018**, *18* (11), 4358−4363.
(81) Broughton, J. P.; Deng, X.; Yu, G.; Fasching, C. L.; Servellita, V.; Singh, J.; Miao, X.; Streithorst, J. A.; Granados, A.; Sotomayor-Gonzalez, A.; Zorn, K.; Gopez, A.; Hsu, E.; Gu, W.; Miller, S.; Pan, C.-Y.; Guevara, H.; Wadford, D. A.; Chen, J. S.; Chiu, C. Y. CRISPR−Cas12-Based Detection of SARS-CoV-2. *Nat. Biotechnol.* **2020**, *38*, 870−874.
(82) Qiu, G.; Gai, Z.; Tao, Y.; Schmitt, J.; Kullak-Ublick, G. A.; Wang, J. Dual-Functional Plasmonic Photothermal Biosensors for Highly Accurate Severe Acute Respiratory Syndrome Coronavirus 2 Detection. *ACS Nano* **2020**, *14* (5), 5268−5277.
(83) Chen, Z.; Zhang, Z.; Zhai, X.; Li, Y.; Lin, L.; Zhao, H.; Bian, L.; Li, P.; Yu, L.; Wu, Y.; Lin, G. Rapid and Sensitive Detection of Anti-SARS-CoV-2 IgG, Using Lanthanide-Doped Nanoparticles-Based Lateral Flow Immunoassay. *Anal. Chem.* **2020**, *92* (10), 7226−7231.
(84) Seo, G.; Lee, G.; Kim, M. J.; Baek, S.-H.; Choi, M.; Ku, K. B.; Lee, C.-S.; Jun, S.; Park, D.; Kim, H. G.; Kim, S.-J.; Lee, J.-O.; Kim, B. T.; Park, E. C.; Kim, S. I. Rapid Detection of COVID-19 Causative Virus (SARS-CoV-2) in Human Nasopharyngeal Swab Specimens Using Field-Effect Transistor-Based Biosensor. *ACS Nano* **2020**, *14* (4), 5135−5142.
(85) Kaushik, A.; Tiwari, S.; Dev Jayant, R.; Marty, A.; Nair, M. Towards Detection and Diagnosis of Ebola Virus Disease at Point-of-Care. *Biosens. Bioelectron.* **2016**, *75*, 254−272.
(86) Kaushik, A.; Jayant, R. D.; Tiwari, S.; Vashist, A.; Nair, M. Nano-Biosensors to Detect Beta-Amyloid for Alzheimer's Disease Management. *Biosens. Bioelectron.* **2016**, *80*, 273−287.
(87) Kaushik, A.; Mujawar, M. Point of Care Sensing Devices: Better Care for Everyone. *Sensors* **2018**, *18* (12), 4303.
(88) Kaushik, A.; Tiwari, S.; Jayant, R. D.; Vashist, A.; Nikkhah-Moshaie, R.; El-Hage, N.; Nair, M. Electrochemical Biosensors for Early Stage Zika Diagnostics. *Trends Biotechnol.* **2017**, *35* (4), 308−317.
(89) Kaushik, A.; Yndart, A.; Kumar, S.; Jayant, R. D.; Vashist, A.; Brown, A. N.; Li, C.-Z.; Nair, M. A Sensitive Electrochemical Immunosensor for Label-Free Detection of Zika-Virus Protein. *Sci. Rep.* **2018**, *8* (1), 9700.
(90) Wang, C. J.; Ng, C. Y.; Brook, R. H. Response to COVID-19 in Taiwan: Big Data Analytics, New Technology, and Proactive Testing. *JAMA* **2020**, *323* (14), 1341.
(91) Song, Y.; Jiang, J.; Wang, X.; Yang, D.; Bai, C. Prospect and Application of Internet of Things Technology for Prevention of SARIs. *Clinical eHealth* **2020**, *3*, 1−4.
(92) Allam, Z.; Jones, D. S. On the Coronavirus (COVID-19) Outbreak and the Smart City Network: Universal Data Sharing

https://dx.doi.org/10.1021/acsabm.0c01004
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

Standards Coupled with Artificial Intelligence (AI) to Benefit Urban Health Monitoring and Management. *Healthcare* **2020**, *8* (1), 46.
(93) Dandekar, R.; Barbastathis, G. Quantifying the effect of quarantine control in Covid-19 infectious spread using machine learning. *medRxiv* Apr. 6, 2020, 2020.04.03.20052084. https://www.medrxiv.org/content/10.1101/2020.04.03.20052084v1 (accessed 2020-05-13).
(94) Bai, L.; Yang, D.; Wang, X.; Tong, L.; Zhu, X.; Zhong, N.; Bai, C.; Powell, C. A.; Chen, R.; Zhou, J.; Song, Y.; Zhou, X.; Zhu, H.; Han, B.; Li, Q.; Shi, G.; Li, S.; Wang, C.; Qiu, Z.; Zhang, Y.; Xu, Y.; Liu, J.; Zhang, D.; Wu, C.; Li, J.; Yu, J.; Wang, J.; Dong, C.; Wang, Y.; Wang, Q.; Zhang, L.; Zhang, M.; Ma, X.; Zhao, L.; Yu, W.; Xu, T.; Jin, Y.; Wang, X.; Wang, Y.; Jiang, Y.; Chen, H.; Xiao, K.; Zhang, X.; Song, Z.; Zhang, Z.; Wu, X.; Sun, J.; Shen, Y.; Ye, M.; Tu, C.; Jiang, J.; Yu, H.; Tan, F. Chinese Experts' Consensus on the Internet of Things-Aided Diagnosis and Treatment of Coronavirus Disease 2019 (COVID-19). *Clinical eHealth* **2020**, *3*, 7−15.
(95) Srinivasa Rao, A. S. R.; Vazquez, J. A. Identification of COVID-19 Can Be Quicker through Artificial Intelligence Framework Using a Mobile Phone−Based Survey When Cities and Towns Are under Quarantine. *Infect. Control Hosp. Epidemiol.* **2020**, *41* (7), 826−830.
(96) Zhang, H.; Saravanan, K. M.; Yang, Y.; Hossain, M. T.; Li, J.; Ren, X.; Pan, Y.; Wei, Y. Deep Learning Based Drug Screening for Novel Coronavirus 2019-NCov. *Interdiscip. Sci.: Comput. Life Sci.* **2020**, *12*, 368−376.
(97) Zhou, Y.; Hou, Y.; Shen, J.; Huang, Y.; Martin, W.; Cheng, F. Network-Based Drug Repurposing for Novel Coronavirus 2019-NCoV/SARS-CoV-2. *Cell Discovery* **2020**, *6* (1), 1−18.
(98) Kilic, T.; Weissleder, R.; Lee, H. Molecular and Immunological Diagnostic Tests of COVID-19: Current Status and Challenges. *iScience* **2020**, *23* (8), 101406.
(99) Forssén, P.; Samuelsson, J.; Lacki, K.; Fornstedt, T. Advanced Analysis of Biosensor Data for SARS-CoV-2 RBD and ACE2 Interactions. *Anal. Chem.* **2020**, *92* (17), 11520−11524.
(100) Gorshkov, K.; Susumu, K.; Chen, J.; Xu, M.; Pradhan, M.; Zhu, W.; Hu, X.; Breger, J. C.; Wolak, M.; Oh, E. Quantum-Dot-Conjugated SARS-CoV-2 Spike Pseudo-Virions Enable Tracking of Angiotensin Converting Enzyme 2 Binding and Endocytosis. *ACS Nano* **2020**, *14* (9), 12234−12247.
(101) Moitra, P.; Alafeef, M.; Dighe, K.; Frieman, M. B.; Pan, D. Selective Naked-Eye Detection of SARS-CoV-2 Mediated by N Gene Targeted Antisense Oligonucleotide Capped Plasmonic Nanoparticles. *ACS Nano* **2020**, *14* (6), 7617−7627.
(102) Rabiee, N.; Bagherzadeh, M.; Ghasemi, A.; Zare, H.; Ahmadi, S.; Fatahi, Y.; Dinarvand, R.; Rabiee, M.; Ramakrishna, S.; Shokouhimehr, M.; Varma, R. S. Point-of-Use Rapid Detection of SARS-CoV-2: Nanotechnology-Enabled Solutions for the COVID-19 Pandemic. *Int. J. Mol. Sci.* **2020**, *21* (14), 5126.
(103) Tymm, C.; Zhou, J.; Tadimety, A.; Burklund, A.; Zhang, J. X. J. Scalable COVID-19 Detection Enabled by Lab-on-Chip. *Cell. Mol. Bioeng.* **2020**, *13* (4), 313−329.

https://dx.doi.org/10.1021/acsabm.0c01004
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX