ACS APPLIED BIO MATERIALS

www.acsabm.org

Review

Microfluidics-Based Point-of-Care Testing (POCT) Devices in Dealing with Waves of COVID-19 Pandemic: The Emerging Solution

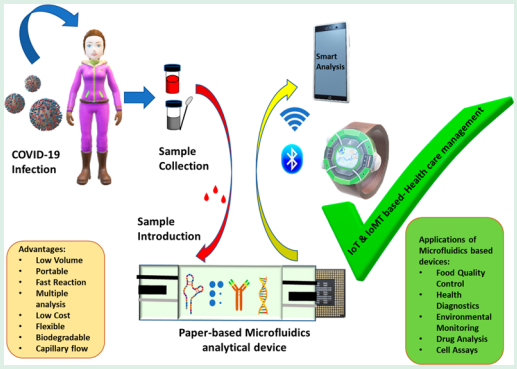
Avinash Kumar, Arpana Parihar,* Udwesh Panda, and Dipesh Singh Parihar

Cite This: https://doi.org/10.1021/acsabm.1c01320

Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: Recent advances in microfluidics-based point-of-care testing (POCT) technology such as paper, array, and beads have shown promising results for diagnosing various infectious diseases. The fast and timely detection of viral infection has proven to be a critical step for deciding the therapeutic outcome in the current COVID-19 pandemic, which in turn not only enhances the patient survival rate but also reduces the disease-associated comorbidities. In the present scenario, rapid, noninvasive detection of the virus using low cost and high throughput microfluidics-based POCT devices embraces the advantages over existing diagnostic technologies, for which a centralized lab facility, expensive instruments, sample pretreatment, and skilled personnel are required. Microfluidic-based multiplexed POCT devices can be a boon for clinical diagnosis in developing countries that lacks a centralized health care system and resources. The microfluidic devices can be used for disease diagnosis and exploited for the development and testing of drug efficacy for disease treatment in model systems. The havoc created by the second wave of COVID-19 led several countries' governments to the back front. The lack of diagnostic kits, medical devices, and human resources created a huge demand for a technology that can be remotely operated with single touch and data that can be analyzed on a phone. Recent advancements in information technology and the use of smartphones led to a paradigm shift in the development of diagnostic devices, which can be explored to deal with the current pandemic situation. This review sheds light on various approaches for the development of cost-effective microfluidics POCT devices. The successfully used microfluidic devices for COVID-19 detection under clinical settings along with their pros and cons have been discussed here. Further, the integration of microfluidic devices with smartphones and wireless network systems using the Internet-of-things will enable readers for manufacturing advanced POCT devices for remote disease management in low resource settings.



KEYWORDS: *COVID-19, point-of-care testing, infectious disease, diagnostics, microfluidics, detection*

1. INTRODUCTION

In the year 2019, a chain of acute atypical respiratory disorders came about in the metropolis of China. It quickly spread from Wuhan to different regions. It has been quickly revealed that a unique coronavirus became the reason. The novel coronavirus was named due to the extreme acute metabolism syndrome coronavirus-2 (SARS-CoV-2) and excessive similarity (~80%) to SARS-CoV-2, which brought on acute respiratory distress syndrome and excessive mortality from 2002 to 2003.[1] It is believed that the SARS-CoV-2 infection initially originated in bats and was transmitted through animals than to humans associated with the food market in Wuhan city of China. Then later it was identified that human-to-human transmission competed for the main role in the succeeding outbreak.[2] The sickness because of this virus is named Coronavirus sickness (COVID-19), and it is considered a deadly disease. This name was declared with the aid of the World Health Organization. COVID-19 has affected a huge population worldwide, being pronounced in over one-hundred international locations and territories.[3,4] Globally, as of February 25, 2022, there are 430 257 564 confirmed instances of COVID-19, collectively with 5 922 049 deaths as per a WHO report.[5] Various diagnostic techniques for the detection of this disease that are currently being used are shown in Figure 1.

The difficulty of tracking and controlling COVID-19 infections globally is nonetheless unsatisfactory and limited because of a deficiency of responsible caretakers, medical centers, and the shortness of diagnostic equipment, vaccines, and capsules to control the contamination. Recently, some

Received: December 30, 2021
Accepted: April 11, 2022

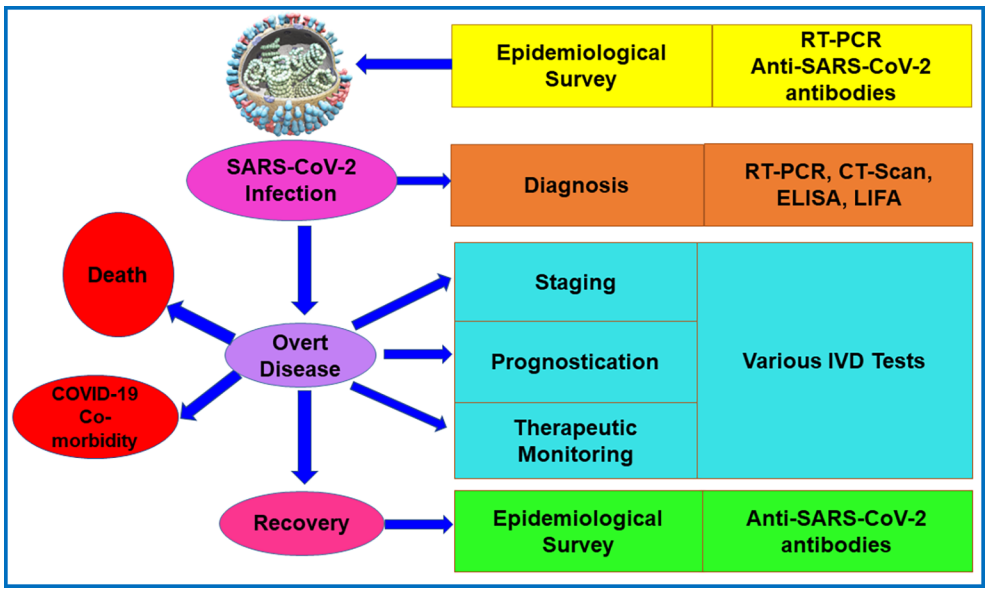


Figure 1. Diagnostic tests and methodologies for detection of SARS-CoV-2.

animals and humans have been observed constantly to understand the COVID-19 pathogenesis for facilitating the healing and vaccine discovery. Until then, to prevent COVID-19 infection, the best alternatives that someone can implement as controllable measures are inclusive life at home, hygiene, use of mask, maintaining social distancing, carrying out yoga, holding suitable immunity, etc.[6] The role of diagnostic tests to detect SARS-CoV-2 infection is crucial to not only identify the infectious agent but also decide the quarantine period to further stop the infection chain. In the present COVID-19 pandemic, rapid and prompt diagnosis of viral infection has proven to be a significant step in determining therapy outcomes, which not only improves patient survival but also reduces disease-related comorbidities. Rapid, noninvasive viral detection using low-cost, high-throughput microfluidics-based POCT devices offers advantages over existing diagnostic technologies, which require a centralized lab facility, expensive tools, sample pretreatment, and skilled employees. The second wave of COVID-19 wreaked havoc on several countries' governments, forcing them to retreat. Because diagnostic kits, medical devices, and human resources are in short supply, there is a need for technology that can be operated remotely with a single touch and data that can be analyzed on a phone. Recent advances in information technology and the widespread usage of smartphones have resulted in a paradigm change in the creation of diagnostic equipment that can be used to combat the present pandemic. This article discussed numerous ways for developing low-cost microfluidics POCT devices. The merits and cons of successfully employing microfluidic systems for COVID-19 detection in clinical settings have been discussed here. Furthermore, a brief insight over Internet-of-Things enabled POCT devices for remote disease management in low-resource settings by integrating microfluidic devices with smartphones and wireless network systems have been presented.

2. INSTANCES OF THE VARIOUS WAVES OF COVID-19: IMPACT ON WORLD

As predicted by many researchers, human beings around the world have seen the rise of COVID-19 instances in various countries in which the epidemic first emerged. The new waves of COVID-19 emerged with a high incidence of deaths, suggesting that the present diagnostic techniques or extended sources have failed to detect variants of SARS-CoV-2. Larger heterogeneous nations like the United States and Brazil, where the COVID-19 associated death rate is much higher, appear to revel in a mixture among the nevertheless ongoing first wave and a probable second wave coming from nearby geographic regions. One can hypothesize that older people are much more susceptible to this new epidemic wave. On the other hand, with the first wave of the ailment, more youthful people had been no longer located to be symptomatic and this would lead to unexpected considerations. SARS-CoV-2 has a large spectrum of ailments and symptoms. It has been identified that maximum infections are asymptomatic or oligo-symptomatic. The degree of severity of the disease depends on underlining fitness conditions, sex, and age. It is likewise recognized that even though effective, the neutralizing antibodies may also decay fast, permitting hosts to be reinfected with coronavirus in a brief length of time. The first confirmed case of SARS-CoV-2 reinfection ended in much less symptomatic contamination in assessment to the primary episode of infection; however, next reinfection instances may also bring about a greater excessive consecutive second infection.[7−9]

While seeking to develop a vaccine for intense acute respiratory syndrome and the Middle East respiratory syndrome, it is been detected a phenomenon named antibody-mediated immune reaction enhancement, which makes the symptoms more severe in patients.[10,11] Therefore, the second and consecutively the third wave of COVID-19 infections may also constitute many reinfection instances. Because of the second wave, many more young people have been inflamed all through the primary wave of the infection, which is being misdiagnosed because the first infection became asymptomatic or oligo-symptomatic. As particular immunity waned or the virus was mutated due to antigenic drift, those uncovered younger people would possibly act as a new prone population to reload the epidemic, the second infection being more symptomatic or intense. Because of varied immune

https://doi.org/10.1021/acsabm.1c01320
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

Table 1. Comparison between COVID-19 First, Second, and Third Waves

waves	time	measures for precaution	symptoms	rate of mortality	effect on economy	social activities	vaccine	reinfection	mutations
1st wave	March 2020	very high	fever, chest pain, headache, anosmia, sore throat	very high	completely stopped	banned	none	none	none
2nd wave	July 2020	mandatory	cold and fever, pneumonia, dyspnoea	increased	affected	decreased	research	appeared	none
3rd wave	Christmas 2021	people neglected	flu-like symptoms, psychological effect	comparatively lower	less affected	normal	available	common	new variants emerged

responses to SARS-CoV-2, such as heterogeneous antibody-mediated immune reactions, it is hard to apply serologic tests for seroprevalence studies. Although the length of viral dropping can be better among asymptomatic people, as much as 40% of asymptomatic people will produce IgG in comparison to 12.9% of symptomatic instances. The decay of normal IgG or neutralizing antibodies is rapid in symptomatic and asymptomatic people.[12] It is more likely that a few infected people will now have no longer increased protective immunity or they need a couple of infections to increase protection.

On a normal note, the second wave of COVID-19 hit the countries that had eased the regulations and no longer took the proper precautions for the future. Quarantine measures had wide-ranging and probably durable mental illness impacts on the overall population, in particular, wherever it lasted for several months.[13,14] Indeed, psychiatric records showed a threat element for experiencing tension signs, symptoms, and anger 4−6 months after uplifting of quarantine.[15−17] Being quarantined entails dropping everyday workouts and a lack of private and social contacts that make life difficult and offer mental illness, and it comes with big prices for people with intellectual illnesses. There is a pressing need to keep away from letting techniques get used to mitigate the symptoms of COVID-19 patients struggling with psychiatric disorders. Now, more than ever, greater assistance is needed for this huge and inclined populace.[18]

The SARS-COV-2 epidemic began in Wuhan, China, with the first patient appearing in December 2019; nevertheless, the first wave was discovered globally in March 2020. The fundamental reasons for this wave are still unknown. The first wave was seen as a calamity that severely impacted every aspect of life, posed a serious problem in public health, and disrupted social and economic activity worldwide. For instance, the global economy was harmed; goods production was almost halted in all regions, and the jobless rate skyrocketed. Another societal issue emerged such as increasing family violence among youngsters as a result of their prolonged stay at home.[19,20]

The third wave of COVID-19 saw various alterations and distinct traits including an increase in affected people owing to home contact. Furthermore, the widespread availability of fast antigen testing assays in early detection and isolation in case of severe infections lowered the fatality rates compared to the previous waves. The identification of a novel strain (B.1.1.7) with increased potential transmissibility was the most significant aspect of this wave; as a result, reinfections became more prevalent. These mutations that developed inside the virus may be the primary cause of the third wave, along with social activities between persons who did not take necessary safeguards. Vaccination, on the other hand, yielded excellent effects among patients, health care personnel, and the elderly.[21] Table 1 briefly compares the different waves and their effects on the world.

3. NEW VARIANTS OF COVID-19

SARS-CoV-2 has a strong propensity for evading transmission barriers, especially when illnesses are prevalent. Coronavirus mutations are thought to be an ideal step for immunological escape. This might happen with partial resistance at first but with superior resistance, if coronavirus strains reinfection occurs. It is worth noting that the higher the infection rate, the greater the likelihood of mutations. This way, the virus will be able to survive and spread. Virus spread remains uncontrollable until we attain herd immunity without imposing constraints. The introduction of N501Y mutants recently connected with super spreading events and epidemics has seen boosted transmissibility. Surprisingly, the variant was first identified in Denmark among sick minks, but its appearance in other places suggests that it may spread independently from such animals. This mutation enhanced SARS-COV-2's capacity to attach to the human receptor angiotensin-converting enzyme 2 (ACE2), thereby accelerating the spread of the COVID-19 pandemic.[22]

The variants that have lately emerged are omicron (B.1.1.529) in South Africa and delta in India (lineage B.1.1617). The first delta case was reported in October 2020, and the variant has a higher incidence of transmission and infection than other previously discovered variants.[23,24] However, omicron was identified on November 9, 2021. The omicron variant was differentiated by its high diffusion speed and the transmission rate that is significantly higher than that of previous variants due to the increased number of mutations. The omicron variant's large number of mutations in the S protein may boost the virus's capacity to resist infection-blocking antibodies and other immune responses such as the T cell response. This result is consistent with preliminary evidence indicating a higher risk of reinfection with omicron compared to other strains, but data are still limited. The multiple mutations in spike protein, more than 30 changes in the viral region, are crucial for the virus's entry into human cells, according to early research. These omicron alterations have also been found in prior COVID-19 strains, including alpha and delta variants. However, numerous omicron mutations have not previously been identified, necessitating more research. The number of alterations was double compared to the delta variant.[25,26] The RBD of the omicron variant had ten alterations, whereas delta variants had just two. According to recent research, the virus's mutation group (H655Y, N679 K, P681H) is connected with increased entry ability to the human cell, implying enhanced transmissibility. Furthermore, R203 K and G204R alterations were previously discovered in the alpha strain and also in the omicron strain, and these mutations increased infection rates.

However, there is presently no evidence that omicron symptoms vary from those of other strains. Initially, infections were detected among younger persons (university students) who had a lesser illness. Understanding the total degree of sickness caused by omicron will take several days if not weeks.

https://doi.org/10.1021/acsabm.1c01320
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

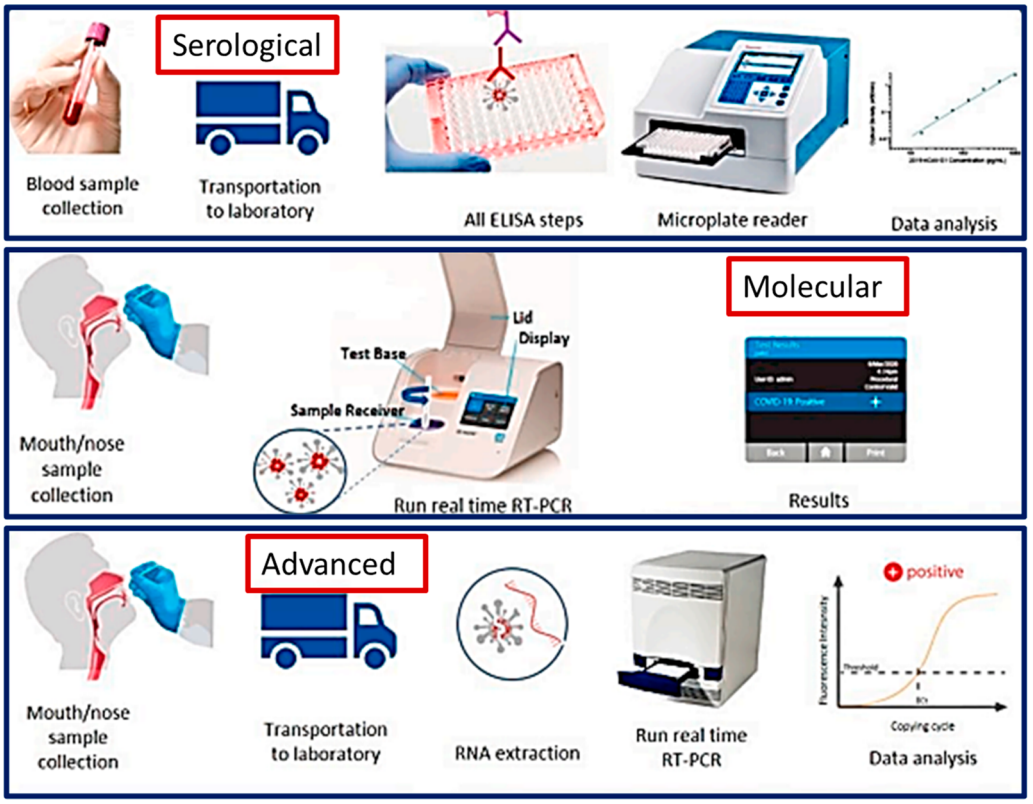


Figure 2. Most commonly used diagnostics for SARS-CoV-2. Reproduced with permission from ref 34. Copyright 2021 Elsevier.

According to an African Medical Association study, omicron is seven-times more infectious than the delta version, although recorded cases and fatalities in Africa have continued to fall, and those infected with omicron did not experience any major worsening of their health.[27]

4. LIMITATIONS OF CURRENTLY AVAILABLE DIAGNOSTIC TECHNOLOGY

Currently, a "medical analysis" of COVID-19 is being carried out by chest CT and RT-PCR. Other than in a clinical context, RT− PCR testing accounts for the largest proportion of surveillance testing carried out at administrative facilities or schools. However, due to poorly scheduled specimen collection and poor specimen handling, the chances of false results increased. Further, the need for experienced laboratory workers, long wait times to get results, and the need for expensive instruments, the nucleic acid amplification-based RT-PCR can be complicated in resource-poor settings. The typical RT-PCR is time-consuming, but it is no longer as time-consuming as the time it takes to transport the specimens to the laboratory, which might take days. RT-PCR results additionally rely closely on the sort of sampling processes such as oropharyngeal swabs (32−48%), nasopharyngeal swabs (63%), bronchoalveolar lavage fluid (79−93%), sputum (72−76%), and stool (29%).[28] Further, the scarcity of primers and other reagents needed to conduct the tests limits its further use.[29] New diagnostics are being intensively developed to overcome the limitations of RT-PCR. Investigations are ongoing to evaluate the efficacy of these tests, however limited. Present predicaments for immunodiagnostic procedures encompass a loss of specificity, that is, connected to false positive and false negative results due to closely associated strains of SARS-CoV-2 and cross-reactions with autoantibodies in autoimmune diseases. Immunodiagnostic assays can provide reliable results only after 7 to 11 days of infection and are consequently much less beneficial in the analysis of acute infection.[30] Outside the physical confines of the testing platform, data generated by nucleic acid amplification and serology testing fail to capture critical SARS-CoV-2 parameters such as the length of time a person is infectious or the prevalence of positive haplotypes in a community. Combining metagenomic detection techniques with nucleic acid amplification approaches might give new understandings to physicians and epidemiologists. Although RT-PCR is the current standard for detecting viral nucleic acids, new methods such as pulse-managed amplification are also being investigated. Pulse-managed amplification may not require ribonucleic acid extraction and can be completed in 10 min using a small instrument.[31] In the future, S- and N-based immunodiagnostic methods will be used in conjunction with nucleic acid amplification tests to improve SARS-CoV-2 detection sensitivity at a low cost.[32] Future efforts in the direction of the improvement of novel diagnostic systems might also be productive if the assessments are correct, particular, and smooth to run, generate results in a brief time, and are reasonably priced for mass-production. Given each of the strengths and boundaries of modern-day diagnostics and their singular output values, the results must be cautiously scrutinized before making choices on therapeutics in medical and nonmedical settings. It is likewise vital to recollect different techniques consisting of low-cost mass pooling and metagenomic profiling to expect futuristic outbreaks.

https://doi.org/10.1021/acsabm.1c01320
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

5. ADVANCED DIAGNOSTICS FOR DETECTION OF SARS-COV-2

COVID-19 prevention, detection, management, and treatment are all intertwined, and each aspect of COVID-19 control has an impact over the others. The proper and initial testing of COVID-19 is important to lower the danger of spreading of disease via permitting isolation and getting in touch with tracing. Consequently, the maximum big public health effect comes from the speedy finding of inflamed patients. Clinical findings of SARS-CoV-2 are based totally on medical signs and symptoms and records of touch with probably infected people. Since the medical manifestations and symptoms of patients (pneumonia, dyspnoea, fever, cough, and respiration signs and symptoms) are not definitive, the role of diagnostic and serological tests is critical for the analysis of SARS-CoV-2.[33] The cost of clinic strategies relies upon the type of test, the time for results, accuracy of assay, and the specified sources for testing. In other words, the fast identity of suspected people is the primary approach to follow suitable timely measures and restrict spread. A pictorial depiction of the most commonly used diagnostics for SARS-CoV-2 is presented in Figure 2.

5.1. Serological Approaches. An assay to measure the antibody-mediated immune response against viral agents is called serological testing.[35] However, this method cannot identify current viral infection but determines whether or not a person is or has been infected via means of figuring out an antibody immune reaction against infections. Since these assays no longer dictate the early stage of contamination, the European Centre for Disease Prevention and Control (ECDC) has encouraged COVID-19 serological testing to be done solely for epidemiological and monitoring purposes.[36] Detection of previous infections even without testing out the ailment is feasible with these strategies and is the principal advantage of serological methods. Numerous serological tests are available for the detection of SARS-CoV-2, many of which have been advertised as POC and fast strategies. However, the accuracy of these POC tests continues to be challenging.[37] The serological assays of SARS-CoV-2 detect ranges of numerous immunoglobulin, which is in response to combat SARS-CoV-2 infection. A fast serological assay is a cellular nonautomatic approach for comparing membrane-based immunoassays and providing qualitative data quickly (approximately 5−20 min). The advantages encompass less sample volume (a small blood group is enough), quick results, cost-effectiveness, and ease of interpretation. In addition, this can be easily used in places in bedside or near-to-affected person situations.[38] Rapid serological assays can be utilized for figuring out COVID-19 antigens and COVID-19 antibodies. The ECDC regularly releases up-to-date advisories and encourages the description of the procedure.[39] The European countries union protests that these tests being incorrect and dubious upon analysis and surveillance conveyed skeptical components in the direction of the overall performance of test kits.[40] Furthermore, the proof report from Cassaniti and their team's observation explained a fast check sensitivity underneath 20%, therefore ensuing in a huge scale SARS-CoV-2 false-analysis.[41] Thus, each tool ought to go through a validation method earlier than its scientific application. In light of these types of limitations, it has certain positive points such as low-cost and being trustworthy, providing quantitative facts that are important for longitudinal titter surveillance, professional lab employees overall testing and subjective analysis, and everlasting check on consequences. These diagnostics can suffice shortages in the laboratory method and maintain strict inner excellent management; however, in the future, the external quality evaluation will be needed.[42]

5.2. Molecular Approaches. Many industrial corporations and scientific teams have advanced testing equipment for testing a positive-sense single-stranded ribonucleic acid virus. The virus's whole genetic pattern was placed into the Global Initiative on Sharing All Influenza Database, which provided the records needed for genome molecular detection. The following enlisted molecular approaches are available for COVID-19 diagnosis.

5.2.1. Reverse Transcription-Polymerase Chain Reaction (RT-PCR). Amplification of minute quantities of viral nucleic material in an aggregate of the different nucleic acid mixtures is successfully performed using RT-PCR, and it is presently the mainstream method of COVID-19 detection in respiratory tract samples. Besides, some researchers have applied this to the serum and stool samples as a testing method.[43−45] A current technique has employed the use of salivary samples and is hence considered a noninvasive and secure method for medical workers.[46,47] In this technique, the reverse transcriptase, initially converts the viral ribonucleic acid into deoxyribonucleic acid using a small primer and the complementary deoxyribonucleic acid, is produced. A fluorescent-tagged probe specific to this deoxyribonucleic acid depicts the amplification of deoxyribonucleic acid in real-time. After several amplification cycles, an electric sign displays the viral cDNA.[48] Normally in the RT-PCR test, 1−2 steps are included. The single-step method contains a single primer tube; the 2-step process makes use of a couple of tubes to run the reactions. In addition, it can store cDNA for quantification of diverse goals with minute starting materials.[49] However, the standard technique for the COVID-19 detection is the single-step technique as it is far quicker, requires much less sample, has reductions in analysis time, and decreases the chances of pipetting mistakes. Through RT-PCR technology, certain COVID-19 biomarkers, such as nucleocapsid (N), as well as the RNA-dependent RNA polymerase, ORF1b or ORF8, and envelope (E) genes, have been detected in the virus's prognosis.[50−52] Although this technique has significantly been carried out with the detection of COVID-19, some limitations include costly equipment, tedious sample processing, professional personnel, an obstacle in the detection of mutant, and longer time for results. Thus, the development of the RT-PCR technique that can well address these obstacles is a critical issue awaiting solutions.

5.2.2. Isothermal Nucleic Acid Amplification. RT-PCR methods have a barrier in the form of the necessity for specialized heat cycling equipment.[53] Isothermal nucleic acid amplification eliminates the requirement for this and enables genome amplification at a constant temperature. Reverse transcription loop-mediated isothermal amplification (RT-LAMP) has been brought as a simple and economical approach to detect COVID-19, which makes use of a chain of 4 target-unique primers to enhance the sensitivity of mixed LAMP and reverse transcription-primer based techniques. Photometry is used to measure turbidity generated by the usage of magnesium pyrophosphate as a byproduct of the amplification mechanism. The photometric or fluorescent assay produces real-time results. The demand for the most effective heating and real-time monitoring steps turns RT-LAMP right into a speedy and touchy device for virus

https://doi.org/10.1021/acsabm.1c01320
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

Table 2. Methodologies for Detection of SARS-CoV-2 along with Advantage

approaches	test	advantage	sample type
serological	chemiluminescence immunoassay (CLIA)	sensitive and rapid	blood serum or plasma
	COVID antigen assay	rapid	
	enzyme-linked immunosorbent assay (ELISA)	rapid	
molecular	nucleic acid hybridization using microarray	sensitive	upper respiratory specimens
	amplicon-based metagenomic sequencing	different coronavirus strains have been identified	
	RT-PCR	gold standard test and sensitive	
	RT-LAMP	there is no need for a thermal cycler, effective use of time it is not necessary to have access to a high-tech laboratory	
POCT and nanotechnology	biosensors	sensitive, rapid and easy to use	upper respiratory specimens, as well as blood or urine
	lateral flow assays	specificity is quite high, quick and simple, straightforward to use as there is no need for a laboratory	blood or urine

detection.[54] Presently, Abbott Diagnostics makes use of RT-LAMP for COVID-19 detection as a POC and they use nasal swabs for sample collection. However, it is limited to at least one sample/run.[51,55] Also, the colorimetric LAMP detects viral ribonucleic acid in molecular lysate samples, and it is a better speedy diagnostic method for the detection of RNA of SARS-CoV-2.[52] The different isothermal amplification approaches are known as transcription-mediated amplification (TMA) and may expand particular areas of each RNA and DNA.[51] TMA makes use of T7 RNA polymerase mixed with a retroviral reverse transcriptase enzyme. As a result, each RT-PCR kit and TMA can be performed on Hologic's Panther fusion platform.[56] High-quality results and instantaneous screening of respiratory viruses with signs of SARS-CoV-2 are the primary advantages of Panther's fusion method. Herein, the reaction is initiated by hybridization of the viral ribonucleic acid target with a specific size probe and a second T7 promoter using a magnetic field. Then the reverse transcription of the T7 promoter primer converts ribonucleic acid to a corresponding DNA. Followed by the disintegration of the target ribonucleic acid occurring at the same time as generating a T7 primer together with single-stranded complementary deoxyribonucleic acid from a ribonucleic acid−deoxyribonucleic acid hybrid. Also, T7 ribonucleic acid polymerase is used to supply ribonucleic acid amplicons with the help of extra primers. These amplicons re-enter the TMA system, which at last ends in the era of billions of ribonucleic acid amplicons in a short time. The detection technique employs single-stranded nucleic acid probes that are specific to a fluorophore and a quencher. The real-time hybridization of probes to ribonucleic acid amplicons results in the fluorophore emitting a signal. CRISPR has been advanced for the testing of COVID-19. In CRISPR-based detection approaches, Cas nucleases have been used (Cas12 and Cas13).[57−59] Cas13 has been used as a nonspecific RNase in the detection of RNA/DNA in a technique known as SHERLOCK.[57] Amplification of the aimed ribonucleic acid with the aid of a mixture of T7 and reverse transcription recombinase polymerase amplification (RT-RPA) transcription methods in one step SHERLOCK approach.[60] This activates Cas13, which then cleaves a reporter ribonucleic acid, allowing the fluorescent dye to be released from a quencher. The CRISPR-nCoV has used the SHERLOCK approach in the detection of the COVID-19 genome with exquisite sensitivity in specimens in fifty-two affected persons.[61] Cas12 is a ribonucleic acid-directed DNase that cleaves single-stranded deoxyribonucleic acid from a target collection in a way termed DETECTOR.[58] This method has lately been adopted by several organizations to detect SARS-CoV-2. The first stage in this method is isothermal amplification of viral RNA once it has been converted to DNA. The Cas12 enzyme is then triggered by employing certain target sequences in amplified DNA, and it cleaves a single-stranded DNA reporter to release a fluorescence signal. When combined with fast isothermal amplification techniques, the CRISPR-based methodology can produce quick readouts and sensitive results. They can also be connected to lateral flow assays, which are ideal candidates for simple point-of-care testing. The advantages of this technique include a short turnaround time scale, high sensitivity, and reduced bias generation, but high-cost devices, the need for professional staff, and tedious sampling methods are a few obstacles that must also be taken into account.[62−64]

5.2.3. Nucleic Acid Hybridization Using Microarray. Microarray assays have also been used to identify SARS-CoV-2 nucleic acids efficiently and sensitively. The microarray tests begin with the generation of cDNA from viral RNA, which is subsequently identified using precise probes. To load selected cDNAs, solid-phase oligonucleotides constant microarray trays are utilized. In this hybridization method, the existence of viral-specific nucleic acid can be demonstrated.[65] Microarray tests were used to determine the mutations and single nucleotide polymorphisms associated with the SAR-CoV-2 genome.[66] This might help to detect different COVID-19 mutational variants and subtypes more quickly. The MERS coronavirus, like influenza and respiratory syncytial viruses, has been identified using portable microarray chips.[67] Microarray methods that employ a scanner to reveal the hybridization between the probe and the target gene are a quick, sensitive, one-of-a-kind, and accurate method of detection. One can also screen many microbial genes at the same time using this method. Although it can be used to identify numerous samples, this technique does not always allow for the investigation of particular viral genes in restricted samples.[68]

5.2.4. Amplicon-Based Metagenomic Sequencing. The amplicon with integrated metagenomic sequencing has been carried out in the testing of COVID-19 and is known as amplicon-based metagenomic sequencing. Metagenomic sequencing was applied to detect the associated microbiome of infected individuals. Amplicon-based sequencing is used to

https://doi.org/10.1021/acsabm.1c01320
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

Table 3. POCT Devices Based on Nucleic Acid Detection of SARS-CoV-2

based on nucleic acid						
device	POCT test	duration	sample type	company	positive/negative agreement	ref
Biomeme SARS-CoV-2 real-time RT-PCR test	real-time PCR	1 h	NPS/NS/OS/NPW-/NA/aspirate	Biomeme, Inc.	97.46%/98.51%	71
Xpert Xpress SARS-CoV-2 test	real-time PCR	45 min	NPS/NW/aspirate	Cepheid	100%/100%	72, 73
ePlex respiratory pathogen panel 2	eSensor technology	2 h	NPS	GenMark Diagnostics, Inc.	99.02%/98.41%	74, 75
automatic integrated gene detection system	real-time PCR	1.5 h	OS/ALF/sputum-/stool	Lifereal Biotechnology Co., Ltd.	97.62%/100%	76, 77
ARIES SARS-CoV-2 assay	real-time PCR	2 h	NPS	Luminex Corporation	100%/100%	78
LamPORE assay	nanopore sequencing combined with LAMP	2 h	NS/NPS/OS	Oxford Nanopore Technologies	99.1%/99.6%	79, 80
Sherlock CRISPR SARS-CoV-2 kit	RT-LAMP and CRISPR	1 h	NS/NPS/OS/NPW/aspirate/NA/BLF	Sherlock BioSciences, Inc.	97%/100%	81, 82
automatic CPA nucleic acid analyzer	CPA	55 min	OS/sputum	Ustar Biotechnologies (Hangzhou) Ltd.	98%/95.4%	83, 84

evaluate the ability of touch tracing, viral evolution analysis, and molecular epidemiology of the disease. Also, additional evaluation on collection divergences is furnished via metagenomic processes inclusive of collection of impartial single primer amplification (SISPA). This twin technique may be used to determine the mutant variants of COVID-19 and other related recombinants. Moore and their team employed MinION patterning for fast COVID-19 testing and other upper respiratory system swabs.[69] Illumina has furnished a next-generation shotgun metagenomic sequencing method that is now no longer the most effective diagnostics of distinctive coronavirus; however, it can be used to detect different organisms.[51] This procedure can be used beneficially to check the availability of full reference databases, available methods for bioinformatics testing, and the discovery of rare taxa. The main disadvantage of this method is that it is prone to biases in viable population measurement.[70]

Various diagnostic approaches are summarized in Table 2 along with advantages. Besides, Tables 3 and 4 enlist some of the devices based on nucleic acid (Table 3) and antibody (Table 4) for detection of SARS-CoV-2 infection.

6. MICROFLUIDIC INTEGRATED SMART DIAGNOSTIC APPROACHES FOR DETECTION OF SARS-COV-2

The microfluidics-based point-of-care (POC) diagnostics are a great addition to the diagnostic devices for the detection of SARS-CoV-2. Certain human illnesses leave detectable biomarkers in our circulatory system. As a result, blood testing has become one of the most widely used methods of disease biomarker analysis. Circulating tumor cells, circulating exosomes, and circulating tumor deoxyribonucleic acid have all recently emerged as new cancer diagnostic markers.[97,98] The better testing of these biomarkers needs devices that could process a small volume of blood inputs with excessive spatial-temporal accuracy and in an excessive outrun way. Microfluidic-based methods can satisfy these requirements. The combination of various techniques onto microfluidic chips has brought the development of many integrated platforms. Various methodologies that have been commercialized for oncological disease biomarker analysis and tracking have come to be a reality. Current development in genetic material isolation and enhanced detection of microfluidic chips, collectively with isothermal amplification of deoxyribonucleic acid and ribonucleic acid, has assisted circulating tumor deoxyribonucleic acid and pathogen genetic material testing in an integrated microfluidic device. These advancements in the field of microfluidics for disease detection have provided us with a critical toolkit for dealing with growing health issues. In the SARS-CoV-2 pandemic, a number of the present technologies have enabled fast affirmation of the pathogen with the testing kits that provide quick results. Also, the continuing pandemic additionally uncovered the restrictions of the traditional PCR-based methods that require skilled employees in a centralized lab setup. Microfluidics-based diagnostics have the potential to conquer these challenges.[99,100]

During this ongoing SARS-CoV-2 pandemic, aside from the PCR-primarily-based testing, LFA-based rapid assays were extensively used for mass screening of the virus.[101,102] Multiple agencies have fast evolved and launched merchandise of diagnostic devices that require a microliter of blood and give accurate results.[103,104] This can significantly supplement and identify the virus in asymptomatic persons and also identify former infections. However, antibody-based testing cannot detect the genetic material and therefore cannot give information about past infections. A quicker, transportable, and specific one-step genetic detection package will accordingly be a critical requirement for the containment of a pandemic.[105] Incorporating microfluidic-based genetic material detection approaches have gone through fantastic technological development in the recent couple of years.[106,107]

There are successful demonstrations of virus detection, genetic material testing, and result visualization on an easy microfluidic-based method. These devices were analyzed for testing genetic material from COVID-19 affected person and offer higher overall efficiency compared to LFA assays and the maximum of that rely on reverse transcriptase LAMP.[108−110] Even though the applicable strategies for process laboratory improvement of devices going on, a few trials were executed to validate the opportunity of making use of those systems for helping modern medical screening.[111] This has been regarded as an unparalleled period for the rising microfluidic-based genetic material testing technology to illustrate their actual functionality and, in addition, enhance their overall efficacy in medical setup for onsite point-of-care testing. The SARS-CoV-2 pandemic has uncovered the restrictions of the modern testing approaches even with the maximum evolved regions of the world. While carrying out analysis, the right way to make

https://doi.org/10.1021/acsabm.1c01320
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

Table 4. POCT Devices Based on Serological Estimation of Antibody for Diagnosis of COVID-19

		based on immunoassay				
device	POCT test	biomarker	duration	sample type	company	positive/negative agreement	ref
BinaxNOW COVID-19 Ag Card	lateral flow	antigen	15 min	NS	Abbott Diagnostics Scarborough, Inc.	91.7%/100%	85, 86
WANTAI SARS-CoV-2Ab Rapid Test	lateral flow (colloidal gold)	total antibody	15 min	serum/plasma (dipotassium EDTA, lithium heparin, and sodium citrate)/VWB	Beijing Wantai Biological Pharmacy Enterprise Co., Ltd.	100%/98.8%	87
Sofia SARS Antigen FIA	lateral flow immunofluorescent sandwich assay	antigen	15 min	NPS/NS	Quidel Corporation	96.7%/100%	88
Novel Coronavirus 2019-nCoV Antibody Test	lateral flow, (up-converting phosphor immunochromatographic)	IgM and IgG antibody	15 min	serum/plasma	Beijing hot view Biotechnology Co., Ltd.		89
LumiraDx SARS-CoV-2Ag Test	microfluidic immunofluorescence assay	antigen	12 min	NS	LumiraDx UK Ltd.	97.6%/96.6%	90
xMAP SARS-CoV-2 Multi-Antigen IgG Assay	96 plate (multiplexed microsphere-based assay)	IgG antibody	Less than 3 h	serum/dipotassium EDTA plasma	Luminex Corporation	96.3%/99.3%	91, 92
BioCheck SARS-CoV-2 IgG and IgM combo test	chemiluminescence	IgM and IgG antibody	30 min	serum	BioCheck, Inc.	99.1%/97.2%	93, 94
Ellume COVID-19 HomeTest	lateral flow (fluorophore)	antigen	15 min	NS	Ellume Limited	95%/97%	95, 96

the method quicker is via a high throughput process. The success in growing integrated liquid biopsy systems and microfluidic POCT for infectious diseases has stimulated viable answers. Probably, SARS-CoV-2 will not be the last pandemic that we will experience. Being technologically ready and able to be easily modified for the next pandemic is a lesson we should learn from the contemporary one. There remains a pressing requirement for fast and high throughput SARS-CoV-2 diagnostic strategies as portable POCT systems.[111] Recently, miniature biosensors have shown capacity as an analytical platform due to their specific properties, consistency of results, high sensitivity, reliable specificity, and fast analysis.[112−115] For instance, Sawank et al. fabricated a microfluidic nano immunoassay named NIA for the detection of anti-SARS-CoV-2 IgG in 1024 samples simultaneously on a single device. The design of the microfluidic NIA device showed in Figure 3. The developed device showed 98% sensitivity and 100% specificity. They also repurposed glucose test strips for easy and low-cost sampling of blood from an infected person via a simple finger prick. They also found comparable efficacy of the NIA device over an ELISA-based method.[116]

A biosensor generally consists of a signal analyzer, transducer, and biological receptor that can detect targets without delay and offers signals in the form of optical and electric indicators.[117,118] Regular improvement in nano-technology and engineered intensified systems has decreased the signal-to-noise ratio and improved the detection period for POCT. Biosensor-based target analysis is being considered a possible option for relieving the load on PCR-based techniques, which have been proven to be a superior platform throughout the pandemic. Biosensors-based wearable devices have been employed for easy and quick transmission tracing from sign to tester without the need for a state-of-the-art information analysis system based on understanding.[119−121] Electrochemical biosensors are the most extensively used miniaturized tool that draws a great deal of interest owing to the superiorities consisting of ease, low price, and simplicity of prototype. An electrochemical biosensor generally comprises a custom-designed electrode on which a receptor is placed for time-dependent, precise, and specific target analyte screening. Electrical signal is linked to the presence of the analyte of interest which can be obtained using potentiometric or amperometric methods.[122,123]

Analysis of SARS-CoV-2 was done by Tripathy and their team using an electrochemical biosensor. They used electro-deposited Au nanoparticles over a transducing element.[124] The researchers found that this approach provides quick data gathering, demonstrating its potential as a smart POCT device to lessen the need for large equipment. By introducing a 3-D printing approach, Md. Ali and their team created a 3-dimensional reduced-graphene-oxide electrode and integrated it with a microfluidic tool as an electrochemical sensor.[125] Also, 3-D electrodes have been functionalized with viral antigens to allow testing of antibodies against COVID-19. The sensor shows a LOD of 2.8 × 10−15 M. The magnetic beads were combined with a carbon-based electrode to create a small electrochemical sensor for COVID-19 detection.[126] Using magnetic beads, the outer magnetic chamber provides benefits such as increasing preconcentration and eliminating the washing step while maintaining advantages such as sensitive and reliable detection, anti-interference from seasonal H1N1 influenza virus, and so on. One of the current studies uses paper-based electrochemical sensors because of the benefits

https://doi.org/10.1021/acsabm.1c01320
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

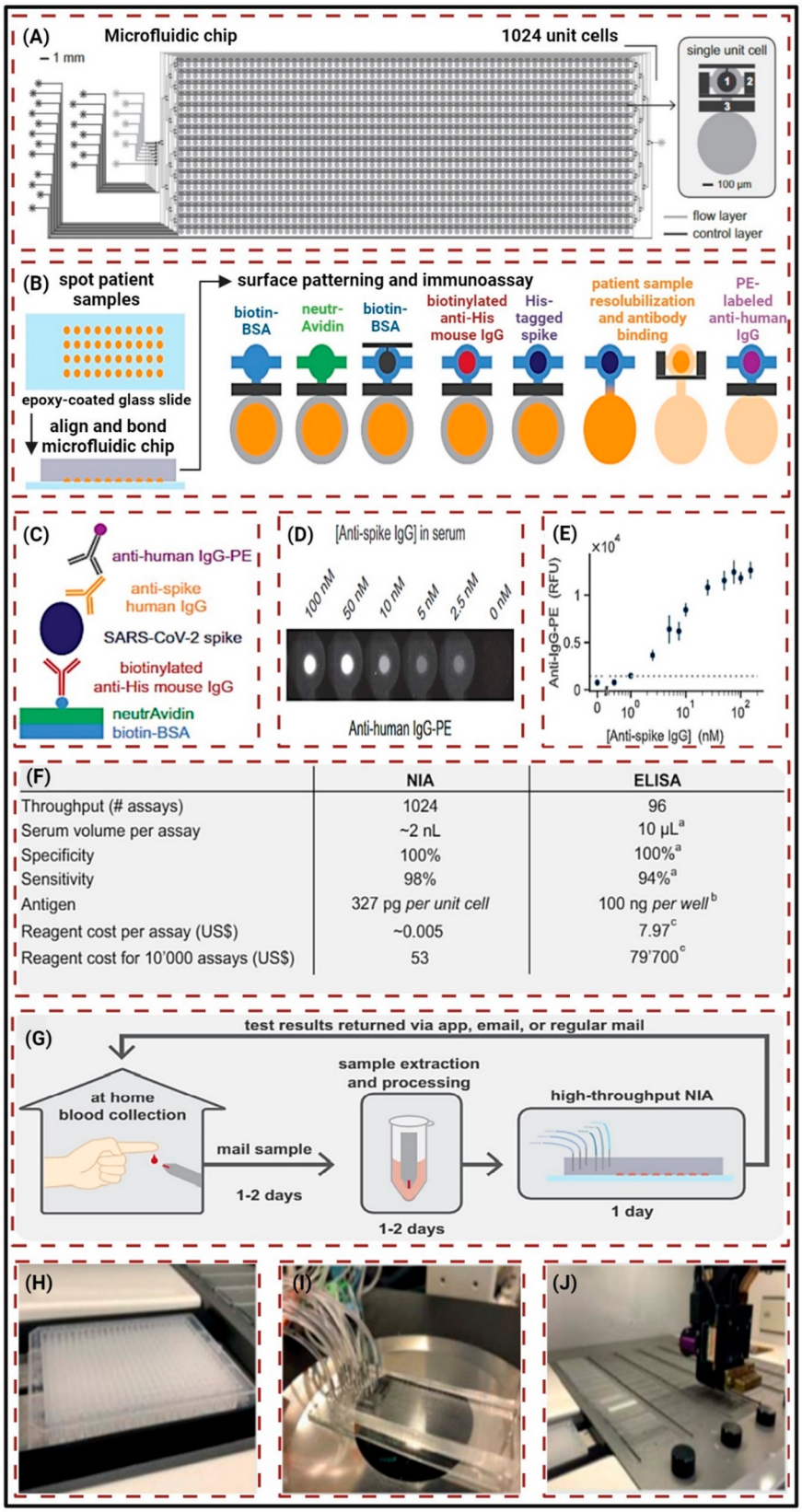


Figure 3. Detection of SARS-CoV-2 using high throughput microfluidic nano immunoassay. (A) The design of a microfluidic chip consists of 1024 unit cells. (B) Illustration showing the experimental process. (C) Process of sandwich immunoassay on the chip. (D) Fluorescence response of antihuman IgG-PE for the anti-spike antibodies in human serum. (E) Image showing LOD (dashed) and concentration of antihuman IgG-PE against anti-spike IgG. (F) Comparing parameters between high throughput nano immunoassay and the conventional ELISA technique. (G) Easy, fascinating NIA-based diagnosis process. (H) Spotting plate. (I) Micro arraying. (J) Nano immunoassay. Reproduced with permission from ref 116. Creative Commons License (CC BY 4.0).

https://doi.org/10.1021/acsabm.1c01320
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

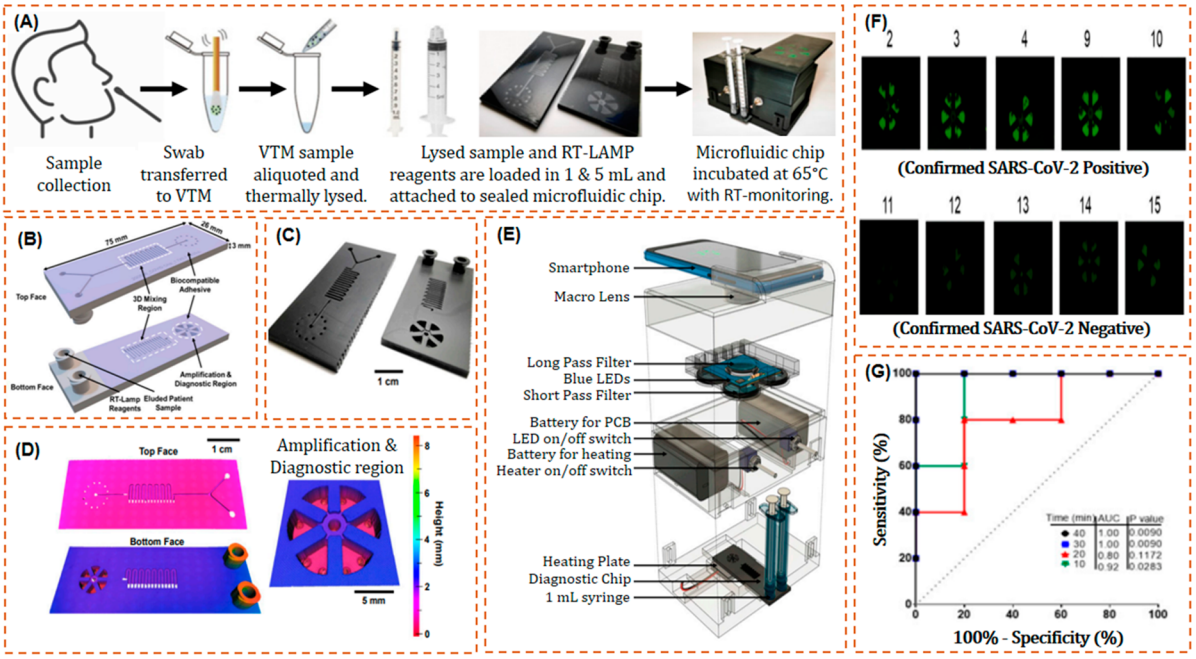


Figure 4. (A) Workflow used for the SARS-CoV-2 detection. (B) Microfluidic diagnostic cartridge was used for SARS-CoV-2 detection. (C) Disposable microfluidic cartridge. (D) 3-D scans of the microfluidic cartridge top and bottom focused image of the diagnostic and amplification region. (E) Labeled image of the smartphone coupled instrument showing components in a magnified view. (F) Fluorescence images of the results of positive and negative SARS-CoV-2 analysis on the real-time RT-LAMP at the diagnostic and amplification chip. (G) ROC curves showing sensitivity and specificity were analyzed for positive samples against the negative samples. Reproduced with permission from ref 108. Creative Commons License (CC BY 4.0).

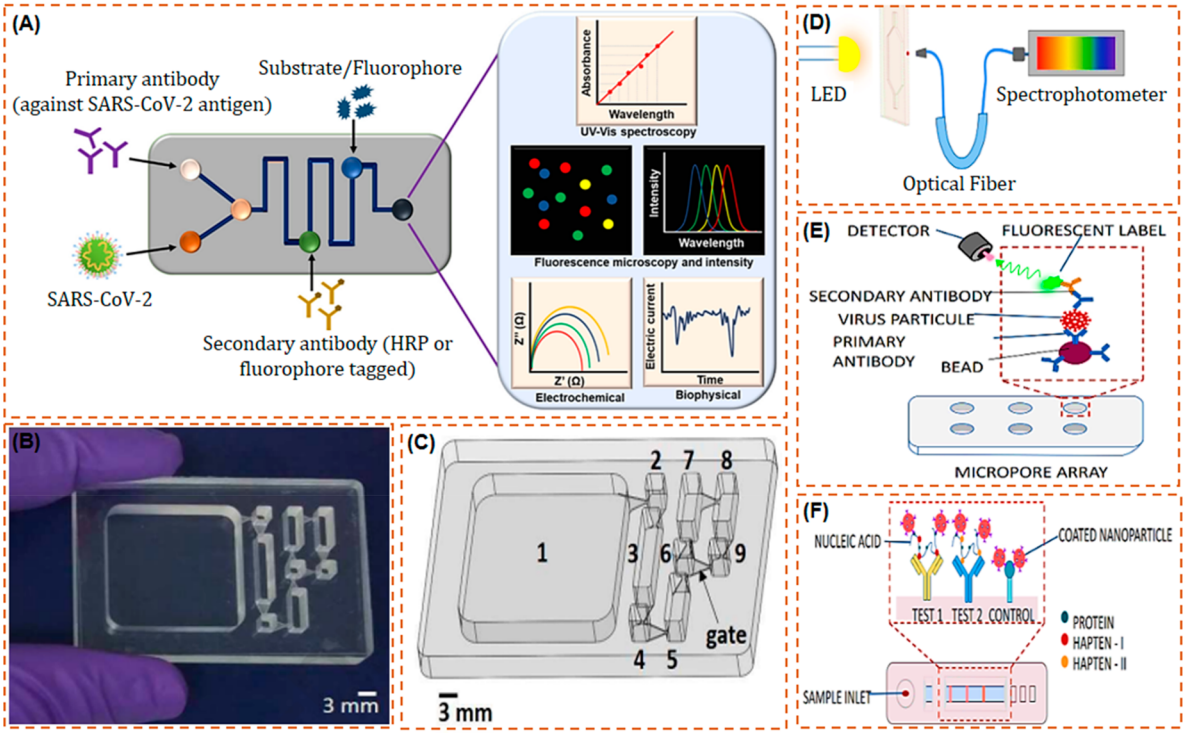


Figure 5. (A) Illustration of microfluidics integrated with other techniques for the detection of SARS-CoV-2 Reproduced with permission from ref 129. Creative Commons License (CC BY 4.0). (B) IFAST RT-LAMP device with (1) chamber for sample (2−8) chamber for detection (9) through gates. Reproduced with permission from ref 129. Copyright 2021 Elsevier. (C) IFAST RT-LAMP fabricated microfluidic device for detection of SARS-CoV-2. Optical-based detection techniques for detection of respiratory viruses. Reproduced with permission from ref 130. Copyright 2021 Elsevier. (D) Absorbance and transmittance-based technique. (E) Fluorescent based technique. (F) Paper-based microfluidic device for colorimetric detection. Reproduced with permission from ref 131. Creative Commons License (CC BY 4.0).

https://doi.org/10.1021/acsabm.1c01320
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

Table 5. Microfluidic Devices for Detection of COVID-19

material	microfluidic device	detection target	duration	sample type	selection	ref
gold@Fe3O4 nanocomposite	electrochemical sensor	nucleic acid		artificial and clinical RNA samples	against SARS-CoV-2, MERS-CoV, HCoV-OC43	132
gold nanoislands	plasmonics and photothermal effect	nucleic acid		synthesized samples	against SARS-CoV-2	142
gold nanoparticles	paper-based electrochemical sensor	nucleic acid	<5 min	COVID-19 positive patients	against MERS-CoV and SARS-CoV-2 viral RNA	128
graphene sheet	field-effect transistor	spike (S) protein	real-time electrical response	clinical sample for COVID-19patients		143
gold nanoparticles	surface plasmon resonance and colorimetric assay	nucleic acid	10 min	isolated RNA	against MERS-CoV viral RNA	144

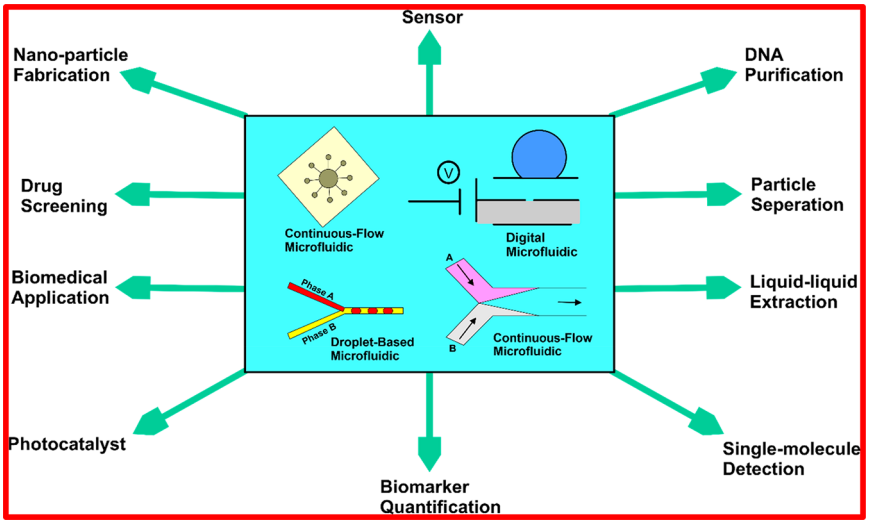


Figure 6. Application areas of microfluidics devices.

Table 6. Some Microfluidic Device Types with Their Advantage and Disadvantage in Detecting Biomolecules

type of device	advantages	disadvantages	ref
PDMS	highly sensitive can be controlled easily, less cost, need a little amount of sample, high efficacy	need special education and equipment for use, presently no medical centers are using this	145−150
Chip	easy to use, fast output, demands little amount of small amount of sample, easily detectable, manufactured easily	need a special instrument, more costly	151−155
μPAD	simple to use, cheapest device, faster outputs, easy storage, and disposal, needs a little sample	it has a poor detection limit, must be in a research setting only, needs a nonambient environment	156−159
LFSA	simple to use at home or in the medical center, cost-effective, faster outputs	it has a poor detection limit, must be in a research setting only	160−164

such as low price, being transportable, and easy disposable format. They print electrodes on paper. Yakoh and their team made the electrochemical tool to test COVID-19 antibodies, and the sensor gives results within 30 min.[127] The paper-based sensor has the potential to revolutionize the POCT platform with the desired sensitivity and property, particularly as they are cost-effective, transportable, and offer simple replacement options. Alafeef and his colleagues developed the detecting probes using a paper-based electrochemical technique for genetic material testing.[128] A portable rapid isothermal amplification (RT-LAMP) device was developed by Ganguli et al. for the detection of SARS-CoV-2 in clinical nasal swab samples. The schematic of an easy and accessible point-of-care device is shown in Figure 5. The device showed a LOD of 50 RNA copies per microliter and took 30 min for real-time detection of the viral genome. Further, herein additive manufacturing-based 3D cartridge has been used, and the device is coupled with a smartphone-based reader (Figure 4).[108]

In another study, a potential microfluidic approach for the detection of antibodies against SARS-CoV-2 has been proposed (Figure 5A). The ease of integration of microfluidic platforms with absorbance, fluorescence, and other diagnostic approaches makes them advantageous over conventional diagnostic strategies (Figure 5).[129]

With the specific layout of the nanomaterial-based sensing platform, the sensor offers high sensitivity and rapid results within 5 min. Importantly, the sensor tool also provides quantitative target analysis with a linear range of detection from 585.4 copies per μL to 5.854×10^7 copies per μL with a susceptibility of 231 copies per μL. To facilitate the quick result for consumer and at-home analysis, the information transmission is another challenge that ought to be considered aside from the electrochemical sensing aspect. Zhao and their team validated that their fabricated sensor may be tailored to a

https://doi.org/10.1021/acsabm.1c01320
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

cell phone for COVID-19 ribonucleic acid detection, which reduces the dependency on various kits and lab methods for COVID-19 detection.[132] Such a "plug-and-play" way can probably offer a transportable medium for the clients to evaluate the testing result outputs flexibly. The current advancement in electrochemical methods coupled with wireless medium to allow the rapid detection of SARS-CoV-2 is primarily based on huge scale graphene electrodes.[133] Table 5 represents some nanocomposite materials used for the detection of SARS. The validated "SARS-CoV-2 RapidPlex" is cost-effective and reveals high sensitivity, offering multiplexed data on key biomarkers of the SARS-CoV-2 virus, which include viral contamination, immune reaction, and sickness seriousness, with the capacity of home-based prognosis. The broad application of microfluidics in various areas ranging from small valves to biomedical sensors and equipment is shown in Figure 6. Some of the advantages of various microfluidic devices are listed in Table 6.

The primary difficulty for nucleic acid testing (NAT) is to achieve low-cost, high-throughput, automated nucleic acid (NA) detection from raw samples (e.g., whole blood), which can be solved by fully integrated microfluidic devices that are simple to produce and operate. The completely integrated NA detection is critical, and the sample-in-qualitative-answer-out technique is very simple to implement due to the minimal requirements for NA extraction purity and amplification efficiency. As a result, it is ideal for NA detection with "yes" or "no" answers, for instance, in the case of the Acquired Immune Deficiency Syndrome (AIDS) test and genotyping. NA detection signals on qualitative integrated microfluidic devices mostly comprise colorimetric and fluorescent signals.[134−138]

The colorimetric signal of integrated devices can be read with the naked eye without the need for any apparatus, which decreases the cost and resource requirements. In comparison, the limit of detection of fluorescence in integrated devices is lower than that of colorimetric detection. Because of the downsizing of fluorescent readout devices, sample-in-fluorescent-answer-out systems have promising potential for NA qualitative detection. The biggest barrier to commercialization for these high-quality devices is a lack of user-friendliness induced by frequent manual interventions during detection. To match clinic needs, detection sensitivity and stability must be increased further.[139]

Sample-in-quantitative-answer-out technology can give precise information for optimum clinic intervention in applications where accurate detection findings are required. A range of quantitative detection methods based on electrochemistry, fluorescence, absorbance, and surface plasmon resonance (SPR) has been proposed to achieve this goal. Fluorescent signals based on dye molecule labels have been widely implemented on point-of-care devices for quantitative readout using image processing software or portable advanced practice providers. Thus, when paired with isothermal amplification techniques, microfluidic devices with fluorescent signal output capacity can achieve sample-to-quantitative-answer out for NA detection.[138]

In contrast to qualitative detection, quantitative detection with higher sensitivity can enable dynamic monitoring and illness categorization, indicating a high potential for extensive clinical use. Real-time isothermal amplification (e.g., real-time LAMP and real-time RPA) techniques based on a periodic acquisition of fluorescence or absorbance signal have been widely used for quantitative results output, similar to traditional real-time PCR for quantitative NA detection. However, today's quantitative procedures necessitate extensive peripheral signal processing systems, which include signal capture, analysis, and transmission modules. As a result, most extant sample-in-quantitative-answer-out solutions take the form of a disposable chip and a reusable device. For practical POC applications, instrument-independent detection is recommended, particularly in resource-constrained settings. As a result, the analytical instrument's downsizing is crucial to boost mobility and save energy, making it ideally suited for field application. Meanwhile, the conversion of computer-based data processing onto mobile terminals would help with commercialization.[139] Existing portable commercially accessible quantitative instruments, such as glucometers and pressure meters, have been introduced for indirect analyte quantification, indicating the tremendous potential to commercialize instrument-free integrated quantitative NA detection.[140,141]

7. INTERNET OF THINGS (IOT)-ENABLED AND SMARTPHONE COUPLED DEVICES FOR DETECTION OF SARS-COV-2

An artificial intelligence (AI)-aided radiologic analysis system for SARS-CoV-2 such as computed tomography of the chest area is now taken into consideration because of its excessive efficiency in detection of pneumonia-like symptoms. In a meta-evaluation of 50 466 patients, as many as 97% of SARS-CoV-2 sufferers had a typical chest CT.[165] Few reviews showed that computed tomography experiments could perceive COVID-19 infection in advance in comparison to viral RT-PCR.[166] In addition, chest computed tomography imaging showed abnormalities in sufferers with moderate or no symptoms.[167] In the computed tomography, maximum sufferers confirmed more than one ground-glass opacity and infiltrating shadows on bilateral lobules and subareas, while in severe condition, pulmonary consolidation also occurred.[168] Because of the rapid spread of the virus, faster result interpretation is required by radiologists to study chest radiographic images. Artificial intelligence is taken into consideration as an aid to help radiologists in SARS-CoV-2 pneumonia analysis. Wang et al. have set up AI algorithms for the correct analysis of SARS-CoV-2 pneumonia primarily based on computed tomography parameters through deep learning technique.[169−171] With help of a massive computed tomography database arising from 3777 infected persons, AI-based algorithms not only help in the treatment of novel pneumonia caused by coronavirus but also can differentiate it from different types of pneumonia from ordinary ones with the support of a mixture of image-primarily based and quantifiable scientific factors. In addition, researchers investigated the connection between imaging functions and scientific biomarkers and integrated it into AI, which helps in viral prognostics. However, using the state-of-the-art implementation strategies the chest CT scans is not appropriate as a frontline diagnostic. To broaden the diagnostic field to fight against SARS-CoV-2, we should also look to broaden an AI-integrated X-ray or CT as a quick, rapid detecting device for the analysis of pneumonia caused by SARS-CoV-2.[172] Further, AI can be very beneficial with the monitoring and control of SARS-CoV-2,[173] in terms of high detecting accuracy of affected cases, which enhance the survival of significantly unwell patients, presenting the best therapeutic plan, and in the finding of antiviral medicines. Artificial

https://doi.org/10.1021/acsabm.1c01320
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

intelligence-powered robots also can carry out duties for disinfection and aid social distancing; this is typically done without involving humans and for that reason decreasing the risk of infection spread rate in public. With the speedy improvement of the Wi-Fi net era and the growing population of smartphone users, the Mobile Health system has emerged as a valuable technique for healthcare maintenance for humans. An AI-based scientific machine can offer online analytic help to hospitals and clinics in gathering the affected person's data history, symptoms, data of CT imaging, results of laboratory blood tests, or even correlate with the state-of-the-art epidemiology facts (e.g., the state-of-the-art incidence of COVID-19 within the region or traveling history of person), which helps in danger evaluation and perceive the suspected SARS-CoV-2 infection, hence presenting therapeutic decision-making choices for the medical care providers. For containment of SARS-CoV-2 in China, greater than 190 public scientific establishments and almost 100 net hospitals throughout China supplied online unfastened session offerings, this keeping off track of affected person touch and direct sanatorium visits, and simultaneously providing care to the affected person while keeping off the danger of nosocomial COVID-19 contamination. Big facts from mobile information, tour data, and social media facts can offer tour styles and information on sufferers with viral contamination, which may be helped to tune affected people near contacts and predict outbreaks. The Allen Institute of Artificial Intelligence, in partnership with leading research studies establishments, has launched an open studies database with weekly information at the SARS-CoV-2 to boost up new studies tasks that provide present-time data.[174] Data software structures inclusive of geographic statistics structures, mapping dashboards, and case-monitoring programs can permit close to real-time tracking of affected person trajectories and social-networking response to a viral transmission. As per the population travel information, danger maps and the trajectories of remarkable transmitters and near contacts can be documented. The structures can screen the temporal and spatial transmission of SARS-CoV-2 and have been proven to be a well-timed and powerful tracking device to tune the virus spreading rate. It can suggest the facts to suitable authorities for immediate responses.[175] The visible and interactive international epidemic map made by the studies group at J H University in the United States of America is presently the maximum extensively employed SARS-CoV-2 epidemic monitoring map.[176] For the epidemiology of SARS-CoV-2 in China, the United States, Canada, and Australia data are gathered. The National Health Commission from China, in association with the industry, launched an "intimate touch measurement" software in February 2020, and through this device, the general public can take a look at if they were or are in near contact with a recognized infected COVID-19 person. However, privatizing issues will not permit this to be carried out in different countries. Telemedicine and eHealth providers seek advice from the usage of computer program structures to offer healthcare distantly. It provides real-time interactive visible, textual input audio, and facts communications to supply scientific-care, session, analysis facts, and remedy. Telemedicine and eHealth have deployed the usage of smartphones, VoIP, and video discussions.[177] Telemedicine restricts publicity of inclined sufferers while concurrently granting healthcare providers the possibility to offer care. Furthermore, telemedicine may permit sufferers to reach their doctors at a distance through the eHealth app inclusive of computer systems as well as mobiles permitting the doctors to see the patients via display screen earlier than they could go to the hospital.[178] This may result in a tremendous decline in pointless disease cases via inspiring self-isolation and social distancing.[179,180] Even though telemedicine can begin with cell smartphone consults, different laptop technology inclusive of webcam-enabled nonpublic computer systems, smartphones, and excessive-pace net may be hired to offer healthcare to sufferers. While the face-to-face session is certainly critical for a medical doctor analyzing an affected person, it is far untenable at some stages in pandemics. Leite et al. encouraged outpatients inclusive of the ones now no longer infected with the SARS-CoV-2 virus, especially the excessive-sensitive categories (pregnant women, older peoples, etc.), to use telemedicine as it could offer secure and handy options as a remedy without the need to visit the care center.[181−183] IoT integrated health care applications aid sufferers to be handled at their homes, with a better degree of care, also aid supplies of data digitally and help physicians to provide care to the individual under emergency situations through 911 calls, lowering the demand for movement to the emergency unit. This digital emergency facility could help to allocate works among the specialist scientific practitioners.[184] Mobile health entails the usage of appropriate tools and hand-held gadgets geared up to control hospital-based therapy operations in terms of scientific facts and availing experience of earlier infected/diseased conditions. This software can be utilized to get the right scientific statistics, which would be utilized by doctors to aid dissemination of such statistics with different scientific practitioners in real-time.[177] Self-quarantine and social isolation are being assessed by the use of social networking applications. Even though eHealth structures cannot update interaction on a one-on-one basis, they offer ease for folks who experience loneliness and depression because of the live-at domestic order/lockdown. These programs may be hooked up and utilized in smartphones having different OS. It can be assessed using the laptop software program in Windows structures and Apple MacBook among others. Medical programs contain applications that offer healthcare in both synchronous and asynchronous manners to patients. The eHealth structures provide health care manual and assets especially to sufferers dwelling in undeveloped regions wherein health care is inadequate. Besides, eHealth platforms enable sufferers to get suggestions from faraway physicians during catastrophe or emergency. For instance, one scientific program called K Health provides Doctor on Demand and Primary Care, while another known as Teladoc can be downloaded on mobile application manager and used for health care management. These scientific programs offer patients to certified physicians for non-emergency health issues too and are encouraged via way of means of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) compliant in the US.[185] Contact tracing is a critical step for society to control the spread of COVID-19. Currently, touch tracing programs are getting used throughout the world. As an example, the Singaporean authorities launched a cell software TraceTogether, advanced to assist fitness officers in monitoring infected men or women and who they will have been in touch with. In Israel, a regulation program led the authorities to tune the facts of people with suspected contamination. In Taiwan, health care establishments via smartphone track and informed people for quarantine.[186] Health and health programs are currently

https://doi.org/10.1021/acsabm.1c01320
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

employed as a result of quarantine and social isolation that promote sedentary behavior and decreased bodily interest, which is a kind of health burden for a population that spends 60% of its time involved in sluggish activities. Therefore, the usage of fitness and health programs has the potential to lessen the ill effect of sedentary behaviors, enhance mental fitness, and maintain the drowsing habits. Software MyFitnessPal, which gives a diet regime and calorie tracker, is getting used to offer the advantage of healthy life.[185]

8. FARSIGHTEDNESS AND PREPAREDNESS HOLD PROMISE TO DEAL WITH FUTURE PANDEMICS

Regular disease monitoring in viral illnesses is essential for being capable of dealing with pandemics and reducing the social and economic health burden of the country. Nations that have accomplished well in dealing with SARS-CoV-2, for example, South Korea and Vietnam, had precise infection monitoring systems.[187] India had made a fairly powerful "Integrated Diseases Surveillance Program (IDSP)", that offered information about the infection—outbreaks; however, it was not presenting such information after February. To suffice the need, the Indian Government commenced a new portal for SARS-CoV-2 update.[188] A powerful ailment surveillance system reviews not only surprising uncommon health incidences but also additionally routine records on viral sequence from each health care provider. As a result, every usual burst of fever and symptoms raises a local alarm, allowing for a well-timed and sufficient response. These indications and symptoms-based evaluations inform the local bodies, which must be followed up with confirmation tests performed in a lab network. In larger metropolitan regions, the IDSP's symptom-based statistics detect afflicted individuals' death and are useful in the early identification of recent chains of contamination and adverse reaction to them. A reliable digital illness monitoring tool that is seamlessly integrated with health management information systems is also an important aspect of building durability. The actual health facts furnished through such a method are worthwhile but not best for presenting early signs of a deadly disease; however, they provide additional support for monitoring the spread of the epidemic, forecasting, and getting ready the care portal for the surge.[189] It also identifies areas where access to certain vital health services is needed, which needs to be addressed as soon as possible. However, there are several inadequacies in current health management data architectures. The lack of interoperability between the IDSP's virtual platform and the HMIS is one issue. In addition, in most states, the HMIS no longer has personal area information. Furthermore, neither the disease surveillance system nor the HMIS gathers information that may be disaggregated for understanding sickness relationships with inequity such as migrant workers, the elderly, or other disadvantaged populations who could be a source of disease transmission. Countries that are exceptionally good in health information systems, just like the National Health Services (NHS) in the United Kingdom, had provided greater awareness of the COVID-19. They had started initial research of mode of transmission of viral infection, from their well-maintained infected person information, and use this to perceive the spreading chains and contact tracing for the SARS-CoV-2 mortality/morbidity rate of their country.[190] There is also a requirement to link HMIS with data from other fields. For example, there is a need to link healthcare data with environmental and weather-change measurements, as well as predictions of extreme weather, to see how this affects each chronic pollution and pandemic outbreak.[191] Similarly, we additionally require integration of financial information with the wellbeing system, as a model, the effect of the huge variety of economic occasions like modifications in trade coverage or economic disaster just like the international economic disaster of 2009, on the health effects and health systems performance.[192] One of the demanding situations we are facing in those records is associated with the time-bound of the data series and problems of integration. The health records regularly lag 12 months behind, while monetary records are more on time.[193] While handling emergencies, the facts needed can be exceptional from the information needed for ordinary purposes.[194] To cope with these problems, there is huge demand for funding in HR training, modern and handy ways, if possible open supply, and precise governance. This will be visible in Germany where a lab had been prepared to make greater than 50 000 tests mid February; even if COVID-19 spread into a large part of China, they have a strong initial forecasting system, that had been "maximally equipped". Among the essential and least mentioned factors of constructing robust health care systems is the capacity to control international and native chains of infection for critical therapeutic products. One indicator of this is that every country's public health infrastructure must have reliable procurement and distribution networks. In India, a few states, such as Kerala, Tamil Nadu, and Rajasthan, have systems in place; nevertheless, logistics may be an issue for others. Such home capability will offer enough portions of essential drug treatments, diagnostics, devices, vaccines, and a private protecting system that the United States requires. SARS-CoV-2 has proven to us that during a disaster, international supply chains are unreliable and unfair. The European countries and the United States are possible to go into superior marketing dedications with the intention to nook supplies or medicinal drug even earlier than they're made. But India has a popularity of being the drugstore of the growing international world due to the fact that it has the capacity to manufacture all critical drugs and diagnostics that are now no longer present in India, in accordance with the complete international requirement. However, this may have a long way to be fulfilled and need investment in from developed countries. We should apprehend what went wrong in the course of this COVID-19 pandemic and why we needed to import nearly all of the medical equipment, tablets, and personal protective kits that the United States required. This might assist us to plan to quickly reconstruct our local capability in manufacturing and domestic productivity of critical clinical items.[192,195] Health system response in the course of Ebola illnesses in Liberia turned into praise considering that they supplied loose offerings for human beings without Ebola. Public coverage in India to take care of all sufferers coming to hospitals is difficult to handle due to deficiency of consumables and basic amenities. One of the primary desires of public health structures is to make certain economic safety. In addition, the cost of health care during lockdowns and unemployment affected the normal life of millions of people. The economic safety toward the cost of medical care is that almost all operating human beings require a better stage of public health care funds than presently allocated.

https://doi.org/10.1021/acsabm.1c01320
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

9. FOURTH-DIMENSION FUTURISTIC APPROACH FOR DISEASE DIAGNOSTIC AND PROGNOSTIC

Setting up a network of production, distribution, and health care monitoring is a high priority for society and clinical institutions to be better prepared for future pandemics or natural catastrophes. Having pretested diagnostics that can be quickly synthesized to fill time-sensitive shortfalls for critical care demands would allow centers to provide the best possible patient care while also protecting their clinical employees. Clear regulatory guidelines and curated layout archives are critical to assisting those efforts. Establishing and strengthening the alliances and networks that were formed during SARS-CoV-2 Surge 1 might be crucial to averting future threats and shortages. With strong network involvement and assistance networks, a more resilient community can emerge to become even more powerful when localized surges or disasters happen, and more distant community nodes can backfill supplies. The use of municipalities and academic institutions to create flexible networks of human capital and industrial capacity results in shorter and less frequent catastrophe response waves.[196] Concerning COVID-19 ribonucleic acid detection, greater work is required to achieve a simple, distinctly powerful method for enrichment of COVID-19 ribonucleic acid from patients samples for direct amplification. Further, the mixture of efficient isothermal RNA amplification and excessive sensitivity detection technology (which includes electrochemical biosensors) is required for fast, short-time, and efficient detection of the SARS-CoV-2 genome. The current review showed that biosensors have the brilliant capacity for fast, excessive-accurate, cost-effective COVID-19 ribonucleic acid detection. Microfluidic-integrated biosensors provide viral enrichment, ribonucleic acid extraction, and amplification altogether incorporated into disposable sensors on a single platform. Microfluidic chips have been successfully used for the sample-to-end result of COVID-19 ribonucleic acid detection.[197] Given that it commonly takes 1 to 2 weeks for human B cells to supply and produce generally traceable antibodies into the serum after viral infection; hence, there may be fewer serum antibodies in the early phase of SARS-CoV-2 infection, which can provide false-negative results in the case of LFIA. Therefore, COVID-19, proteins, and viral genome detection are considered better techniques for giving direct initial evidence of COVID-19 infection.[198] Finding these biomarkers will be the most effective method for early POC screening of SARS-CoV-2 sufferers. However, the viral proteins and viral particles are very little in the body fluids of SARS-CoV-2 patients.[199−201] Therefore, novel, promising, excessive-sensitivity POCT immunosensors, which include NIR emitting nanoparticles, magnetic nanoparticle-based LFAs, and electrochemical biosensors, for detection of SARS-CoV-2 antigen, antibodies, and virus particles, are the need of the hour. While point-of-care biosensors are broadly available, further enhancements are needed to deliver high throughput results. The current common diagnostic kits contain IgG test strips and take less assay time; however, their sensitivity and specificity needed to be improved.[202] To improve detection efficiency, a few sensitivity enhancement techniques must be applied to the biosensors such as fluid dynamic management, enzyme-based signal improvement techniques, and sample pretreatment strategies.[203−205] To enhance detection sensitivity, the functionality of multiplexing is vital, which also improves assay productivity.[206] In particular, the clubbing of each IgG/IgM and RNA test could provide the information on the initial and later stages of SARS-CoV-2 infection, providing accurate and reliable results.[207] Also, to make the testing assay easier to perform, multiple processing steps starting from sample pretreatment to signal detection must be incorporated into a single biosensor. Importantly, recent research has integrated sample-to-answer techniques right into single biosensors to find antibodies and genetic material of the virus, which can be performed for the detection of SARS-CoV-2.[208] Moreover, integrating a sample collector in the biosensors could make it greater user-friendly. For example, incorporating a microneedle for the painless series of blood samples can make the biosensor less invasive and could additionally lessen affected person anxiety and stress.[209] Since blood samples can be taken with a single push of a button, the usage of biosensors needs little skill or education. Besides blood testing sensors, greater point-of-care biosensors are being evolved to detect the SARS-CoV-2 virus in saliva.[210,211] This method is noninvasive, and the sample is simple to acquire transport and test. Future research must also be cognizant of developing transportable and miniaturized biosensors.[212] Storing reagents on-chip could be most suitable to cut off the requirement for storage units, for example, refrigerator and freezer.[213] Moreover, integrating a transportable electric temperature control unit could strengthen assay functionality, mainly for genetic material assessments kits that needed a heater for amplification.[214,215] This feature is beneficial specifically in low-resource settings. Data quantification is likewise vital as it should be compared to assess the sufferers' health conditions.[216] It will be done through growing telephone applications that permit data characterization in remote settings while permitting information storage to tune sufferers' health status. Employing Internet-of-Things (IoT) provides sufferers' test outcomes with medical care workers and allows evaluation and monitoring of affected person fitness statistics for onsite real-time health care monitoring.[217,218] In summary, the easy, fast, less costly, and transportable biosensors have shown potential in point-of-care testing in this pandemic time. Given that the virus may be transmitted to a healthy person from a patient, the improvement of home-based point-of-care biosensors is of supreme significance to permit self-assessment and instantaneously self-quarantine as soon as a person is tested positive to keep away from spreading the virus.[207] It is envisioned that the emerging point-of-care biosensors will be made on a huge scale for mass testing of SARS-CoV-2 cases to combat the pandemic. Future lockdowns are likely to come. Information technology could be capable of supporting the clinical factors, vaccination statistics, and therapeutic strategies directly; also we can share knowledge, experiences, and technology to tackle futuristic pandemics. It is very difficult to set up a worldwide common data management platform for public health records because of numerous factors which include technical, geopolitical, and moral challenges. To this level, statistics data banks can at the least assist endorsing and constructing a countrywide common health data portal for society health records sharing. Moreover, COVID-19 investment opportunities, to get economic aid to place several thoughts into practice would help to manage economic losses. For example, the United States National Science Foundation and National Institutes of Health have presented projects that provide financial aid to address demanding situations due to the coronavirus. In addition, more college students with statistics and data science backgrounds can be employed as interns. Because a large number of small organizations in

https://doi.org/10.1021/acsabm.1c01320
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

industries which include tourism, food service, and commercial stores are being hit toughest through the pandemic, information technology faculty should gather students, as a part of mini commercial enterprise proprietors. This could assist in shaping statistics data collection and management in the pandemic. Several colleges are supporting this and mentoring micro commercial enterprise proprietors on deploying virtual technology to cope with the challenges of commercial enterprise continuity.[219] Some professors have been involved in virtual answer improvement projects, for example, tackling misinformation and arranging activities, which include online hackathons to acquire human beings with numerous talents to paintings on solutions to combat SARS-CoV-2.[220,221] At last, a number of the evolved technology and alertness for this pandemic might also be beneficial after the COVID-19 ends for better preparedness of futuristic pandemics.[222] The involvement of computational approaches can be useful for future scientific settings and could produce a big technological revolution to treat human health-associated problems in a real-time manner. Artificial intelligence avoids human emotional problems, religion and ethical faith, and fatigue.[223] Optimal decision-making intelligence and nonstop upgrading through networks and deep learning could be remarkable gear to help clinical doctors with the analysis and in finding the disease in a brief time.[224] Artificial intelligence-based deep learning algorithms have lots of boundaries at small and large levels for the medical care area. These bottlenecks consisting of unregulated algorithms, unsupervised studying implementations, affected the personal data confidentiality, and records set size, call for big interest toward human-computer interface and the usage of AI.[223] The reproducibility of diagnostic tests is one of the main boundaries in molecular drug findings that takes a few years to release powerful components in the marketplace after scientific research.[225] Analyzing a big set of complex and numerous health care records should be controlled via way of means of the evaluation of large records and ML gear to decrease hassle and false-positive data.[226] Lastly, AI itself-sufficient and cannot over-ride human involvement. AI in the clinical professional can reap a particular remedy overall performance and identify the best diagnostic at the very best possible level.

10. CONCLUSIONS

The article deals with the impact of COVID-19 first, second, and third wave along with the symptoms and precautions that are being addressed. The evolution of diagnostic methods from conventional to more sophisticated microfluidics and AI integrated processes has been discussed. The rapid detection methods using microfluidics technology and biosensors kept the health monitoring system growing at a very convenient pace. The use of machine learning and artificial intelligence coupled together with the latest technologies of biosensors and mobile phones made it possible for general human beings to take care of themselves, be aware of the environment, and also helped them to get a lot of information on the spread of disease and its preventive controls. The vaccines are still gaining some exposure to the use of IoT and maintaining a database so that a track of vaccinated people can be maintained. The efficacy of medicines and vaccines undergoing trials is about to be released for common people when all the relevant procedures are completed. So far, it is clear that this pandemic bought up many issues concerning health-based technology and the milestones that humans have achieved to date.

AUTHOR INFORMATION

Corresponding Author

Arpana Parihar − *Industrial Waste Utilization, Nano and Biomaterials, CSIR-Advanced Materials and Processes Research Institute (AMPRI), Bhopal, Madhya Pradesh 462026, India;* orcid.org/0000-0003-3678-9405; Email: arpana_parihar@yahoo.com

Authors

Avinash Kumar − *Department of Mechanical Engineering, Indian Institute of Information Technology Design & Manufacturing Kancheepuram, Chennai 600127, India*

Udwesh Panda − *Department of Mechanical Engineering, Indian Institute of Information Technology Design & Manufacturing Kancheepuram, Chennai 600127, India*

Dipesh Singh Parihar − *Engineering College Tuwa, Godhra, Gujarat 388713, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsabm.1c01320

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The fellowship provided by DST under the DST-WOS-B scheme to A.P. is duly acknowledged.

REFERENCES

(1) Ksiazek, T. G.; Erdman, D.; Goldsmith, C. S.; Zaki, S. R.; Peret, T.; Emery, S.; Tong, S.; Urbani, C.; Comer, J. A.; Lim, W.; et al. A Novel Coronavirus Associated with Severe Acute Respiratory Syndrome. *New England Journal of Medicine* **2020**, *348* (20), 1953−1966.

(2) Li, Q.; Guan, X.; Wu, P.; Wang, X.; Zhou, L.; Tong, Y.; Ren, R.; Leung, K. S. M.; Lau, E. H. Y.; Wong, J. Y.; Xing, X.; Xiang, N.; Wu, Y.; Li, C.; Chen, Q.; Li, D.; Liu, T.; Zhao, J.; Liu, M.; Tu, W.; Chen, C.; Jin, L.; Yang, R.; Wang, Q.; Zhou, S.; Wang, R.; Liu, H.; Luo, Y.; Liu, Y.; Shao, G.; Li, H.; Tao, Z.; Yang, Y.; Deng, Z.; Liu, B.; Ma, Z.; Zhang, Y.; Shi, G.; Lam, T. T. Y.; Wu, J. T.; Gao, G. F.; Cowling, B. J.; Yang, B.; Leung, G. M.; Feng, Z. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *New England Journal of Medicine* **2020**, *382* (13), 1199−1207.

(3) Zhang, J.; Litvinova, M.; Wang, W.; Wang, Y.; Deng, X.; Chen, X.; Li, M.; Zheng, W.; Yi, L.; Chen, X.; Wu, Q.; Liang, Y.; Wang, X.; Yang, J.; Sun, K.; Longini, I. M.; Halloran, M. E.; Wu, P.; Cowling, B. J.; Merler, S.; Viboud, C.; Vespignani, A.; Ajelli, M.; Yu, H. Evolving Epidemiology and Transmission Dynamics of Coronavirus Disease 2019 Outside Hubei Province, China: A Descriptive and Modelling Study. *Lancet Infectious Diseases* **2020**, *20* (7), 793−802.

(4) Zheng, M.; Gao, Y.; Wang, G.; Song, G.; Liu, S.; Sun, D.; Xu, Y.; Tian, Z. Functional Exhaustion of Antiviral Lymphocytes in COVID-19 Patients. *Cellular and Molecular Immunology* **2020**, *17* (5), 533−535.

(5) World Health Organization. *WHO Coronavirus*; WHO, 2020. Vol. *April*, pp 18−19.

(6) Yuki, K.; Fujiogi, M.; Koutsogiannaki, S. COVID-19 Pathophysiology: A Review. *Clinical Immunology* **2020**, *215* (April), 108427.

(7) Long, Q.; Tang, X.; Shi, Q.; Li, Q.; Deng, H.; Yuan, J.; Hu, J.; Xu, W.; Zhang, Y.; Lv, F.; Su, K.; Zhang, F.; Gong, J.; Wu, B.; Liu, X.; Li, J.; Qiu, J.; Chen, J.; Huang, A. Clinical and Immunological Assessment of Asymptomatic SARS-CoV-2 Infections. *Nat. Med.* **2020**, *26*, 1200.

https://doi.org/10.1021/acsabm.1c01320
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

(8) To, K. K.-W.; Hung, I. F.-N.; Ip, J. D.; Chu, A. W.-H.; Chan, W.-M.; Tam, A. R.; Fong, C. H.-Y.; Yuan, S.; Tsoi, H.-W.; Ng, A. C.-K.; Lee, L. L.-Y.; Wan, P.; Tso, E. Y.-K.; To, W.-K.; Tsang, D. N.-C.; Chan, K.-H.; Huang, J.-D.; Kok, K.-H.; Cheng, V. C.-C.; Yuen, K.-Y. COVID-19 Re-Infection by a Phylogenetically Distinct SARS-Coronavirus-2 Strain Confirmed by Whole Genome Sequencing. *Clin. Infect. Dis.* **2021**, *73*, 1−25.
(9) Tillett, R. L.; Sevinsky, J. R.; Hartley, P. D.; Kerwin, H.; Crawford, N.; Gorzalski, A.; Laverdure, C.; Verma, S. C.; Rossetto, C. C.; Jackson, D.; Farrell, M. J.; Van Hooser, S.; Pandori, M. Genomic Evidence for Reinfection with SARS-CoV-2 : A Case Study. *SSRN J.* **2020**, *3099* (20), 1−7.
(10) Wen, J.; Cheng, Y.; Ling, R.; Dai, Y.; Huang, B.; Huang, W.; Zhang, S.; Jiang, Y. Antibody-Dependent Enhancement of Coronavirus. *International Journal of Infectious Diseases* **2020**, *100*, 483−489.
(11) Khan, M. T.; Islam, M. J.; Parihar, A.; Islam, R.; Jerin, T. J.; Dhote, R.; Ali, M. A.; Laura, F. K.; Halim, M. A. Immunoinformatics and Molecular Modeling Approach to Design Universal Multi-Epitope Vaccine for SARS-CoV-2. *Inform Med. Unlocked* **2021**, *24*, 100578.
(12) Long, Q. X.; Tang, X. J.; Shi, Q. L.; Li, Q.; Deng, H. J.; Yuan, J.; Hu, J. L.; Xu, W.; Zhang, Y.; Lv, F. J.; Su, K.; Zhang, F.; Gong, J.; Wu, B.; Liu, X. M.; Li, J. J.; Qiu, J. F.; Chen, J.; Huang, A. L. Clinical and Immunological Assessment of Asymptomatic SARS-CoV-2 Infections. *Nature Medicine* **2020**, *26* (8), 1200−1204.
(13) Brooks, S. K.; Webster, R. K.; Smith, L. E.; Woodland, L.; Wessely, S.; Greenberg, N.; Rubin, G. J. Rapid Review The Psychological Impact of Quarantine and How to Reduce It: Rapid Review of the Evidence. *Lancet* **2020**, *395*, 912−920.
(14) Hawryluck, L.; Gold, W. L.; Robinson, S.; Pogorski, S.; Galea, S.; Styra, R. SARS Control and Psychological Effects of Quarantine, Toronto, Canada. *Emerging Infectious Diseases* **2004**, *10* (7), 1206−1212.
(15) Jeong, H.; Yim, H. W.; Song, Y. J.; Ki, M.; Min, J. A.; Cho, J.; Chae, J. H. Mental Health Status of People Isolated Due to Middle East Respiratory Syndrome. *Epidemiol Health* **2016**, *38*, No. e2016048.
(16) Cukor, J.; Wyka, K.; Jayasinghe, N.; Weathers, F.; Giosan, C.; Leck, P.; Roberts, J.; Spielman, L.; Crane, M.; Difede, J. A. Prevalence and Predictors of Posttraumatic Stress Symptoms in Utility Workers Deployed to the World Trade Center Following the Attacks of September 11, 2001. *Depression and Anxiety* **2011**, *28* (3), 210−217.
(17) Alvarez, J.; Hunt, M. Risk and Resilience in Canine Search and Rescue Handlers after 9/11. *Journal of Traumatic Stress* **2005**, *18* (5), 497−505.
(18) Stefana, A.; Youngstrom, E. A.; Hopwood, C. J.; Dakanalis, A. The COVID-19 Pandemic Brings a Second Wave of Social Isolation and Disrupted Services. *European Archives of Psychiatry and Clinical Neuroscience* **2020**, *270* (6), 785−786.
(19) Soriano, V.; Ganado-Pinilla, P.; Sanchez-Santos, M.; Gómez-Gallego, F.; Barreiro, P.; de Mendoza, C.; Corral, O. Main Differences between the First and Second Waves of COVID-19 in Madrid, Spain. *International Journal of Infectious Diseases* **2021**, *105*, 374−376.
(20) Graichen, H. What Is the Difference between the First and the Second/Third Wave of Covid-19? - German Perspective. *Journal of Orthopaedics* **2021**, *24*, A1−A3.
(21) Soriano, V.; de Mendoza, C.; Gómez-Gallego, F.; Corral, O.; Barreiro, P. Third Wave of COVID-19 in Madrid, Spain. *International Journal of Infectious Diseases* **2021**, *107*, 212−214.
(22) Soriano, V.; Fernández-Montero, J. v. New Sars-Cov-2 Variants Challenge Vaccines Protection. *AIDS Reviews* **2021**, *23* (1), 57−58.
(23) *Classification of Omicron (B.1.1.529): SARS-CoV-2 Variant of Concern*; WHO, 2021. https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern (accessed 03-06-2022).
(24) Aouissi, H. A. Algeria's Preparedness for Omicron Variant and for the Fourth Wave of COVID-19. *Global Health & Medicine* **2021**, *3* (6), 413−414.
(25) Ry, T. A.; Song, Y.; Masaki, F. Preparation for the Challenge of Heavily Mutated Omicron Variant. *Clinical and Translational Medicine* **2021**, *11* (12), No. e679.
(26) Quarleri, J.; Galvan, V.; Delpino, M. V. Omicron Variant of the SARS-CoV-2: A Quest to Define the Consequences of Its High Mutational Load. *GeroScience 2021 44:1* **2022**, *44* (1), 53−56.
(27) El-Shabasy, R. M.; Nayel, M. A.; Taher, M. M.; Abdelmonem, R.; Shoueir, K. R.; Kenawy, E. R. Three Waves Changes, New Variant Strains, and Vaccination Effect against COVID-19 Pandemic. *Int. J. Biol. Macromol.* **2022**, *204*, 161−168.
(28) Xu, Y.; Cheng, M.; Chen, X.; Zhu, J. Current Approaches in Laboratory Testing for SARS-CoV-2. *International Journal of Infectious Diseases* **2020**, *100*, 7−9.
(29) D'Cruz, R. J.; Currier, A. W.; Sampson, V. B. Laboratory Testing Methods for Novel Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2). *Frontiers in Cell and Developmental Biology*; Frontiers Media S.A., 2020. DOI: 10.3389/fcell.2020.00468.
(30) Abduljalil, J. M. Laboratory Diagnosis of SARS-CoV-2: Available Approaches and Limitations. *New Microbes and New Infections*; Elsevier Ltd, 2020. DOI: 10.1016/j.nmni.2020.100713.
(31) Katrin, Z.; Maria, W.; Christian, K.; Rosina, E.; Katharina, M.; Roman, W.; Kilian, S. Rapid Detection of SARS-CoV-2 by Pulse-Controlled Amplification (PCA). *medRxiv* **2020**, DOI: 10.1101/2020.07.29.20154104.
(32) Infantino, M.; Damiani, A.; Gobbi, F. L.; Grossi, V.; Lari, B.; Macchia, D.; Casprini, P.; Veneziani, F.; Villalta, D.; Bizzaro, N.; Cappelletti, P.; Fabris, M.; Quartuccio, L.; Benucci, M.; Manfredi, M. Serological Assays for SARS-CoV-2 Infectious Disease: Benefits, Limitations and Perspectives. *Isr Med. Assoc J.* **2020**, *22* (4), 203−210.
(33) Filipić, A.; Gutierrez-Aguirre, I.; Primc, G.; Mozetič, M.; Dobnik, D. Cold Plasma, a New Hope in the Field of Virus Inactivation. *Trends in Biotechnology*; Elsevier Ltd, 2020; pp 1278−1291. DOI: 10.1016/j.tibtech.2020.04.003.
(34) Pérez-López, B.; Mir, M. Commercialized Diagnostic Technologies to Combat SARS-CoV2: Advantages and Disadvantages. *Talanta* **2021**, *225*, 121898.
(35) Pan, Y.; Zhang, D.; Yang, P.; Poon, L. L. M.; Wang, Q. Viral Load of SARS-CoV-2 in Clinical Samples. *The Lancet Infectious Diseases*; Lancet Publishing Group, 2020; pp 411−412. DOI: 10.1016/S1473-3099(20)30113-4.
(36) Miller, S.; Chiu, C.; Rodino, K. G.; Miller, M. B. Point-Counterpoint: Should We Be Performing Metagenomic next-Generation Sequencing for Infectious Disease Diagnosis in the Clinical Laboratory? *Journal of Clinical Microbiology* **2020**, *58* (3). DOI: 10.1128/JCM.01739-19.
(37) Sidiq, Z.; Hanif, M.; Dwivedi, K. K.; Chopra, K. K. Benefits and Limitations of Serological Assays in COVID-19 Infection. *Indian Journal of Tuberculosis*; Tuberculosis Association of India, 2020; pp S163−S166. DOI: 10.1016/j.ijtb.2020.07.034.
(38) Kobayashi, Y.; Mitsudomi, T. Management of Ground-Glass Opacities: Should All Pulmonary Lesions with Ground-Glass Opacity Be Surgically Resected? *Translational Lung Cancer Research*; AME Publishing Company, 2013; pp 354−363. DOI: 10.3978/j.issn.2218-6751.2013.09.03.
(39) Fang, Y.; Zhang, H.; Xie, J.; Lin, M.; Ying, L.; Pang, P.; Ji, W. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. *Radiology*; Radiological Society of North America Inc., 2020; pp E115−E117. DOI: 10.1148/radiol.2020200432.
(40) Xie, X.; Zhong, Z.; Zhao, W.; Zheng, C.; Wang, F.; Liu, J. Chest CT for Typical Coronavirus Disease 2019 (COVID-19) Pneumonia: Relationship to Negative RT-PCR Testing. *Radiology* **2020**, *296* (2), E41−E45.
(41) Mahmoudi, T.; de la Guardia, M.; Baradaran, B. Lateral Flow Assays towards Point-of-Care Cancer Detection: A Review of Current Progress and Future Trends. *TrAC - Trends in Analytical Chemistry*; Elsevier B.V., 2020. DOI: 10.1016/j.trac.2020.115842.
(42) Singh, M.; Kumar, A.; Khan, A. R. Capillary as a Liquid Diode. *Physical Review Fluids* **2020**, *5* (10), 102101.

https://doi.org/10.1021/acsabm.1c01320
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

(43) Mizumoto, K.; Kagaya, K.; Zarebski, A.; Chowell, G. Estimating the Asymptomatic Proportion of Coronavirus Disease 2019 (COVID-19) Cases on Board the Diamond Princess Cruise Ship, Yokohama, Japan, 2020. *Eurosurveillance.*; European Centre for Disease Prevention and Control (ECDC), 2020. DOI: 10.2807/1560-7917.ES.2020.25.10.2000180.
(44) Bendavid, E.; Mulaney, B.; Sood, N.; Shah, S.; Ling, E.; Bromley-Dulfano, R.; Lai, C.; Weissberg, Z.; Saavedra-Walker, R.; Tedrow, J.; Tversky, D.; Bogan, A.; Kupiec, T.; Eichner, D.; Gupta, R.; Ioannidis, J.; Bhattacharya, J. COVID-19 Antibody Seroprevalence in Santa Clara County, California. *International Journal of Epidemiology* **2021**, *50*, 410−419.
(45) Gallo, G.; La Torre, M.; Pietroletti, R.; Bianco, F.; Altomare, D. F.; Pucciarelli, S.; Gagliardi, G.; Perinotti, R. Italian Society of Colorectal Surgery Recommendations for Good Clinical Practice in Colorectal Surgery during the Novel Coronavirus Pandemic. *Techniques in Coloproctology*; Springer, 2020; pp 501−505. DOI: 10.1007/s10151-020-02209-6.
(46) Smithgall, M. C.; Dowlatshahi, M.; Spitalnik, S. L.; Hod, E. A.; Rai, A. J. Types of Assays for SARS-COV-2 Testing: A Review. *Lab Medicine*; Oxford University Press, 2021; pp E59−E65. DOI: 10.1093/LABMED/LMAA039.
(47) Takeuchi, Y.; Furuchi, M.; Kamimoto, A.; Honda, K.; Matsumura, H.; Kobayashi, R. Saliva-Based Pcr Tests for Sars-Cov-2 Detection. *Journal of Oral Science* **2020**, *62* (3), 350−351.
(48) VanGuilder, H. D.; Vrana, K. E.; Freeman, W. M. Twenty-Five Years of Quantitative PCR for Gene Expression Analysis. *BioTechniques.* **2008**, *44*, 619−626.
(49) Wong, M. L.; Medrano, J. F. Real-Time PCR for MRNA Quantitation. *BioTechniques.*; Eaton Publishing Company, 2005; pp 75−85. DOI: 10.2144/05391RV01.
(50) Aguiar, E. R. G. R.; Navas, J.; Pacheco, L. G. C. The COVID-19 Diagnostic Technology Landscape: Efficient Data Sharing Drives Diagnostic Development. *Frontiers in Public Health*; Frontiers Media S.A., 2020. DOI: 10.3389/fpubh.2020.00309.
(51) Carter, L. J.; Garner, L. V.; Smoot, J. W.; Li, Y.; Zhou, Q.; Saveson, C. J.; Sasso, J. M.; Gregg, A. C.; Soares, D. J.; Beskid, T. R.; Jervey, S. R.; Liu, C. Assay Techniques and Test Development for COVID-19 Diagnosis. *ACS Central Science* **2020**, *6* (5), 591−605.
(52) Zhang, Y.; Odiwuor, N.; Xiong, J.; Sun, L.; Nyaruaba, R. O.; Wei, H.; Tanner, N. Rapid Molecular Detection of SARS-CoV-2 (COVID-19) Virus RNA Using Colorimetric LAMP. *medRxiv* **2020**, DOI: 10.1101/2020.02.26.20028373.
(53) Notomi, T.; Okayama, H.; Masubuchi, H.; Yonekawa, T.; Watanabe, K.; Amino, N.; Hase, T. Loop-Mediated Isothermal Amplification of DNA. *Nucleic Acids Res.* **2000**, *28* (12), No. e63-e63.
(54) Thai, H. T. C.; Le, M. Q.; Vuong, C. D.; Parida, M.; Minekawa, H.; Notomi, T.; Hasebe, F.; Morita, K. Development and Evaluation of a Novel Loop-Mediated Isothermal Amplification Method for Rapid Detection of Severe Acute Respiratory Syndrome Coronavirus. *Journal of Clinical Microbiology* **2004**, *42* (5), 1956−1961.
(55) Vashist, S. K. In Vitro Diagnostic Assays for COVID-19: Recent Advances and Emerging Trends. *Diagnostics*; MDPI AG, 2020. DOI: 10.3390/diagnostics10040202.
(56) Loeffelholz, M. J.; Tang, Y. W. Laboratory Diagnosis of Emerging Human Coronavirus Infections-the State of the Art. *Emerging Microbes and Infections*; Taylor and Francis Ltd., 2020; pp 747−756. DOI: 10.1080/22221751.2020.1745095.
(57) Gootenberg, J. S.; Abudayyeh, O. O.; Lee, J. W.; Essletzbichler, P.; Dy, A. J.; Joung, J.; Verdine, V.; Donghia, N.; Daringer, N. M.; Freije, C. A.; Myhrvold, C.; Bhattacharyya, R. P.; Livny, J.; Regev, A.; Koonin, E. V.; Hung, D. T.; Sabeti, P. C.; Collins, J. J.; Zhang, F. Nucleic Acid Detection with CRISPR-Cas13a/C2c2. *Science (1979)* **2017**, *356* (6336), 438−442.
(58) Chen, J. S.; Ma, E.; Harrington, L. B.; Da Costa, M.; Tian, X.; Palefsky, J. M.; Doudna, J. A. CRISPR-Cas12a Target Binding Unleashes Indiscriminate Single-Stranded DNase Activity. *Science (1979)* **2018**, *360* (6387), 436−439.
(59) Li, S. Y.; Cheng, Q. X.; Li, X. Y.; Zhang, Z. L.; Gao, S.; Cao, R. B.; Zhao, G. P.; Wang, J.; Wang, J. M. CRISPR-Cas12a-Assisted Nucleic Acid Detection. *Cell Discovery*; Nature Publishing Groups, 2018. DOI: 10.1038/s41421-018-0028-z.
(60) Liu, D.; Shen, H.; Zhang, Y.; Shen, D.; Zhu, M.; Song, Y.; Zhu, Z.; Yang, C. A Microfluidic-Integrated Lateral Flow Recombinase Polymerase Amplification (MI-IF-RPA) Assay for Rapid COVID-19 Detection. *Lab Chip* **2021**, *21* (10), 2019−2026.
(61) Hou, T.; Zeng, W.; Yang, M.; Chen, W.; Ren, L.; Ai, J.; Wu, J.; Liao, Y.; Gou, X.; Li, Y.; Wang, X.; Su, H.; Gu, B.; Wang, J.; Xu, T. Development and Evaluation of a Rapid CRISPR-Based Diagnostic for COVID-19. *PLoS Pathogens* **2020**, *16* (8), No. e1008705.
(62) Russo, A.; Minichini, C.; Starace, M.; Astorri, R.; Calò, F.; Coppola, N. Current Status of Laboratory Diagnosis for Covid-19: A Narrative Review. *Infection and Drug Resistance*; Dove Medical Press Ltd., 2020; pp 2657−2665. DOI: 10.2147/IDR.S264020.
(63) Singh, R. K.; Kumar, A.; Kant, R.; Gupta, A.; Suresh, E.; Bhattacharya, S. Design and Fabrication of 3-Dimensional Helical Structures in Polydimethylsiloxane for Flow Control Applications. *Microsystem Technologies* **2014**, *20* (1), 101−111.
(64) Park, J. S.; Hsieh, K.; Chen, L.; Kaushik, A.; Trick, A. Y.; Wang, T.-H.; Park, J. S.; Trick, A. Y.; Wang, T.-H.; Hsieh, K.; Chen, L.; Kaushik, A. Digital CRISPR/Cas-Assisted Assay for Rapid and Sensitive Detection of SARS-CoV-2. *Advanced Science* **2021**, *8* (5), 2003564.
(65) Chen, Q.; Li, J.; Deng, Z.; Xiong, W.; Wang, Q.; Hu, Y. Q. Comprehensive Detection and Identification of Seven Animal Coronaviruses and Human Respiratory Coronavirus 229E with a Microarray Hybridization Assay. *Intervirology* **2010**, *53* (2), 95−104.
(66) Guo, X.; Geng, P.; Wang, Q.; Cao, B.; Liu, B. Development of a Single Nucleotide Polymorphism DNA Microarray for the Detection and Genotyping of the SARS Coronavirus. *Journal of Microbiology and Biotechnology* **2014**, *24* (10), 1145−1454.
(67) Hardick, J.; Metzgar, D.; Risen, L.; Myers, C.; Balansay, M.; Malcom, T.; Rothman, R.; Gaydos, C. Initial Performance Evaluation of a Spotted Array Mobile Analysis Platform (MAP) for the Detection of Influenza A/B, RSV, and MERS Coronavirus. *Diagnostic Microbiology and Infectious Disease* **2018**, *91* (3), 245−247.
(68) Behzadi, P.; Ranjbar, R.; Alavian, S. M. Nucleic Acid-Based Approaches for Detection of Viral Hepatitis. *Jundishapur Journal of Microbiology*; Kowsar Medical Publishing Company, 2015; p 17449. DOI: 10.5812/jjm.17449.
(69) Moore, S. C.; Penrice-Randal, R.; Alruwaili, M.; Randle, N.; Armstrong, S.; Hartley, C.; Haldenby, S.; Dong, X.; Alrezaihi, A.; Almsaud, M.; Bentley, E.; Clark, J.; García-Dorival, I.; Gilmore, P.; Han, X.; Jones, B.; Luu, L.; Sharma, P.; Shawli, G.; Sun, Y.; Zhao, Q.; Pullan, S. T.; Carter, D. P.; Bewley, K.; Dunning, J.; Zhou, E. M.; Solomon, T.; Beadsworth, M.; Cruise, J.; Crook, D. W.; Matthews, D. A.; Davidson, A. D.; Mahmood, Z.; Aljabr, W.; Druce, J.; Vipond, R.; Ng, L.; Renia, L.; Openshaw, P. J. M.; Kenneth Baillie, J.; Carroll, M. W.; Stewart, J.; Darby, A.; Semple, M.; Turtle, L.; Hiscox, J. A. Amplicon-Based Detection and Sequencing of SARS-CoV-2 in Nasopharyngeal Swabs from Patients with COVID-19 and Identification of Deletions in the Viral Genome That Encode Proteins Involved in Interferon Antagonism. *Viruses* **2020**, *12* (10), 1164.
(70) Stefanini, I.; Cavalieri, D. Metagenomic Approaches to Investigate the Contribution of the Vineyard Environment to the Quality of Wine Fermentation: Potentials and Difficulties. *Frontiers in Microbiology.*; Frontiers Media S.A., 2018; p 991. DOI: 10.3389/fmicb.2018.00991.
(71) *COVID-19 (SARS-CoV-2) Testing*; Biomeme, 2021. https://info.biomeme.com/covid-19 (accessed 07-04-2021).
(72) *WHO Emergency Use Assessment Coronavirus Disease (COVID-19) IVDs PUBLIC REPORT Product: Xpert Xpress SARS-CoV-2 EUL Number: EUL-0511-070-00 Outcome: Accepted*; WHO, 2020.
(73) *GeneXpert System*; Cepheid, 2021. https://www.cepheid.com/en/systems/GeneXpert-Family-of-Systems/GeneXpert-System (accessed 07-04-2021).

(74) *Rapid Assessment of the GenMark EPlex SARS-CoV-2 Test*; Public Health England, 2020.
(75) *The ePlex System: The True Sample-to-Answer Solution*; GenMark, 2021. https://www.genmarkdx.com/systems/eplex-system/ (accessed 07-04-2021).
(76) Li, Y.; Li, J.; Zhang, Y.; Dai, L.; Li, L.; Liu, J.; Zhang, S.; Wu, X.; Hu, Y.; Qin, C.; Jiang, T.; Kang, X. Development of an Automatic Integrated Gene Detection System for Novel Severe Acute Respiratory Syndrome-Related Coronavirus (SARS-CoV2). *Emerging Microbes and Infections* **2020**, *9* (1), 1489−1496.
(77) *Diagnosis-Hangzhou*; LifeReal Biotechnology Co., Ltd, 2021. http://en.lifereal.com.cn/productclass_5/ (accessed 07-04-2021).
(78) *Coronavirus (COVID-19) Research Testing Solutions*; Luminex, 2021. https://www.luminexcorp.com/covid19-testing-solutions/ (accessed 07-04-2021).
(79) *LamPORE Assay*; Nanopore, 2021. https://nanoporetech.com/covid-19/lampore (accessed 07-04-2021).
(80) Peto, L.; Rodger, G.; Carter, D.; Osman, K.; Yavuz, M.; Johnson, K.; Raza, M.; Parker, M.; Wyles, M.; Andersson, M.; Justice, A.; Vaughan, A.; Hoosdally, S.; Stoesser, N.; Matthews, P.; Eyre, D.; Peto, T. E.; Carroll, M.; de Silva, T.; Crook, D.; Evans, C.; Pullan, S. Diagnosis of SARS-CoV-2 Infection with LamPORE, a High-Throughput Platform Combining Loop-Mediated Isothermal Amplification and Nanopore Sequencing. *Journal of Clinical Microbiology* **2021**, *59*, 2020.09.18.20195370.
(81) *Sherlock CRISPR SARS-CoV-2 Kit*; Sherlock Biosciences, 2020. https://sherlock.bio/wp-content/uploads/2020/06/SherlockBrochure-FP_FINAL_June-2020.pdf (accessed 07-04-2021).
(82) Joung, J.; Ladha, A.; Saito, M.; Kim, N.-G.; Woolley, A. E.; Segel, M.; Barretto, R. P. J.; Ranu, A.; Macrae, R. K.; Faure, G.; Ioannidi, E. I.; Krajeski, R. N.; Bruneau, R.; Huang, M.-L. W.; Yu, X. G.; Li, J. Z.; Walker, B. D.; Hung, D. T.; Greninger, A. L.; Jerome, K. R.; Gootenberg, J. S.; Abudayyeh, O. O.; Zhang, F. Detection of SARS-CoV-2 with SHERLOCK One-Pot Testing. *New England Journal of Medicine* **2020**, *383* (15), 1492−1494.
(83) *EasyNAT Novel-Coronavirus (2019-nCoV) Real-Time Molecular Diagnostic System*; USTAR Biotechnologies (Hangzhou) Ltd., 2021. http://en.bioustar.com/intro/24.html (accessed 07-04-2021).
(84) *Ustar EasyNAT Diagnostic Kit for Novel-Coronavirus (COVID-19) RNA Molecular testing reagents*; YouTube, 2020. https://www.youtube.com/watch?v=4k5bm1EL6J8 (accessed 07-04-2021).
(85) *BinaxNOW COVID-19 Ag Card Home Test - Instructions for Use*; Abbott U.S., 2021.
(86) *Taking COVID-19 Testing to a New Level*; Abbott U.S., 2021. https://www.abbott.com/BinaxNOW-Tests-NAVICA-App.html (accessed 07-04-2021).
(87) *COVID-19 Serology and Molecular Tests*; Wantai, 2021. https://www.ystwt.cn/covid-19/ (accessed 07-04-2021).
(88) *Sofia SARS Antigen FIA*; Quidel, 2021. https://www.quidel.com/immunoassays/rapid-sars-tests/sofia-sars-antigen-fia (accessed 07-04-2021).
(89) *Battling coronavirus_Beijing hot view biology*; Beijing Hotgen Biotechn Co., Ltd., 2021. http://www.hotgen.com.cn/ky/upt.html (accessed 07-04-2021).
(90) *The LumiraDx SARS-CoV-2 Ag Test is a rapid microfluidic immunoassay detecting SARS-CoV-2 antigen*; LumiraDx, 2021. https://www.lumiradx.com/uk-en/what-we-do/diagnostics/test-technology/antigen-test (accessed 07-04-2021).
(91) Guedez-López, G. V.; Alguacil-Guillén, M.; González-Donapetry, P.; Bloise, I.; Tornero-Marin, C.; González-García, J.; Mingorance, J.; García-Rodríguez, J.; Montero-Vega, M. D.; Romero, M. P.; García-Bujalance, S.; Cendejas-Bueno, E.; Ruiz-Carrascoso, G.; Lázaro-Perona, F.; Falces-Romero, I.; Gutiérrez-Arroyo, A.; Girón de Velasco-Sada, P.; Rico Nieto, A.; Loeches, B.; Ruiz-Bastián, M.; Gómez-Arroyo, B.; García-Clemente, P.; Liras-Hernández, M. G.; García-Sánchez, C.; Sánchez-Castellano, M.; San José-Villar, S.; Tato, E.; Romero Huertas, C.; Molina Muñoz, E. Evaluation of Three Immunochromatographic Tests for Rapid Detection of Antibodies against SARS-CoV-2. *European Journal of Clinical Microbiology and Infectious Diseases* **2020**, *39* (12), 2289−2297.
(92) *xMAP SARS-CoV-2 Antibody Testing*; Luminex Corporation, 2021. https://www.luminexcorp.com/xmap-sars-cov-2-antibody-testing/ (accessed 07-04-2021).
(93) Uzochukwu, V. *BioCheck SARS-CoV-2 IgM and IgG Antibody Combo Test Kit Instructions for Use For Use under an Emergency Use Authorization (EUA) Only For Prescription Use Only For in Vitro Diagnostic Use Only*; U.S. FDA, 2020.
(94) *BioCheck SARS-CoV-2 IgM and IgG Combo Test Kits*; BioCheck, Inc., 2021. http://www.biocheckinc.com/ (accessed 07-04-2021).
(95) *COVID-19 Response*; Ellume, 2021. https://www.ellumehealth.com/covid19-response/ (accessed 07-04-2021).
(96) *Ellume COVID-19 Home Test Product Overview for Healthcare Professionals*; U.S. FDA, 2021.
(97) Vaidyanathan, R.; Soon, R. H.; Zhang, P.; Jiang, K.; Lim, C. T. Cancer Diagnosis: From Tumor to Liquid Biopsy and Beyond. *Lab on a Chip* **2019**, *19* (1), 11−34, DOI: 10.1039/c8lc00684a.
(98) Ranjan, P.; Parihar, A.; Jain, S.; Kumar, N.; Dhand, C.; Murali, S.; Mishra, D.; Sanghi, S. K.; Chaurasia, J. P.; Srivastava, A. K.; Khan, R. Biosensor-Based Diagnostic Approaches for Various Cellular Biomarkers of Breast Cancer: A Comprehensive Review. *Anal. Biochem.* **2020**, *610*, 113996.
(99) Jiang, K.; Jokhun, D. S.; Lim, C. T. Microfluidic Detection of Human Diseases: From Liquid Biopsy to COVID-19 Diagnosis. *J. Biomech.* **2021**, *117*, 110235.
(100) Kumar, A.; Gupta, A.; Syed, R. K.; Akhtar, N.; Tiwari, N.; Ramkumar, J.; Bhattacharya, S. Optimization of laser machining process for the preparation of photomasks, and its application to microsystems fabrication. *J. Micro/Nanolith. MEMS MOEMS* **2013**, *12*, 041203.
(101) Li, N.; Wang, P.; Wang, X.; Geng, C.; Chen, J.; Gong, Y. Molecular Diagnosis of COVID-19: Current Situation and Trend in China (Review). *Experimental and Therapeutic Medicine* **2020**, *20* (5), 1−1.
(102) Li, G.; Tang, W.; Yang, F. Cancer Liquid Biopsy Using Integrated Microfluidic Exosome Analysis Platforms. *Biotechnol. J.* **2020**, *15* (5), e1900225 DOI: 10.1002/biot.201900225.
(103) Demey, B.; Daher, N.; François, C.; Lanoix, J. P.; Duverlie, G.; Castelain, S.; Brochot, E. Dynamic Profile for the Detection of Anti-SARS-CoV-2 Antibodies Using Four Immunochromatographic Assays. *Journal of Infection* **2020**, *81* (2), No. e6.
(104) Lin, Q.; Wen, D.; Wu, J.; Liu, L.; Wu, W.; Fang, X.; Kong, J. Microfluidic Immunoassays for Sensitive and Simultaneous Detection of IgG/IgM/Antigen of SARS-CoV-2 within 15 min. *Anal. Chem.* **2020**, *92* (14), 9454−9458.
(105) Raimondi, M. T.; Donnaloja, F.; Barzaghini, B.; Bocconi, A.; Conci, C.; Parodi, V.; Jacchetti, E.; Carelli, S. Bioengineering Tools to Speed up the Discovery and Preclinical Testing of Vaccines for SARS-CoV-2 and Therapeutic Agents for COVID-19. *Theranostics* **2020**, *10* (16), 7034−7052.
(106) Yeh, Y. T.; Gulino, K.; Zhang, Y. H.; Sabestien, A.; Chou, T. W.; Zhou, B.; Lin, Z.; Albert, I.; Lu, H.; Swaminathan, V.; Ghedin, E.; Terrones, M. A Rapid and Label-Free Platform for Virus Capture and Identification from Clinical Samples. *Proc. Natl. Acad. Sci. U. S. A.* **2020**, *117* (2), 895−901.
(107) Zhuang, J.; Yin, J.; Lv, S.; Wang, B.; Mu, Y. Advanced "Lab-on-a-Chip" to Detect Viruses - Current Challenges and Future Perspectives. *Biosensors and Bioelectronics* **2020**, *163*, 112291 DOI: 10.1016/j.bios.2020.112291.
(108) Ganguli, A.; Mostafa, A.; Berger, J.; Aydin, M.; Sun, F.; Valera, E.; Cunningham, B. T.; King, W. P.; Bashir, R.; Bashir, R. Rapid Isothermal Amplification and Portable Detection System for SARS-CoV-2. *Proc. Natl. Acad. Sci. U.S.A.* **2020**, *117*, 22727.
(109) Huang, W. E.; Lim, B.; Hsu, C. C.; Xiong, D.; Wu, W.; Yu, Y.; Jia, H.; Wang, Y.; Zeng, Y.; Ji, M.; Chang, H.; Zhang, X.; Wang, H.; Cui, Z. RT-LAMP for Rapid Diagnosis of Coronavirus SARS-CoV-2. *Microbial Biotechnology* **2020**, *13* (4), 950−961.

https://doi.org/10.1021/acsabm.1c01320
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

(110) Dao Thi, V. L.; Herbst, K.; Boerner, K.; Meurer, M.; Kremer, L. P. M.; Kirrmaier, D.; Freistaedter, A.; Papagiannidis, D.; Galmozzi, C.; Stanifer, M. L.; Boulant, S.; Klein, S.; Chlanda, P.; Khalid, D.; Miranda, I. B.; Schnitzler, P.; Kräusslich, H. G.; Knop, M.; Anders, S. A Colorimetric RT-LAMP Assay and LAMP-Sequencing for Detecting SARS-CoV-2 RNA in Clinical Samples. *Science Translational Medicine* **2020**, *12* (556), No. eabc7075.
(111) Kumar, R.; Nagpal, S.; Kaushik, S.; Mendiratta, S. COVID-19 Diagnostic Approaches: Different Roads to the Same Destination. *VirusDisease.* **2020**, *31*, 97−105, DOI: 10.1007/s13337-020-00599-7.
(112) Morales-Narváez, E.; Dincer, C. The Impact of Biosensing in a Pandemic Outbreak: COVID-19. *Biosens. Bioelectron.* **2020**, *163*, 112274.
(113) Bhalla, N.; Pan, Y.; Yang, Z.; Payam, A. F. Opportunities and Challenges for Biosensors and Nanoscale Analytical Tools for Pandemics: COVID-19. *ACS Nano.* **2020**, *14* (7), 7783−7807, DOI: 10.1021/acsnano.0c04421.
(114) Khan, R.; Parihar, A.; Sanghi, S. K. *Biosensor Based Advanced Cancer Diagnostics : From Lab to Clinics*; Elsevier, 2022.
(115) Ranjan, P.; Singhal, A.; Sadique, M. A.; Yadav, S.; Parihar, A.; Khan, R. Scope of Biosensors, Commercial Aspects, and Miniaturized Devices for Point-of-Care Testing from Lab to Clinics Applications. *Biosensor Based Advanced Cancer Diagnostics* **2022**, 395−410.
(116) Swank, Z.; Michielin, G.; Yip, H. M.; Cohen, P.; Andrey, D. O.; Vuilleumier, N.; Kaiser, L.; Eckerle, I.; Meyer, B.; Maerkl, S. J. A High-Throughput Microfluidic Nanoimmunoassay for Detecting Anti-SARS-CoV-2 Antibodies in Serum or Ultralow-Volume Blood Samples. *Proc. Natl. Acad. Sci. U. S. A.* **2021**, *118* (18), No. e2025289118.
(117) Choi, J. R. Development of Point-of-Care Biosensors for COVID-19. *Frontiers in Chemistry* **2020**, *8*, 517 DOI: 10.3389/fchem.2020.00517.
(118) McRae, M. P.; Simmons, G. W.; Christodoulides, N. J.; Lu, Z.; Kang, S. K.; Fenyo, D.; Alcorn, T.; Dapkins, I. P.; Sharif, I.; Vurmaz, D.; Modak, S. S.; Srinivasan, K.; Warhadpande, S.; Shrivastav, R.; McDevitt, J. T. Clinical Decision Support Tool and Rapid Point-of-Care Platform for Determining Disease Severity in Patients with COVID-19. *Lab Chip* **2020**, *20* (12), 2075−2085.
(119) 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 Sensors* **2020**, *5* (6), 1506−1513.
(120) Parihar, A.; Pandita, V.; Kumar, A.; Parihar, D. S.; Puranik, N.; Bajpai, T.; Khan, R. 3D Printing: Advancement in Biogenerative Engineering to Combat Shortage of Organs and Bioapplicable Materials. *Regen Eng. Transl Med.* **2021**. DOI: 10.1007/s40883-021-00219-w.
(121) Asghari, A.; Wang, C.; Yoo, K. M.; Rostamian, A.; Xu, X.; Shin, J. D.; Dalir, H.; Chen, R. T. Fast, Accurate, Point-of-Care COVID-19 Pandemic Diagnosis Enabled through Advanced Lab-on-Chip Optical Biosensors: Opportunities and Challenges. *Applied Physics Reviews* **2021**, *8* (3), 031313.
(122) de Eguilaz, M. R.; Cumba, L. R.; Forster, R. J. Electrochemical Detection of Viruses and Antibodies: A Mini Review. *Electrochem. Commun.* **2020**, *116*, 106762 DOI: 10.1016/j.elecom.2020.106762.
(123) Thiyagarajan, N.; Chang, J. L.; Senthilkumar, K.; Zen, J. M. Disposable Electrochemical Sensors: A Mini Review. *Electrochem. Commun.* **2014**, *38*, 86−90, DOI: 10.1016/j.elecom.2013.11.016.
(124) Tripathy, S.; Singh, S. G. Label-Free Electrochemical Detection of DNA Hybridization: A Method for COVID-19 Diagnosis. *Transactions of the Indian National Academy of Engineering* **2020**, *5* (2), 205−209.
(125) Ali, M. A.; Hu, C.; Jahan, S.; Yuan, B.; Saleh, M. S.; Ju, E.; Gao, S. J.; Panat, R. Sensing of COVID-19 Antibodies in Seconds via Aerosol Jet Nanoprinted Reduced-Graphene-Oxide-Coated 3D Electrodes. *Adv. Mater.* **2021**, *33* (7), 2006647.
(126) Vezza, V. J.; Butterworth, A.; Lasserre, P.; Blair, E. O.; MacDonald, A.; Hannah, S.; Rinaldi, C.; Hoskisson, P. A.; Ward, A. C.; Longmuir, A.; Setford, S.; Farmer, E. C. W.; Murphy, M. E.; Corrigan, D. K. An Electrochemical SARS-CoV-2 Biosensor Inspired by Glucose Test Strip Manufacturing Processes. *Chem. Commun.* **2021**, *57* (30), 3704−3707.
(127) Yakoh, A.; Pimpitak, U.; Rengpipat, S.; Hirankarn, N.; Chailapakul, O.; Chaiyo, S. Paper-Based Electrochemical Biosensor for Diagnosing COVID-19: Detection of SARS-CoV-2 Antibodies and Antigen. *Biosensors and Bioelectronics* **2021**, *176*, 112912 DOI: 10.1016/j.bios.2020.112912.
(128) Alafeef, M.; Dighe, K.; Moitra, P.; Pan, D. Rapid, Ultrasensitive, and Quantitative Detection of SARS-CoV-2 Using Antisense Oligonucleotides Directed Electrochemical Biosensor Chip. *ACS Nano* **2020**, *14* (12), 17028−17045.
(129) Gupta, R.; Sagar, P.; Priyadarshi, N.; Kaul, S.; Sandhir, R.; Rishi, V.; Singhal, N. K. Nanotechnology-Based Approaches for the Detection of SARS-CoV-2. *Frontiers in Nanotechnology* **2020**, *2*, 589832 DOI: 10.3389/fnano.2020.589832.
(130) Rodriguez-Mateos, P.; Ngamsom, B.; Walter, C.; Dyer, C. E.; Gitaka, J.; Iles, A.; Pamme, N. A Lab-on-a-Chip Platform for Integrated Extraction and Detection of SARS-CoV-2 RNA in Resource-Limited Settings. *Anal. Chim. Acta* **2021**, *1177*. 338758.
(131) Tarim, E. A.; Karakuzu, B.; Oksuz, C.; Sarigil, O.; Kizilkaya, M.; Al-Ruweidi, M. K. A. A.; Yalcin, H. C.; Ozcivici, E.; Tekin, H. C. Microfluidic-Based Virus Detection Methods for Respiratory Diseases. *Emergent Materials* **2021**, *4* (1), 143−168.
(132) Zhao, H.; Liu, F.; Xie, W.; Zhou, T. C.; OuYang, J.; Jin, L.; Li, H.; Zhao, C. Y.; Zhang, L.; Wei, J.; Zhang, Y. P.; Li, C. P. Ultrasensitive Supersandwich-Type Electrochemical Sensor for SARS-CoV-2 from the Infected COVID-19 Patients Using a Smartphone. *Sensors and Actuators, B: Chemical* **2021**, *327*, 128899.
(133) Torrente-Rodríguez, R. M.; Lukas, H.; Tu, J.; Min, J.; Yang, Y.; Xu, C.; Rossiter, H. B.; Gao, W. SARS-CoV-2 RapidPlex: A Graphene-Based Multiplexed Telemedicine Platform for Rapid and Low-Cost COVID-19 Diagnosis and Monitoring. *Matter* **2020**, *3* (6), 1981−1998.
(134) Phillips, E. A.; Moehling, T. J.; Ejendal, K. F. K.; Hoilett, O. S.; Byers, K. M.; Basing, L. A.; Jankowski, L. A.; Bennett, J. B.; Lin, L.-K.; Stanciu, L. A.; Linnes, J. C. Microfluidic Rapid and Autonomous Analytical Device (MicroRAAD) to Detect HIV from Whole Blood Samples. *Lab on a Chip* **2019**, *19* (20), 3375−3386.
(135) Chang, W. H.; Wang, C. H.; Lin, C. L.; Wu, J. J.; Lee, M. S.; Lee, G. B. Rapid detection and typing of live bacteria from human joint fluid samples by utilizing an integrated microfluidic system. *Biosens. Bioelectron.* **2015**, *66*, 148−154.
(136) Sayad, A.; Ibrahim, F.; Uddin, S. M.; Cho, J.; Madou, M.; Thong, K. L. A microdevice for rapid, monoplex and colorimetric detection of foodborne pathogens using a centrifugal microfluidic platform. *Biosens. Bioelectron.* **2018**, *100*, 96−104.
(137) Trinh, K. T. L.; Stabler, R. A.; Lee, N. Y. Fabrication of a foldable all-in-one point-of-care molecular diagnostic microdevice for the facile identification of multiple pathogens. *Sens. Actuators, B* **2020**, *314*, 128057.
(138) Li, Z.; Bai, Y.; You, M.; Hu, J.; Yao, C.; Cao, L.; Xu, F. Fully Integrated Microfluidic Devices for Qualitative, Quantitative and Digital Nucleic Acids Testing at Point of Care. *Biosens. Bioelectron.* **2021**, *177*, 112952.
(139) Ranjan, P.; Sadique, M. A.; Parihar, A.; Dhand, C.; Mishra, A.; Khan, R. Commercialization of Microfluidic Point-of-Care Diagnostic Devices. *Advanced Microfluidics-Based Point-of-Care Diagnostics* **2022**, 383−398.
(140) Liu, D.; Jia, S.; Zhang, H.; Ma, Y.; Guan, Z.; Li, J.; Zhu, Z.; Ji, T.; Yang, C. J. Integrating Target-Responsive Hydrogel with Pressuremeter Readout Enables Simple, Sensitive, User-Friendly, Quantitative Point-of-Care Testing. *ACS Appl. Mater. Interfaces* **2017**, *9* (27), 22252−22258.
(141) Gu, Y.; Zhang, T. T.; Huang, Z. F.; Hu, S. W.; Zhao, W.; Xu, J. J.; Chen, H. Y. An Exploration of Nucleic Acid Liquid Biopsy Using a Glucose Meter. *Chemical Science* **2018**, *9* (14), 3517−3522.
(142) 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.
(143) 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. Il. 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.
(144) 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.
(145) Qiu, X.; Yang, S.; Wu, D.; Wang, D.; Qiao, S.; Ge, S.; Xia, N.; Yu, D.; Qian, S. Rapid Enumeration of CD4 + T Lymphocytes Using an Integrated Microfluidic System Based on Chemiluminescence Image Detection at Point-of-Care Testing. *Biomed. Microdevices* **2018**, *20* (1), 1−10.
(146) Shen, R.; Liu, P.; Zhang, Y.; Yu, Z.; Chen, X.; Zhou, L.; Nie, B.; Zaczek, A.; Chen, J.; Liu, J. Sensitive Detection of Single-Cell Secreted H2O2 by Integrating a Microfluidic Droplet Sensor and Au Nanoclusters. *Anal. Chem.* **2018**, *90* (7), 4478−4484.
(147) Cui, W.; He, M.; Mu, L.; Lin, Z.; Wang, Y.; Pang, W.; Reed, M.; Duan, X. Cellphone-Enabled Microwell-Based Microbead Aggregation Assay for Portable Biomarker Detection. *ACS Sensors* **2018**, *3* (2), 432−440.
(148) Usuba, R.; Yokokawa, M.; Ackermann, T. N.; Llobera, A.; Fukunaga, K.; Murata, S.; Ohkohchi, N.; Suzuki, H. Photonic Lab-on-a-Chip for Rapid Cytokine Detection. *ACS Sensors* **2016**, *1* (8), 979−986.
(149) Tsai, M. Z.; Hsiung, C. Te; Chen, Y.; Huang, C. S.; Hsu, H. Y.; Hsieh, P. Y. Real-Time CRP Detection from Whole Blood Using Micropost-Embedded Microfluidic Chip Incorporated with Label-Free Biosensor. *Analyst* **2018**, *143* (2), 503−510.
(150) Salim, B.; Athira, M. V.; Kandaswamy, A.; Vijayakumar, M.; Saravanan, T.; Sairam, T. Microfluidic Device for Novel Breast Cancer Screening by Blood Test Using MiRNA Beacon Probe. *Biomed. Microdevices* **2017**, *19* (4), 1−11.
(151) Ding, S.; Mosher, C.; Lee, X. Y.; Das, S. R.; Cargill, A. A.; Tang, X.; Chen, B.; McLamore, E. S.; Gomes, C.; Hostetter, J. M.; Claussen, J. C. Rapid and Label-Free Detection of Interferon Gamma via an Electrochemical Aptasensor Comprising a Ternary Surface Monolayer on a Gold Interdigitated Electrode Array. *ACS Sensors* **2017**, *2* (2), 210−217.
(152) Chuang, C. H.; Du, Y. C.; Wu, T. F.; Chen, C. H.; Lee, D. H.; Chen, S. M.; Huang, T. C.; Wu, H. P.; Shaikh, M. O. Immunosensor for the Ultrasensitive and Quantitative Detection of Bladder Cancer in Point of Care Testing. *Biosens. Bioelectron.* **2016**, *84*, 126−132.
(153) Castiello, F. R.; Tabrizian, M. Multiplex Surface Plasmon Resonance Imaging-Based Biosensor for Human Pancreatic Islets Hormones Quantification. *Anal. Chem.* **2018**, *90* (5), 3132−3139.
(154) Ji, S.; Lee, M.; Kim, D. Detection of Early Stage Prostate Cancer by Using a Simple Carbon Nanotube@paper Biosensor. *Biosens. Bioelectron.* **2018**, *102*, 345−350.
(155) Matta, D. P.; Tripathy, S.; Krishna Vanjari, S. R.; Sharma, C. S.; Singh, S. G. An Ultrasensitive Label Free Nanobiosensor Platform for the Detection of Cardiac Biomarkers. *Biomed. Microdevices* **2016**, *18* (6), 111.
(156) Messina, M. A.; Meli, C.; Conoci, S.; Petralia, S. A Facile Method for Urinary Phenylalanine Measurement on Paper-Based Lab-on-Chip for PKU Therapy Monitoring. *Analyst* **2017**, *142* (24), 4629−4632.
(157) Li, W. Y.; Shi, Z. Z.; Fang, C.; Lu, Y.; Yu, L.; Li, C. M. Integration of Paper and Micropipette Tip to Build a "Sample-in, Answer-out" Point-of-Care Device. *Microfluid. Nanofluid.* **2017**, *21* (4), 71.
(158) Yao, Y.; Li, H.; Wang, D.; Liu, C.; Zhang, C. An Electrochemiluminescence Cloth-Based Biosensor with Smartphone-Based Imaging for Detection of Lactate in Saliva. *Analyst* **2017**, *142* (19), 3715−3724.
(159) Kong, T.; Flanigan, S.; Weinstein, M.; Kalwa, U.; Legner, C.; Pandey, S. A Fast, Reconfigurable Flow Switch for Paper Microfluidics Based on Selective Wetting of Folded Paper Actuator Strips. *Lab Chip* **2017**, *17* (21), 3621−3633.
(160) Oliveira-Rodríguez, M.; Serrano-Pertierra, E.; García, A. C.; Martín, S. L.; Mo, M. Y.; Cernuda-Morollón, E.; Blanco-López, M. C. Point-of-Care Detection of Extracellular Vesicles: Sensitivity Optimization and Multiple-Target Detection. *Biosens. Bioelectron.* **2017**, *87*, 38−45.
(161) Shen, H.; Xu, F.; Xiao, M.; Fu, Q.; Cheng, Z.; Zhang, S.; Huang, C.; Tang, Y. A New Lateral-Flow Immunochromatographic Strip Combined with Quantum Dot Nanobeads and Gold Nanoflowers for Rapid Detection of Tetrodotoxin. *Analyst* **2017**, *142* (23), 4393−4398.
(162) Lin, B.; Guan, Z.; Song, Y.; Song, E.; Lu, Z.; Liu, D.; An, Y.; Zhu, Z.; Zhou, L.; Yang, C. Lateral Flow Assay with Pressure Meter Readout for Rapid Point-of-Care Detection of Disease-Associated Protein. *Lab Chip* **2018**, *18* (6), 965−970.
(163) Ahmad Raston, N. H.; Nguyen, V. T.; Gu, M. B. A New Lateral Flow Strip Assay (LFSA) Using a Pair of Aptamers for the Detection of Vaspin. *Biosens. Bioelectron.* **2017**, *93*, 21−25.
(164) Wolfe, M. G.; Zhang, Q.; Hui, C.; Radford, K.; Nair, P.; Brennan, J. D. Development of a Functional Point-of-Need Diagnostic for Myeloperoxidase Detection to Identify Neutrophilic Bronchitis. *Analyst* **2016**, *141* (23), 6438−6443.
(165) Sun, P.; Qie, S.; Liu, Z.; Ren, J.; Li, K.; Xi, J. Clinical Characteristics of Hospitalized Patients with SARS-CoV-2 Infection: A Single Arm Meta-Analysis. *Journal of Medical Virology* **2020**, *92* (6), 612−617.
(166) Li, Z.; Yi, Y.; Luo, X.; Xiong, N.; Liu, Y.; Li, S.; Sun, R.; Wang, Y.; Hu, B.; Chen, W.; Zhang, Y.; Wang, J.; Huang, B.; Lin, Y.; Yang, J.; Cai, W.; Wang, X.; Cheng, J.; Chen, Z.; Sun, K.; Pan, W.; Zhan, Z.; Chen, L.; Ye, F. Development and Clinical Application of a Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis. *Journal of Medical Virology* **2020**, *92* (9), 1518−1524.
(167) Chen, C.; Zhu, C.; Yan, D.; Liu, H.; Li, D.; Zhou, Y.; Fu, X.; Wu, J.; Ding, C.; Tian, G.; Lan, L.; Liu, X.; Huang, C.; Hecht, R.; Li, L.; Yang, S. The Epidemiological and Radiographical Characteristics of Asymptomatic Infections with the Novel Coronavirus (COVID-19): A Systematic Review and Meta-Analysis. *Int. J. Infect. Dis.* **2021**, *104*, 458−464, DOI: 10.1016/j.ijid.2021.01.017.
(168) Guo, L.; Ren, L.; Yang, S.; Xiao, M.; Chang, D.; Yang, F.; Dela Cruz, C. S.; Wang, Y.; Wu, C.; Xiao, Y.; Zhang, L.; Han, L.; Dang, S.; Xu, Y.; Yang, Q. W.; Xu, S. Y.; Zhu, H. D.; Xu, Y. C.; Jin, Q.; Sharma, L.; Wang, L.; Wang, J. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). *Clinical Infectious Diseases* **2020**, *71* (15), 778−785.
(169) Zhang, K.; Liu, X.; Shen, J.; Li, Z.; Sang, Y.; Wu, X.; Zha, Y.; Liang, W.; Wang, C.; Wang, K.; Ye, L.; Gao, M.; Zhou, Z.; Li, L.; Wang, J.; Yang, Z.; Cai, H.; Xu, J.; Yang, L.; Cai, W.; Xu, W.; Wu, S.; Zhang, W.; Jiang, S.; Zheng, L.; Zhang, X.; Wang, L.; Lu, L.; Li, J.; Yin, H.; Wang, W.; Li, O.; Zhang, C.; Liang, L.; Wu, T.; Deng, R.; Wei, K.; Zhou, Y.; Chen, T.; Lau, J. Y. N.; Fok, M.; He, J.; Lin, T.; Li, W.; Wang, G. Clinically Applicable AI System for Accurate Diagnosis, Quantitative Measurements, and Prognosis of COVID-19 Pneumonia Using Computed Tomography. *Cell* **2020**, *181* (6), 1423−1433.
(170) Mei, X.; Lee, H. C.; Diao, K. Y.; Huang, M.; Lin, B.; Liu, C.; Xie, Z.; Ma, Y.; Robson, P. M.; Chung, M.; Bernheim, A.; Mani, V.; Calcagno, C.; Li, K.; Li, S.; Shan, H.; Lv, J.; Zhao, T.; Xia, J.; Long, Q.; Steinberger, S.; Jacobi, A.; Deyer, T.; Luksza, M.; Liu, F.; Little, B. P.; Fayad, Z. A.; Yang, Y. Artificial Intelligence-Enabled Rapid Diagnosis of Patients with COVID-19. *Nature Medicine* **2020**, *26* (8), 1224−1228.
(171) Wang, C.; Wang, Z.; Wang, G.; Lau, J. Y. N.; Zhang, K.; Li, W. COVID-19 in Early 2021: Current Status and Looking Forward. *Signal Transduction and Targeted Therapy* **2021**, *6* (1), 1−14.
(172) Parihar, A.; Zafar, T.; Khandia, R.; Singh, D.; Barkatullah, P.; Dhote, R.; Mishra, Y. In Silico Analysis for the Repurposing of Broad-Spectrum Antiviral Drugs against Multiple Targets from SARS-CoV-

https://doi.org/10.1021/acsabm.1c01320
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

2: A Molecular Docking and ADMET Approach. *Research Square* **2022**. DOI: 10.21203/rs.3.rs-1242644/v1.
(173) Ting, D. S. W.; Carin, L.; Dzau, V.; Wong, T. Y. Digital Technology and COVID-19. *Nature Medicine* **2020**, *26*, 459−461, DOI: 10.1038/s41591-020-0824-5.
(174) Alimadadi, A.; Aryal, S.; Manandhar, I.; Munroe, P. B.; Joe, B.; Cheng, X. Artificial Intelligence and Machine Learning to Fight Covid-19. *Physiological Genomics* **2020**, *52* (4), 200−202, DOI: 10.1152/physiolgenomics.00029.2020.
(175) Kamel Boulos, M. N.; Geraghty, E. M. Geographical Tracking and Mapping of Coronavirus Disease COVID-19/Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Epidemic and Associated Events around the World: How 21st Century GIS Technologies Are Supporting the Global Fight against Outbreaks and Epidemics. *International Journal of Health Geographics* **2020**, *19* (1), 1−12.
(176) Dong, E.; Du, H.; Gardner, L. An Interactive Web-Based Dashboard to Track COVID-19 in Real Time. *The Lancet Infectious Diseases* **2020**, *20* (5), 533−534, DOI: 10.1016/S1473-3099(20)30120-1.
(177) Okereafor, K.; Adebola, O.; Djehaiche, R.; El, M.; El, B. *Exploring the Potentials of Telemedicine and Other Non-Contact Electronic Health Technologies in Controlling the Spread of the Novel Coronavirus Disease (COVID-19)* **2020**, *8* (4), 1 DOI: 10.6084/M9.FIGSHARE.12479111.V1.
(178) Moazzami, B.; Razavi-Khorasani, N.; Dooghaie Moghadam, A.; Farokhi, E.; Rezaei, N. COVID-19 and Telemedicine: Immediate Action Required for Maintaining Healthcare Providers Well-Being. *Journal of Clinical Virology* **2020**, *126*, 104345.
(179) Vidal-Alaball, J.; Acosta-Roja, R.; PastorHernández, N.; SanchezLuque, U.; Morrison, D.; NarejosPérez, S.; Perez-Llano, J.; Salvador Vèrges, A.; López Seguí, F. Telemedicine in the Face of the COVID-19 Pandemic. *Atencion Primaria* **2020**, *52* (6), 418−422.
(180) Shokri, T.; Lighthall, J. G. Telemedicine in the Era of the COVID-19 Pandemic: Implications in Facial Plastic Surgery. *Facial Plastic Surgery & Aesthetic Medicine* **2020**, *22* (3), 155−156.
(181) Smith, A. C.; Thomas, E.; Snoswell, C. L.; Haydon, H.; Mehrotra, A.; Clemensen, J.; Caffery, L. J. Telehealth for Global Emergencies: Implications for Coronavirus Disease 2019 (COVID-19). *Journal of Telemedicine and Telecare* **2020**, *26* (5), 309−313.
(182) Aslani, N.; Garavand, A. The Role of Telemedicine to Control COVID-19. *Archives of Clinical Infectious Diseases* **2020**, *15*, e102949 DOI: 10.5812/archcid.102949.
(183) Leite, H.; Gruber, T.; Hodgkinson, I. R. Flattening the Infection Curve - Understanding the Role of Telehealth in Managing COVID-19. *Leadership in Health Services* **2020**, *33* (2), 221−226.
(184) Hollander, J. E.; Carr, B. G. Virtually Perfect? Telemedicine for Covid-19. *New England Journal of Medicine* **2020**, *382* (18), 1679−1681.
(185) Banskota, S.; Healy, M.; Goldberg, E. M. 15 Smartphone Apps for Older Adults to Use While in Isolation During the COVID-19 Pandemic. *West J. Emerg Med.* **2020**, *21* (3), 514−525.
(186) Cho, H.; Ippolito, D.; Yu, Y. W. Contact Tracing Mobile Apps for COVID-19: Privacy Considerations and Related Trade-Offs. *arXiv:2003.11511***2020**. DOI: 10.48550/arXiv.2003.11511
(187) Normile, D. Coronavirus Cases Have Dropped Sharply in South Korea. What's the Secret to Its Success? *Science (1979)* **2020**. DOI: 10.1126/science.abb7566.
(188) Sundararaman, T. Health Systems Preparedness for COVID-19 Pandemic. *Indian J. Public Health* **2020**, *64* (6), S91−S93.
(189) Kruk, M. E. Emergency Preparedness and Public Health Systems. Lessons for Developing Countries. *American Journal of Preventive Medicine* **2008**, *34* (6), 529−534, DOI: 10.1016/j.amepre.2008.02.012.
(190) de Lusignan, S.; Dorward, J.; Correa, A.; Jones, N.; Akinyemi, O.; Amirthalingam, G.; Andrews, N.; Byford, R.; Dabrera, G.; Elliot, A.; Ellis, J.; Ferreira, F.; Lopez Bernal, J.; Okusi, C.; Ramsay, M.; Sherlock, J.; Smith, G.; Williams, J.; Howsam, G.; Zambon, M.; Joy, M.; Hobbs, F. D. R. Risk Factors for SARS-CoV-2 among Patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre Primary Care Network: A Cross-Sectional Study. *Lancet Infectious Diseases* **2020**, *20* (9), 1034−1042.
(191) Mayhew, S.; Hanefeld, J. Planning Adaptive Health Systems: The Climate Challenge. *The Lancet Global Health* **2014**, *2* (11), e625−e626, DOI: 10.1016/S2214-109X(14)70313-4.
(192) Karanikolos, M.; Mladovsky, P.; Cylus, J.; Thomson, S.; Basu, S.; Stuckler, D.; MacKenbach, J. P.; McKee, M. Financial Crisis, Austerity, and Health in Europe. *The Lancet.* **2013**, *381* (9874), 1323−1331, DOI: 10.1016/S0140-6736(13)60102-6.
(193) McKee, M.; Karanikolos, M.; Belcher, P.; Stuckler, D. Austerity: A Failed Experiment on the People of Europe. *Clinical Medicine, Journal of the Royal College of Physicians of London* **2012**, *12* (4), 346−350, DOI: 10.7861/clinmedicine.12-4-346.
(194) Bell, M.; Warren, A.; Budd, L. Scales of Governance: The Role of Surveillance in Facilitating New Diplomacy during the 2009−2010 H1N1 Pandemic. *Health and Place* **2012**, *18* (6), 1404−1411.
(195) Parihar, A.; Parihar, D. S.; Ranjan, P.; Khan, R. Role of Microfluidics-Based Point-of-Care Testing (POCT) for Clinical Applications. *Advanced Microfluidics-Based Point-of-Care Diagnostics* **2022**, 39−60.
(196) Manero, A.; Smith, P.; Koontz, A.; Dombrowski, M.; Sparkman, J.; Courbin, D.; Chi, A. Leveraging 3D Printing Capacity in Times of Crisis: Recommendations for COVID-19 Distributed Manufacturing for Medical Equipment Rapid Response. *International Journal of Environmental Research and Public Health* **2020**, *17* (13), 1−17.
(197) Kant, K.; Shahbazi, M. A.; Dave, V. P.; Ngo, T. A.; Chidambara, V. A.; Than, L. Q.; Bang, D. D.; Wolff, A. Microfluidic Devices for Sample Preparation and Rapid Detection of Foodborne Pathogens. *Biotechnology Advances* **2018**, *36* (4), 1003−1024, DOI: 10.1016/j.biotechadv.2018.03.002.
(198) Long, Q. X.; Liu, B. Z.; Deng, H. J.; Wu, G. C.; Deng, K.; Chen, Y. K.; Liao, P.; Qiu, J. F.; Lin, Y.; Cai, X. F.; Wang, D. Q.; Hu, Y.; Ren, J. H.; Tang, N.; Xu, Y. Y.; Yu, L. H.; Mo, Z.; Gong, F.; Zhang, X. L.; Tian, W. G.; Hu, L.; Zhang, X. X.; Xiang, J. L.; Du, H. X.; Liu, H. W.; Lang, C. H.; Luo, X. H.; Wu, S. B.; Cui, X. P.; Zhou, Z.; Zhu, M. M.; Wang, J.; Xue, C. J.; Li, X. F.; Wang, L.; Li, Z. J.; Wang, K.; Niu, C. C.; Yang, Q. J.; Tang, X. J.; Zhang, Y.; Liu, X. M.; Li, J. J.; Zhang, D. C.; Zhang, F.; Liu, P.; Yuan, J.; Li, Q.; Hu, J. L.; Chen, J.; Huang, A. L. Antibody Responses to SARS-CoV-2 in Patients with COVID-19. *Nature Medicine* **2020**, *26* (6), 845−848.
(199) Lv, L.; Xie, X.; Gong, Q.; Feng, R.; Guo, X.; Su, B.; Chen, L. Transcriptional Difference between SARS-COV-2 and Other Human Coronaviruses Revealed by Sub-Genomic RNA Profiling. *bioRxiv* **2020**, DOI: 10.1101/2020.04.16.043224.
(200) Pan, L.; Mu, M.; Yang, P.; Sun, Y.; Wang, R.; Yan, J.; Li, P.; Hu, B.; Wang, J.; Hu, C.; Jin, Y.; Niu, X.; Ping, R.; Du, Y.; Li, T.; Xu, G.; Hu, Q.; Tu, L. Clinical Characteristics of COVID-19 Patients with Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. *American Journal of Gastroenterology* **2020**, *115* (5), 766−773.
(201) Pan, Y.; Long, L.; Zhang, D.; Yuan, T.; Cui, S.; Yang, P.; Wang, Q.; Ren, S. Potential False-Negative Nucleic Acid Testing Results for Severe Acute Respiratory Syndrome Coronavirus 2 from Thermal Inactivation of Samples with Low Viral Loads. *Clin Chem.* **2020**, *66* (6), 794−801.
(202) Hoffman, T.; Nissen, K.; Krambrich, J.; Rönnberg, B.; Akaberi, D.; Esmaeilzadeh, M.; Salaneck, E.; Lindahl, J.; Lundkvist, Å. Evaluation of a COVID-19 IgM and IgG Rapid Test; an Efficient Tool for Assessment of Past Exposure to SARS-CoV-2. *Infection Ecology and Epidemiology* **2020**, *10* (1), 1754538.
(203) Choi, J. R.; Liu, Z.; Hu, J.; Tang, R.; Gong, Y.; Feng, S.; Ren, H.; Wen, T.; Yang, H.; Qu, Z.; Pingguan-Murphy, B.; Xu, F. Polydimethylsiloxane-Paper Hybrid Lateral Flow Assay for Highly Sensitive Point-of-Care Nucleic Acid Testing. *Anal. Chem.* **2016**, *88* (12), 6254−6264.

(204) Gao, X.; Xu, L. P.; Wu, T.; Wen, Y.; Ma, X.; Zhang, X. An Enzyme-Amplified Lateral Flow Strip Biosensor for Visual Detection of MicroRNA-224. *Talanta* **2016**, *146*, 648−654.
(205) Tang, R.; Yang, H.; Choi, J. R.; Gong, Y.; Hu, J.; Feng, S.; Pingguan-Murphy, B.; Mei, Q.; Xu, F. Improved Sensitivity of Lateral Flow Assay Using Paper-Based Sample Concentration Technique. *Talanta* **2016**, *152*, 269−276.
(206) Li, J.; Macdonald, J. Multiplexed Lateral Flow Biosensors: Technological Advances for Radically Improving Point-of-Care Diagnoses. *Biosensors and Bioelectronics* **2016**, *83*, 177−192, DOI: 10.1016/j.bios.2016.04.021.
(207) Rasmi, Y.; Li, X.; Khan, J.; Ozer, T.; Choi, J. R. Emerging Point-of-Care Biosensors for Rapid Diagnosis of COVID-19: Current Progress, Challenges, and Future Prospects. *Anal. Bioanal. Chem.* **2021**, *413*, 4137−4159.
(208) Choi, J. R.; Yong, K. W.; Tang, R.; Gong, Y.; Wen, T.; Li, F.; Pingguan-Murphy, B.; Bai, D.; Xu, F. Advances and Challenges of Fully Integrated Paper-Based Point-of-Care Nucleic Acid Testing. *TrAC - Trends in Analytical Chemistry* **2017**, *93*, 37−50, DOI: 10.1016/j.trac.2017.05.007.
(209) Blicharz, T. M.; Gong, P.; Bunner, B. M.; Chu, L. L.; Leonard, K. M.; Wakefield, J. A.; Williams, R. E.; Dadgar, M.; Tagliabue, C. A.; El Khaja, R.; Marlin, S. L.; Haghgooie, R.; Davis, S. P.; Chickering, D. E.; Bernstein, H. Microneedle-Based Device for the One-Step Painless Collection of Capillary Blood Samples. *Nature Biomedical Engineering* **2018**, *2* (3), 151−157.
(210) Aro, K.; Wei, F.; Wong, D. T.; Tu, M. Saliva Liquid Biopsy for Point-of-Care Applications. *Frontiers in Public Health* **2017**, *5*, 77 DOI: 10.3389/FPUBH.2017.00077.
(211) Parihar, A.; Ranjan, P.; Sanghi, S. K.; Srivastava, A. K.; Khan, R. Point-of-Care Biosensor-Based Diagnosis of COVID-19 Holds Promise to Combat Current and Future Pandemics. *ACS Applied Bio Materials* **2020**, *3* (11), 7326−7343.
(212) Singhal, A.; Parihar, A.; Kumar, N.; Khan, R. High Throughput Molecularly Imprinted Polymers Based Electrochemical Nanosensors for Point-of-Care Diagnostics of COVID-19. *Mater. Lett.* **2022**, *306*, 130898.
(213) Deng, J.; Jiang, X. Advances in Reagents Storage and Release in Self-Contained Point-of-Care Devices. *Advanced Materials Technologies* **2019**, *4* (6), 1800625.
(214) Montes-Cebrián, Y.; Del Torno-De Román, L.; Álvarez-Carulla, A.; Colomer-Farrarons, J.; Minteer, S. D.; Sabaté, N.; Miribel-Català, L.; Esquivel, J. P. "Plug-and-Power" Point-of-Care Diagnostics: A Novel Approach for Self-Powered Electronic Reader-Based Portable Analytical Devices. *Biosensors and Bioelectronics* **2018**, *118*, 88.
(215) Tang, R.; Yang, H.; Gong, Y.; You, M. L.; Liu, Z.; Choi, J. R.; Wen, T.; Qu, Z.; Mei, Q.; Xu, F. A Fully Disposable and Integrated Paper-Based Device for Nucleic Acid Extraction, Amplification and Detection. *Lab Chip* **2017**, *17* (7), 1270−1279.
(216) Liu, J.; Geng, Z.; Fan, Z.; Liu, J.; Chen, H. Point-of-Care Testing Based on Smartphone: The Current State-of-the-Art (2017−2018). *Biosens. Bioelectron.* **2019**, *132*, 17−37.
(217) Xu, D.; Huang, X.; Guo, J.; Ma, X. Automatic Smartphone-Based Microfluidic Biosensor System at the Point of Care. *Biosensors and Bioelectronics* **2018**, *110*, 78−88, DOI: 10.1016/j.bios.2018.03.018.
(218) Yang, T.; Gentile, M.; Shen, C. F.; Cheng, C. M. Combining Point-of-Care Diagnostics and Internet of Medical Things (IOMT) to Combat the Covid-19 Pandemic. *Diagnostics* **2020**, *10* (4), 224 DOI: 10.3390/diagnostics10040224.
(219) Papadopoulos, T.; Baltas, K. N.; Balta, M. E. The Use of Digital Technologies by Small and Medium Enterprises during COVID-19: Implications for Theory and Practice. *International Journal of Information Management* **2020**, *55*, 102192.
(220) Bacq, S.; Geoghegan, W.; Josefy, M.; Stevenson, R.; Williams, T. A. The COVID-19 Virtual Idea Blitz: Marshaling Social Entrepreneurship to Rapidly Respond to Urgent Grand Challenges. *Business Horizons* **2020**, *63* (6), 705−723.
(221) Pan, S. L.; Zhang, S. From Fighting COVID-19 Pandemic to Tackling Sustainable Development Goals: An Opportunity for Responsible Information Systems Research. *International Journal of Information Management* **2020**, *55*, 102196.
(222) *COVID-19 Tech Will Expand Surveillance State in China*; Oxford Analytica, 2020. DOI: 10.1108/OXAN-DB251958.
(223) Rawson, T. M.; Ahmad, R.; Toumazou, C.; Georgiou, P.; Holmes, A. H. Artificial Intelligence Can Improve Decision-Making in Infection Management. *Nature Human Behaviour* **2019**, *3*, 543−545, DOI: 10.1038/s41562-019-0583-9.
(224) Chen, J. H.; Asch, S. M. Machine Learning and Prediction in Medicine — Beyond the Peak of Inflated Expectations. *New England Journal of Medicine* **2017**, *376* (26), 2507−2509.
(225) Schaduangrat, N.; Lampa, S.; Simeon, S.; Gleeson, M. P.; Spjuth, O.; Nantasenamat, C. Towards Reproducible Computational Drug Discovery. *Journal of Cheminformatics* **2020**, *12*, 9 DOI: 10.1186/s13321-020-0408-x.
(226) Ngiam, K. Y.; Khor, I. W. Big Data and Machine Learning Algorithms for Health-Care Delivery. *The Lancet Oncology* **2019**, *20* (5), e262−e273, DOI: 10.1016/S1470-2045(19)30149-4.

https://doi.org/10.1021/acsabm.1c01320
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX