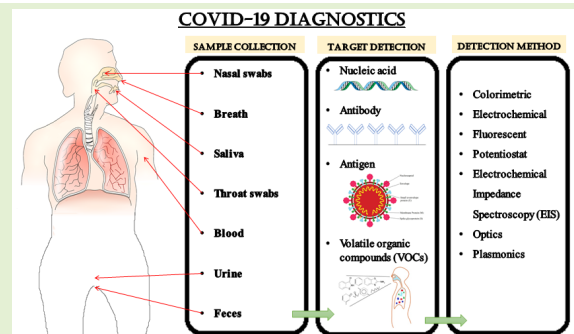


Portable Tools for COVID-19 Point-of-Care Detection: A Review

Elga F. Saki, Samuel A. Setiawan, and Dedy H. B. Wicaksono^{ID}, Member, IEEE

Abstract—Recently, several methods for SARS-CoV-2 detection have been developed to obtain rapid, portable, cheap, and easy-to-use diagnostic tools. This review paper summarizes and discusses studies on the development of point-of-care devices for SARS-CoV-2 diagnosis with comparisons between them from several aspects. Various detection methods of the recently developed portable COVID-19 biosensor will be presented in this review. The discussion is divided into four major classifications based on the target biomarkers of SARS-CoV-2, such as antibodies, nucleic acids, antigens, and metabolic products. An overview of the potential development for future study is also provided. Moreover, basic knowledge of biosensors is also explained for tutoring the implementation of theory into the research of COVID-19 biosensors. This review paper is aimed to provide a tutorial by collecting the information on the development of a point-of-care device for SARS-CoV-2 detection to provide information for further research and propose the new COVID-19 portable diagnostic tool.

Index Terms—COVID-19, SARS-CoV-2, biosensor, point-of-care device, antibody-based tests, antigen-based tests, nucleic acid-based tests, electronic nose, electronic tongue.



I. INTRODUCTION

CORONA Virus Disease 2019 or COVID-19, is an infectious disease caused by a novel human coronavirus, the SARS-CoV-2. SARS-CoV-2 is an abbreviation of the severe acute respiratory syndrome coronavirus 2. The COVID-19 patient was firstly announced in Wuhan, China, in early December 2019. The World Health Organization (WHO) then declared COVID-19 as a global pandemic after the infection spread to other countries around the world [1], [2].

SARS-CoV-2 comes from the family *Coronaviridae* with genus *Betacoronavirus*, similar to other coronaviruses, including MERS-CoV and SARS-CoV having an enveloped and positive-sense single-stranded RNA virus. It has approximately 30,000 bases of RNA length sequence. There are four main protein structures of SARS-CoV-2 (Fig. 1), such as crown-like spike (S-) glycoprotein, membrane (M-) glycoprotein,

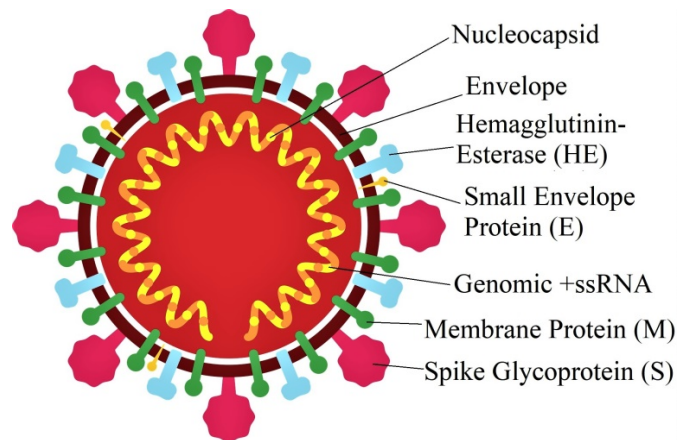


Fig. 1. Schematic of the SARS-CoV-2 virus structure. Adapted from the concept presented by [5].

Manuscript received July 12, 2021; revised August 22, 2021; accepted August 26, 2021. Date of publication September 7, 2021; date of current version October 29, 2021. This work was supported in part by the Swiss German University Central Research Fund under Grant 24/CRF/LGL-ARCS/IX/2020. The associate editor coordinating the review of this article and approving it for publication was Prof. Irene Taurino. (Corresponding author: Elga F. Saki.)

Elga F. Saki and Dedy H. B. Wicaksono are with the Department of Biomedical Engineering, Faculty of Life Sciences and Technology, Swiss German University (SGU), Tangerang 15143, Indonesia (e-mail: elga.fatimahsaki@gmail.com; dedy.wicaksono@sgu.ac.id).

Samuel A. Setiawan is with PT AP&M, Jakarta 12950, Indonesia. Digital Object Identifier 10.1109/JSEN.2021.3110857

envelope (E-) protein on the viral surface, and nucleocapsid (N-) protein. M- and E- proteins protect RNA gene core by forming a ball, where N-protein wraps RNA genetic core [3]. The capability of SARS-CoV-2 entering the target cell is facilitated by S-protein. It forms protrusions to be able to have bindings with target cell receptors for infections and obtaining a crown-like shape for the virus [4].

SARS-CoV-2 is considered to cause more deadly symptoms than the 2009 swine influenza and has high transmissibility.

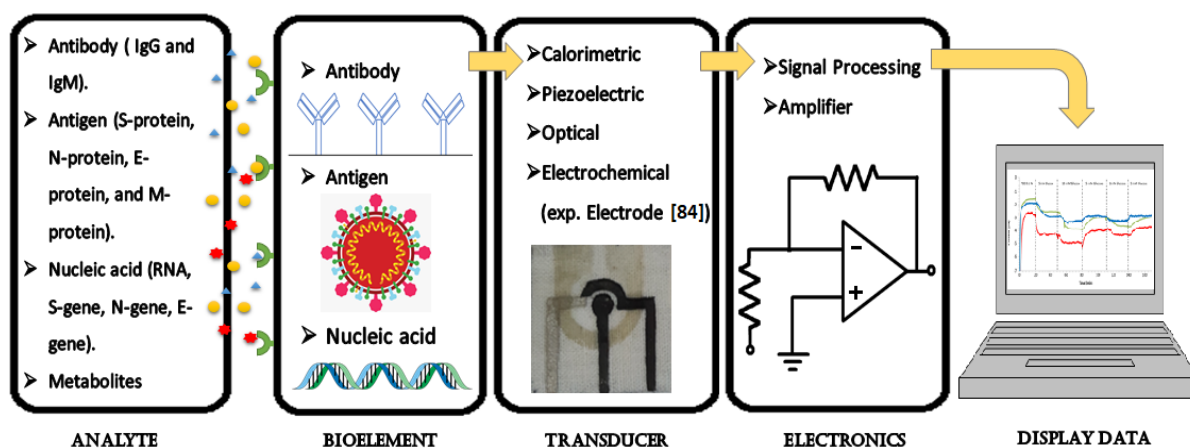


Fig. 2. Illustration of a COVID-19 biosensor structure. IgG = immunoglobulin G; IgM = immunoglobulin M; S-protein = spike protein; N-protein = nucleocapsid protein; E-protein = envelope protein; M-protein = membrane a protein; RNA = ribonucleic acid.

The detection of SARS-CoV-2 infection is extremely important to trace cases and as prevention against the spread of SARS-CoV-2 [6], [7].

Nowadays, there have been four main methods of SARS-CoV-2 detection, namely nucleic acid (NA)-based testing, computed tomography (CT) chest scan, antibody-based testing, and antigen based-testing. CT chest scan possesses relatively high sensitivity (67-100%) but low specificity (25-80%) [8]. The outcomes of CT chest scans are not able to distinguish pneumonia caused by SARS-CoV-2 from other types of viral pneumonia. Antibody-based and antigen-based testing are currently used as rapid detection and will be discussed in more detail below. Whereas NA-based testing, such as quantitative reverse transcription polymerase chain reaction (RT-qPCR) method is the gold standard for SARS-CoV-2 detection since RT-qPCR is very reliable, it offers high sensitivity and specificity [3], [6]–[10]. Yet, most current PCR-based methods do not support rapid and point-of-care diagnosis. However, some recent studies have started to report development of ultrafast PCR systems, including to be used for COVID-19 detection [11]–[13]. Moreover, In 2020, You's group had performed the nucleic acid amplification in a nano-localized environment to significantly increase the thermocycling rate [11]. Nevertheless, these recent developments have not been widely implemented.

Recently, other new technologies for SARS-CoV-2 detection have been developed. Biosensor for SARS-CoV-2 detection offers a new alternative for reliable, economical, and sensitive detection. Biosensors are defined as devices that have a coupling between biological sensing elements, i.e., recognition molecules, to a detector system that uses a transducer. Biosensors have finer performance in terms of sensitivity and selectivity than other diagnostic devices [14]. Biosensors contain two main parts, a bioelement and a transducer. Bioelement is biological elements (nucleic acid, antigen, antibody, etc.) that recognize the target analyte. A transducer is a physicochemical detector element that converts the recognition event into measurable signals (Fig. 2). The variation of the biosensor functions depends on the biochemical specificity of the biologically active materials [15].

Recently, colorimetric method is commonly used for rapid COVID-19 tests. However, it has low sensitivity since the result is qualitative and the perception of interpreting color change might be different from one person to another [16]. Other methods, such as piezoelectric and optical methods, have complex setup and are relatively expensive.

Therefore, an electrochemical method is favorable for portable diagnostic due to its cost-effectiveness, high sensitivity, rapid response, ease of use, and possible miniaturization [17]. Electrochemical biosensors are capable of generating conductometric, potentiometric, amperometric, and impedimetric signals [18]. Those signals can be measured by the corresponding output signal analysis, such as differential pulse voltammetry (DPV), cyclic voltammetry (CV), square wave voltammetry (SWV), and electrochemical impedance spectroscopy (EIS) [19].

Recently, there have been several reviews on COVID-19 diagnostics: In 2020, Bhalla *et al.*, reviewed the challenges and potential bio/chemical sensors [20]. In addition, Leichle, Nicu and Alava explained the possible role of MEMS biosensor for COVID-19 test in general [21]. In the same year, Asif *et al.*, discussed several physicochemical transducers of biosensor for COVID-19 test with emphasis in antigen target [22]. In 2021, the discussion of COVID-19 diagnostics have been more expansive by reviewing molecular-based, serological-based, and radiology-based diagnostics [23]–[25]. In this review, the discussion will be focused more towards COVID-19 diagnostics with better portability, lower cost, and shorter time response, yet enough sensitivity for field or point of care applications. Therefore, detection time and detection limit will be the main two parameters being compared from various reported methods. In addition, we also mention a new emerging approach of surrogate-biomarker-based diagnostic combined with artificial intelligence analysis. Perspective on new designs for COVID-19 portable diagnostic tools will also be discussed. Finally, in this review, the protocol of sample collection, related to the progression of the disease will also be discussed, since this is very much related to the accuracy of the diagnosis. So far, very few reviews had discussed this matter.

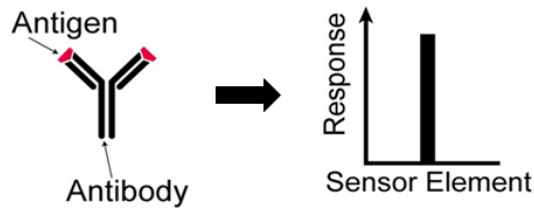


Fig. 3. Specific binding between antibody and antigen. Reprinted with permission from [27]. Copyright © 2016 American chemical society.

II. FIGURE OF MERIT

To assess the implementation of a specific type of biosensor for particular application, including for SARS-CoV-2 detection, its performance can be judged by several properties, such as specificity or selectivity, limit of detection (LOD), sensitivity and accuracy. Specificity or selectivity is the ability of the sensor to recognize a single interest analyte [26]. Fig. 3 shows how the specificity or selectivity of the biosensor was acquired. In this case, a highly specific or selective sensor is obtained by involving antibody as a specific bioelement recognition for antigen detection, antibody has specific information about a single antigen. Therefore, each antibody is only able to bind to the corresponding antigen with no cross-reactivity [27].

During a clinical trial, a biosensor is assessed using samples collected from positive COVID-19 patients and healthy subjects (confirmed by RT-qPCR test). The results are then grouped based on four probabilities, True Negative (TN), True Positive (TP), False Positive (FP), and False Negative (FN) [25]–[27]. The selectivity or specificity of the sensor can thus be calculated using the formula below:

$$\text{Selectivity or Specificity} = \frac{TN}{TN + FP} \times 100\% \quad (1)$$

Limit of detection (LOD) is the minimum detectable level of the target analyte that can be distinguished from zero [31]. Seo *et al.* [32] determined the LOD of their COVID-19 biosensor by comparing the output response from various concentrations of SARS-CoV-2 spike antigen. The biosensor was still able to respond to the concentration as low as 1.6×10^1 pfu/mL and not able to respond below than 1.6×10^1 pfu/mL. Thus 1.6×10^1 pfu/mL was considered as the LOD of this sensor.

Sensitivity defines the alteration in the sensor output per unit change in the sensor input [17]. Sensitivity is related to LOD, with improved sensitivity indicated by a significantly lower value of LOD [17], [31], [33].

The sensitivity of COVID-19 biosensors is mostly determined using clinical samples. The methods are similar like determining selectivity and specificity. However, the formula is different [28], [29], [34].

$$\text{Sensitivity} = \frac{TP}{TP + FN} \times 100\% \quad (2)$$

Accuracy is characterized by how close the sensor output value is to the reference diagnostic output value (acceptable value) [35]. Accuracy of the COVID-19 biosensors is also commonly assessed using clinical samples by applying methods that are the same as the methods for finding sensitivity

and specificity or selectivity. However, the formula used for accuracy calculation is as follows [29], [36], [30], [34]:

$$\text{Accuracy} = \frac{TN + TP}{TN + TP + FN + FP} \times 100\% \quad (3)$$

To date, the reference diagnostic method for SARS-CoV-2 infection still relies on RT-qPCR [37].

Portable COVID-19 diagnostic tools can be broadly divided into four main categories based on the detected analyte: nucleic acid-based, antibody-based, antigen-based, and surrogate-based tests (Fig. 4).

III. NUCLEIC ACID-BASED TEST

To date, there have been several studies on the development of portable COVID-19 diagnostics using nucleic acid (see Table. I). The nucleic acid-based testing of SARS-CoV-2 generally consists of four main steps: sample collection, RNA extraction, amplification, and signal detection [6].

A. Non-Isothermal Amplification-Based Tests

Non-isothermal amplification requires various temperature levels in the process. Polymerase chain reaction (PCR) is one of the techniques that use a non-isothermal amplification method. PCR is a technique commonly used in molecular biology to amplify DNA samples. Generally, there are three steps in PCR method: (1) denaturation, using a high temperature of 90°C–95°C to separate double-stranded DNA into two single stranded DNA chains. (2) Annealing, using the suitable primer that possesses a specific nucleotide sequence with the denatured single-stranded DNA. (3) Extension, utilizes a DNA polymerase to generate a new strand of DNA according to the complementary nucleotide of the single-stranded DNA sequence with a setting temperature of 72°C [38]. Since SARS-CoV-2 contains single-stranded RNA, reverse transcription is involved to reverse transcribe the RNA into complementary DNA (cDNA) strands, then amplification of specific gene is quantified, thus the device is called as quantitative reverse transcription polymerase chain reaction (RT-qPCR) [3], [39]. RT-qPCR enables direct detection of nucleic acid and allows the amplification of genomic material even if the presence of viral RNA in the biological sample is incredibly low. The analytical LOD of RT-qPCR is 1 copy/ μ L [40]. RT-qPCR offers early, sensitive, and specific viral detection. Therefore, RT-qPCR is the gold standard for COVID-19 diagnostic to date. However, RT-qPCR still requires the involvement of manual operations; it is time-consuming, and requires a centralized laboratory. Sample collection is also invasive, and requires critical consumable supplies, e.g. nasal swabs and RNA extraction columns [3], [6], [7], [9].

There have been several studies that utilized non-isothermal amplification techniques for developing portable COVID-19 diagnostics. Rapid and ultrasensitive biosensors using electrochemical detection techniques have been developed by Alafeef *et al.* [17]. The target of their biosensor was nucleocapsid phosphoprotein (N-gene) of SARS-CoV-2 since N-gene is recently recommended for screening test of SARS-CoV-2. The ultrasensitivity was achieved by involving thiol-modified ssDNA-capped gold nanoparticles (AuNPs) on top of a gold

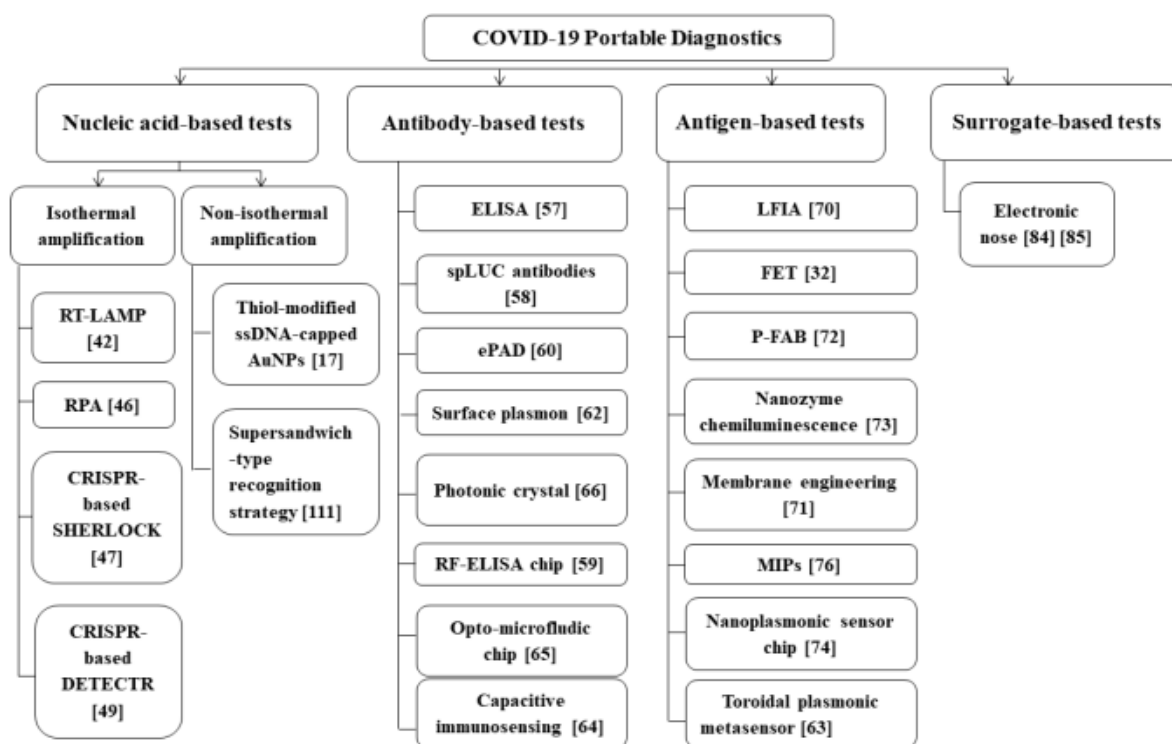


Fig. 4. Classification of portable COVID-19 diagnostic tools. RT-LAMP = reverse transcription loop-mediated isothermal amplification; RPA = recombinase polymerase amplification; ssDNA = single-stranded DNA, AuNPs = gold nanoparticles; CRISPR = clustered regularly interspaced short palindromic repeats; SHERLOCK = Specific High Sensitivity Enzymatic Reporter Unlocking; DETECTR = DNA Endonuclease-Targeted CRISPR Trans Reporter; ELISA = enzyme-linked immunosorbent assay; spLUC = split luciferase; RF = Reciprocasting-flowing; ePAD = electrochemical paper-based device; LFIA = lateral flow immunoassay; FET = Field-effect transistor; MIPs = molecularly imprinted polymers; P-FAB = Plasmonic fiber-optic absorbance.

electrode. The time it took to get the result was within 5 min. The biosensor applied gold nanoparticles (AuNPs) attached to the antisense oligonucleotides (ssDNA) to recognize viral nucleocapsid phosphoprotein (N-gene). The brief steps are shown in Fig. 5. Step A: The sample from infected people was obtained using nasal swabs or saliva. Step B: The SARS-CoV-2 RNA was extracted from the swab sample. Step C: The viral RNA will be applied onto the top of the graphene-ssDNA-AuNP platform. Step D: Incubation for 5 min. Step E: The result will be recorded by the digital electrochemical method.

B. Isothermal Amplification-Based Tests

Isothermal amplification provides methods to amplify nucleic acid sequences by utilizing a single-temperature level [41].

Several studies have attempted to develop portable SARS-CoV-2 detection using isothermal amplification-based, such as reverse transcription loop-mediated isothermal amplification (RT-LAMP). Recently, the study of RT-LAMP has been proposed for SARS-CoV-2 detection. RT-LAMP only requires one constant temperature (usually 65°C), thus it eliminates sophisticated instrumentation in RT-qPCR setup. The combination of reverse transcription (RT) and LAMP can shorten the reaction time significantly without the need for DNA purification step from RT [42]. Two-step LAMP reaction enhanced the sensitivity of the RT-LAMP and was comparable to qPCR [43]. RT-LAMP is also feasible to be integrated

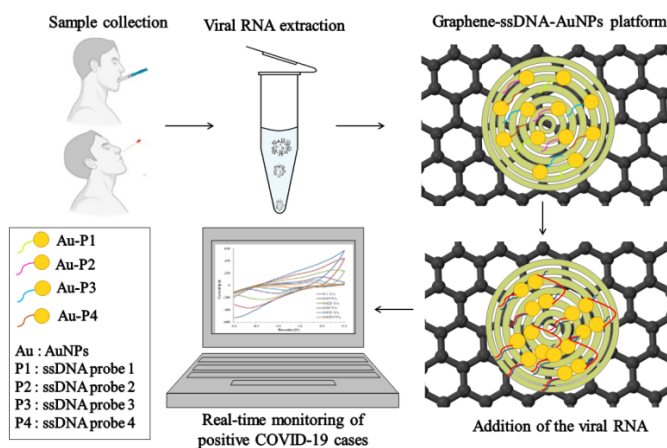


Fig. 5. Schematic of the operation principle of SARS-CoV-2 electrochemical sensing device. Adapted with permission from [17]. Copyright © 2020 American chemical society.

with other technologies, such as semiconductor technology. With this technology, the sensitivity and specificity of the sensor were 91% and 100%, respectively. Interestingly, this device was integrated into a smartphone to show visualization and geolocation, therefore it is possible to obtain real-time identification and epidemiological surveillance [44].

Another alternative for portable nucleic acid detection is recombinase polymerase amplification (RPA). RPA offers a simpler, inexpensive, accurate, convenient, and portable

TABLE I
NUCLEIC ACID-BASED TEST

Ref.	Substrate / Approach	Detection tools	Detection time	LOD
[42]	RT-LAMP	Colorimetry	1 h	-
[102]	One-step RT-LAMP	Colorimetry	20 min	80 copies/ml
[103]	RT-LAMP	Colorimetry	20 min	100 copies/ μ L
[104]	One-step RT-LAMP	Colorimetry	30 min	1000 copies/ml (5 copies)
[105]	RT-LAMP	Colorimetry	40 min	-
[106]	RT-LAMP	Fluorescent	>15 min	1×10^1 - 1×10^2 copies/reaction
[107]	RT-LAMP	Colorimetry	30 min	10^2 copies
[108]	RT-LAMP	Colorimetry, spectrophotometry, and real time fluorescence	>1 h	59 copies/reaction
[109]	RT-LAMP	Colorimetry	45 min	200 virions/ μ L
[110]	Isothermal rolling circle amplification (RCA)	Portable potentiostat	>2 h	1 copy/ μ L
[17]	Thiol-modified ssDNA-capped AuNPs, paper-based	Simple signal conditioning circuit	>5 min	6.9 copies/ μ L
[111]	Supersandwich-type recognition strategy	EIS	-	200 copies/mL (clinics)
[47]	CRISPR-based SHERLOCK	Fluorescent and colorimetric readout	>1 hour	2 aM
[46]	Recombinase polymerase amplification (RPA)	LightMix@Modular	-	-
[49]	Combined isothermal amplification with CRISPR-Cas12 DETECTR technology	fluorescence-based readout	<40 min	10 copies per μ l
[102]	One-step RT-LAMP	Colorimetry	20 min	80 copies/m
[112]	Two-step RT-LAMP	fluorescence-based readout	25 min	2 copies per μ l
[44]	RT-LAMP assay on semiconductor technology	Electrochemical	>20min	10 copies/reaction

RT-LAMP = reverse transcription loop-mediated isothermal amplification, ssDNA = single-stranded DNA, AuNPs = gold nanoparticles, CRISPR = clustered regularly interspaced short palindromic repeats, SHERLOCK = Specific High Sensitivity Enzymatic Reporter Unlocking, DETECTR = DNA Endonuclease-Targeted CRISPR Trans Reporter.

diagnostic. Generally, the steps required in the RPA are as follow: (1) binding of the recombinase to primers and scanning of the double-stranded DNA (dsDNA) for complementary

sequences, (2) insertion of primers by recombinase via strand exchange, (3) binding of the displaced strand to single-stranded binding proteins (SSB) and stabilization of the primer bond, (4) polymerization initiation by *Bacillus subtilis* (Bsu) polymerase, (5) displacement of the parental strand and continuation of the elongation, (6) generation of two new duplexes [45]. The study that used RPA for SARS-CoV-2 detection incorporated several steps: the design of efficient primers and probes to be applied for isothermal amplification of the S1, ORF3, and ORF8 SARS-CoV-2 region names; RNA extraction; RPA assay optimization for isothermal amplification of the named SARS-CoV-2 regions; detection process; and finally, validation. For the RPA assay optimization, TwistAmp® nfo Kit (TANFO02KIT; TwistDX, Maidenhead, UK) was used to undertake the final reactions. The result was reported to have excellent sensitivity of 93% and a specificity of 100% [46]. Nonetheless, the requirement of RPA assay optimization to each SARS-CoV-2 region and the inability to typically distinguish the differences of single base pair in target sequences were the limitations of the recombinase polymerase amplification (RPA) technique [47].

C. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)

Currently, enzymes from the CRISPR-Cas system have also been utilized for rapid, sensitive, specific, and portable sensing of nucleic acids. There are several types of Cas proteins that can be programmed with a CRISPR RNA (crRNA) for diagnostic purposes, such as Cas 12 and Cas13. Cas12 binds specifically to the complementary single and double-stranded DNA targets, while Cas13 binds to RNAs instead of DNAs [48] which makes it possible to be implemented in SARS-CoV-2 RNA detection. CRISPR-based tests identify a sequence of viral SARS-CoV-2 RNA and cut apart any nearby single-stranded RNA. Those cuts become fluorescent particles in the test solution. When a burst of laser light hits the sample, the fluorescent particles light up and show the presence of the viral genetic material [10].

There has been a study that used CRISPR-based SHERLOCK (Specific High Sensitivity Enzymatic Reporter UnLOCKing) technique for SARS-CoV-2 detection. Four main processes were used that include reagent preparation, sample extraction, isothermal target nucleic acid pre-amplification, and CRISPR-Cas13 nucleic acid detection. SHERLOCK is very sensitive, relatively low-cost, and has rapid turnaround time [47]. Nevertheless, SHERLOCK still requires a multi-step nucleic acid amplification process, which may affect precise target quantification [10].

Another study by Broughton *et al.* developed a CRISPR-Cas12-based assay to detect SARS-CoV-2 from an RNA patient sample, called SARS-CoV-2 DNA Endonuclease-Targeted CRISPR Trans Reporter (DETECTR) [33]. In this study, they combined CRISPR-Cas12 DETECTR technology and RT-LAMP. Predefined coronavirus sequences were obtained by Cas12 detection, followed by the cleavage of a reporter molecule to verify the virus detection. The primers were modified to be suitable for LAMP, and Cas12 guide

RNAs (gRNAs) were designed to recognize SARS-like coronaviruses. The accuracy of this approach was comparable to RT-qPCR. Moreover, with this approach, thermocycling was not required thus offering faster turnaround time, with single nucleotide target specificity, accessible integration, ease of use, and portability [49], [50].

In comparison to RT-qPCR which requires multiple temperatures to amplify the nucleic acid, RT-LAMP only requires constant temperature for nucleic acid amplification which results in cost-efficient detection [10]. However, RT-LAMP uses complex primer designs and strand-displacing DNA polymerases for amplification. Whereas RPA requires forward and reverse primers like those used in PCR, but RPA enables amplification at a single temperature similar to RT-LAMP due to the use of DNA polymerases. DNA polymerases do not rely on elevated temperatures like in PCR since they enzymatically separates the DNA strands [51]. CRISPR-based tests, on the other hand, combine the isothermal technique and amplification techniques with specific DNA or RNA targeting ability of crRNA and Cas12 or Cas13 enzymes [52].

IV. ANTIBODY-BASED TEST

Serological-based antibody tests rely on the binding toward SARS-CoV-2 specific antibodies [53]. Every pathogen entering the body will be specifically detected by immunoglobulin G (IgG) and immunoglobulin M (IgM) in blood since IgM and IgG work as the first line of defense during infection. These antibodies can be the specific SARS-CoV-2 antibodies and can be detected by serological tests to determine SARS-CoV-2-infected and non-infected people [54], [55]. The advantages of serological tests over PCR are faster time to result, high throughput, and less workload [56]. There have been several studies on this test with different approaches having different performances (see Table II).

Serological testing based on Enzyme-Linked Immunosorbent Assay (ELISA) is an alternative diagnostic method for SARS-CoV-2. To obtain rapid, simple, and inexpensive diagnostic tools for SARS-CoV-2, paper-based technology has been developed as a substrate material of the diagnostic tools. Kasetsirikul *et al.* [57] proposed paper-based ELISA for SARS-CoV-2 detection. A proof-of-concept was reported by modifying a specific antigen immunological complex on the paper to capture the specific SARS-CoV-2 antibody. The colorimetric assay was used in this technology to acquire color changes due to the presence of target biomolecules conjugated with horseradish peroxidase (HRP) in the reaction between 3, 3',5,5'-tetramethylbenzidine substrate and horseradish peroxidase (TMB/HRP). In their study, the fabrication of paper-based ELISA for SARS-CoV-2 was started by cutting Whatman chromatography (CHR) filter paper with a diameter of 5 cm and placed at the center between two laminate films with a 4 mm diameter hole. The sandwich layer of laminate films and CHR paper (L-CHR) were laminated using a laminator at speed of 10 mm s^{-1} at 103°C . Afterwards, recombinant SARS-CoV-2 nucleocapsid was immobilized on the L-CHR. The surface of L-CHR was washed by the washing solution $0.01 \text{ M PBS (pH 7.4)}$. Blotting paper was added at the bottom to absorb the excess reagents. PBS was dropped twice to flow out

TABLE II
SEROLOGICAL ANTIBODY-BASED

Ref.	Substrate / Approach	Detection tools	Detection time	LOD
[57]	L-CHR (ELISA paper-based)	Colorimetric reaction, camera-image processing Matlab	30 min	$9 \text{ ng } \mu\text{L}^{-1}$
[58]	Nanoluciferase (NanoLuc)	battery-supported portable luminometer	5 min	
[60]	Graphene oxide, paper-based	Square-wave voltammetry	30 min	1 ng/mL
[62]	Surface plasmon resonance (SPR)	A portable SPR instrument	15 min	$1 \text{ } \mu\text{g/mL}$
[113]	PSS, AuNPs, paper-based	Colorimetric reaction, smartphone app	<10 min	1.3 pg mL^{-1}
[66]	Photonic crystal	PRAM digital	15 min	$26.7 \pm 7.7 \text{ pg mL}^{-1}$
[59]	Reciprocasting-flowing (RF) immunobinding (RF-ELISA chip)	Colorimetric reaction, image software	4-5 min	-
[65]	Opto-microfluidic chip	Reflection probe (LSPR-based)	$\sim 30 \text{ min}$	$\sim 0.08 \text{ ng/mL}$
[64]	Non-faradaic capacitive immunosensing	Electrochemical impedance spectroscopy (EIS)	<5min	-

ELISA = enzyme-linked immunosorbent assay, PSS = polystyrene sulfonate, AuNPs = gold nanoparticles, L-CHR = the sandwich paper (whatman chromatography filter paper + laminated films), PRAM = photonic resonator microscopy, LSPR = localized surface plasmon.

the unbounded antigen. L-CHR was placed in the incubator for 10 min and put at room temperature for storage. This method has the potential to be developed further for SARS-CoV-2 clinical screening (Fig. 6). However, colorimetric methods in some cases have lower sensitivity since the reflection of wet surface hindered proper result observation and it also required relatively high immunoagent level to provide an analyzable result [16].

Another approach for detecting SARS-CoV-2 antibodies was proposed by using split luciferase (spLUC) antibody biosensor. Split Nanoluciferase (NanoLuc) fragments, SmBiT and LgBiT, were fused to SARS-CoV-2 protein antigens to fabricate anti-SARS-CoV-2 antibody biosensor. In comparison to ELISA, ELISA assay consumes more than 2 hours to obtain serological data and requires multiple wash and incubation

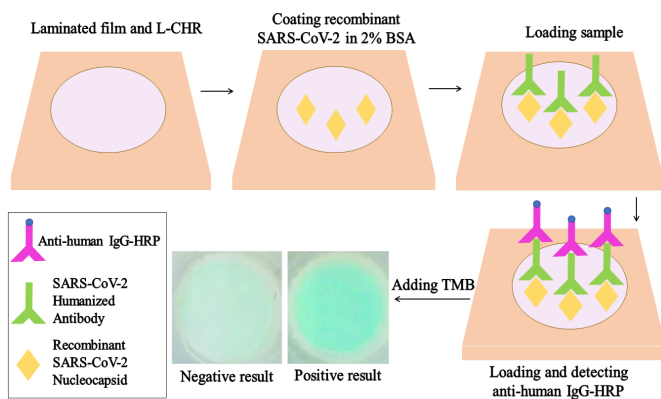


Fig. 6. Fabrication process of the paper-based ELISA for SARS-CoV-2 antibody detection. Adapted from [57] with permission from the royal society of chemistry.

steps, while spLUC assay only takes ≤ 30 min without requiring washing steps. The performance of this biosensor was considerably good with sensitivity and specificity reached $\geq 98\%$ and $\geq 99\%$, respectively [58].

Reciprocating-flowing immunobinding (RF-immunobinding) on a chip was presented to be an alternative method for the COVID-19 biosensor. In this approach, the reciprocating-flowing ELISA (RF-ELISA) chip was developed to solve the time-consuming ELISA protocols. By using the RF method, the sample fluid is allowed to flow through the detection site multiple times to enable repeatable contact between immobilized-antigen and antibodies in the sample [59].

Another study was conducted by Yakoh *et al.* [60] which involved a smartphone and paper-based biosensor. They studied a paper-based electrochemical device (ePAD) to detect IgM and IgG SARS-CoV-2 immunoglobulins. This ePAD consists of working, counter, and closing ePAD. SARS-CoV-2 antibodies in the sample were captured by a receptor-binding domain contained at SARS-CoV-2 spike protein that was immobilized on the working ePAD. Counter and reference electrodes were on counter ePAD, while closing ePAD was used to encapsulate the biohazard sample from the environment. The result of this method was also being compared to traditional lateral flow immunoassay (LFA). This method has higher sensitivity than traditional LFA since this study used an electrochemical technique that is capable of detecting small changes from the event of interest on the electrode surface and used graphene as material. It has relatively high sensitivity and specificity of 100% and 90%, respectively.

Plasmonics is one of the potential label-free detection techniques for SARS-CoV-2 sensing. It tends to provide good resolution even though ultrasensitive performance that comes along with excellent limit detection was still a challenge [61]. Surface plasmon resonance (SPR) sensor has potential to overcome the limitation of ELISA performance. Djaileb *et al.* [62] reported that SPR offered portability, short turnaround time, and label-free testing for antibodies. In this approach, a peptide monolayer was coated onto the SPR sensor and SARS-CoV-2 nucleocapsid recombinant protein was immobilized onto the SPR sensor surface to obtain specific binding to anti-SARS-CoV-2 antibodies [63].

Paper-based electrochemical platform targeting SARS-CoV-2 has been reported to have a finer LOD of 1 ng/mL. Electrochemical approach is able to distinguish small changes from the recognition event on the electrode surface, thus it is suitable for SARS-CoV-2 detection [60]. The electrochemical impedance-based sensing (EIS) was also being considered due to its relatively low-cost, typically label free, and high precision detection. A capacitive sensor for the COVID-19 biosensor was proposed with the interdigitated electrodes design fused to polyethylene terephthalate. This capacitive sensor was successfully able to detect all positive clinical samples from the negative control. In comparison to ELISA, measured impedance values were consistent [64].

Finer performance of the COVID-19 biosensor was achieved by using opto-microfluidic biosensor. The LOD was 0.08 ng/mL. The binding between antibody-antigen shifted the wavelength of the localized surface plasmon resonance (LSPR) peak of the gold nanostructure in microfluidic. Opto-microfluidic chip was successfully demonstrated with high sensitivity and selectivity, without labeling agent. However, this approach has to be improved in the future for producing a larger shift in the LSPR peak and for increasing signal-to-noise ratio [65].

However, the sensitivity of the detection limit in ng/mL is relatively low. Photonic crystal (PC)-based biosensors have higher sensitivity, low-cost, simple, and short turnaround time. Zhao *et al.* [66] studied the “Active Capture + Digital Counting (AC+DC)” assay method. PC biosensor was coated with recombinant COVID-19 spike protein as a surface for the formation of sandwich immunocomplex through specific antigen-antibody binding. The sensitivity of this approach was higher than ELISA and more than 50 times more sensitive than the commercial pGOLD High Accuracy IgG/IgM Assay Kit.

Commercially available antibody tests have been evaluated, including Abbott, Roche, and DiaSorin, the sensitivity of those were 62%, 64%, and 42%, respectively, at 7-14 days after symptom onset [67].

However, the antibodies produced depend on the antibody responses during infection [56]. For general antibody tests, the detection of combined IgG and IgM has a maximum sensitivity of 96% at 22-35 days after the onset of symptom. The maximum sensitivity decreased with IgG-alone detection, which was 88.2% at 15-21 after symptom onset. For the specificity, all types of antibody tests showed 98% specificity from 35 out of 54 studies [68].

Even though antibody detection is not reliable for early detection, antibody-based testing is equally as important as nucleic acid-based and antigen-based testing since it is able to identify false negative results as viral load tends to decrease at the late stage of infection. Moreover, antibodies are more stable than RNA [65].

V. ANTIGEN-BASED TEST

The antigen-based test can be considered for earlier detection of SARS-CoV-2 as an alternative to antibody-based tests. Recently, the antigen test is more commonly used as a rapid test since it is less laborious and requires only a few minutes to

TABLE III
ANTIGEN-BASED

Ref.	Substrate / Approach	Detection tools	Detection time	LOD
[70]	LFIA-based, using scFv-Fc fusion antibodies	Portable LFIA reader (N-antigen)	>20 min	2.5×10^4 pfu/reaction
[32]	Field-effect transistor-based	2634B semiconductor analyzer (S-antigen)	-	1.6×10^1 pfu/mL (culture medium) 2.42×10^2 copies/mL (clinical sample)
[72]	P-FAB	U-bend fiber probe optics (N-antigen)	15 min	10-18 M
[61]	Co-TNTs-based electrochemical sensor	Potentiostat (S antigen)	~30 s	14 to 1400 nM (nano molar)
[73]	Nanozyme chemiluminescence paper-based	CCD or smartphone (S antigen)	16 min	0.1 ng/mL
[114]	Engineered surfaces based on SAMs	quartz crystal microbalance (QCM) (S-antigen)	-	-
[115]	Dielectric modulated FET biosensor	FET sensor (S protein and DNA protein)	-	-
[71]	Membrane engineering	Customized multichannel potentiometer (S antigen)	3 min	1 fg/mL
[76]	Molecularly imprinted polymers (MIPs)	Portable potentiostats (N-antigen)	± 45 min	15 fM
[116]	Screen printed electrode electrochemical diagnostic kit	CV analysis tool	1 min	1.68×10^{-22} $\mu\text{g mL}^{-1}$
[74]	Nanoplasmonic sensor chip	Microplate reader (S-antigen)	15 min	370 vp/mL
[75]	Field-induced transport of a sensor complex	Potentiostat (S antigen)	5 min	4000 copies/mL
[63]	Toroidal plasmonic metasensor	THz metasensors (S antigen)	~80 min	~4.2 fMol

LFIA = lateral flow immunoassay, FET = field-effect transistor, P-FAB = plasmonic fiber-optic absorbance sensor, ssDNA = single-stranded DNA, AuNPs = gold nanoparticle, THz = Terahertz, Co-TNTs = cobalt-functionalized TiO₂ nanotubes, CCD = charge-coupled device, SAMs = self-assembled monolayers, QCM = quartz crystal microbalance, CV = cyclic voltammetry

result [69]. Therefore, several approaches have been proposed (see Table III).

Recently, a new study was developed with a specific biosensor utilizing lateral flow immunoassay (LFIA). The

LFIA-based biosensor was reported to have good sensitivity and specificity, without cross-reactivity with protein from another virus. Phage display technology was utilized to produce four nucleocapsid proteins (N-antigen) of SARS-CoV-2 - specific single-chain variable fragment crystallizable fragment (scFv-Fc) fusion antibodies. The specific binding was obtained between the scFv-Fc antibodies and nucleocapsid protein (N-gene) of SARS-CoV-2. The detection probe was designed using a cellulose nanobead (CNB) since it is more sensitive and stable than gold nanoparticles (AuNPs) [70].

A field-effect transistor-based biosensor for SARS-CoV-2 detection has been proposed by Seo *et al.* [32]. In this study, graphene was added to a SiO₂/Si substrate. Then, on the graphene layer, Au/Cr electrode layer was created to immobilize antibody that is specific toward SARS-CoV-2 spike protein on 1-pyrenebutyric acid N-hydroxysuccinimide ester (PBASE)-modified graphene surface. This approach offers high sensitivity and instantaneous measurements using small amounts of analytes. However, the set-up for measurement was expensive with low-throughput instrumentation, and required high antibody concentration for immobilization.

Another study reported the solution for the aforementioned drawbacks by membrane engineering approach. A selective and sensitive biosensor was utilized in membrane-engineered mammalian cells to detect SARS-CoV-2 S1 spike. The membrane of the kidney cell was engineered by the electro insertion of the SARS-CoV-2 Spike S1 antibody into the cell membrane. Then, the membrane-engineered cells were added onto each of the eight gold screen-printed electrodes on the well of the polydimethylsiloxane (PDMS) layer. Measurable membrane potential was produced by the binding between the electro-inserted receptor molecules and analyte anions. This potential was recorded using a customized multichannel potentiometer [71]. However, viability of the cell is the most critical issue in this approach and cost-efficient operation for routine mass-screening application has not been proven yet. In another work, plasmonic fiber-optic absorbance (P-FAB) biosensor was proposed based on a U-bent optical fiber probe for one-step, wash-free detection of SARS-CoV-2 virus. In this study, the detection principle was optical power loss in the light (change in absorbance/intensity count). The recognition interaction at the bio-immobilized U-bent sensing region of the fiber probe tends to modulate the effective refractive index (RI) or wave absorbance at the biosensor as a function of sample concentration. It was reported to have high sensitivity and potential to be early and rapid COVID-19 diagnostic tools [72].

Enzymatic chemiluminescence analysis (CLIA) offers higher sensitivity in immunodiagnostic even though the traditional chemiluminescence detection needed centralized clinical laboratories due to the use of expensive precision instruments. Moreover, CLIA required horseradish peroxidase (HRP) or alkaline phosphatase (ALP) with complex preparation steps and low storage stability. To solve this problem, a study had proposed a combination of nanozyme chemiluminescence with paper tests for SARS-CoV-2 spike antigen detection. Nanozymes are nanomaterials possessing intrinsic enzyme-mimicking activity. The first step was to form sandwich

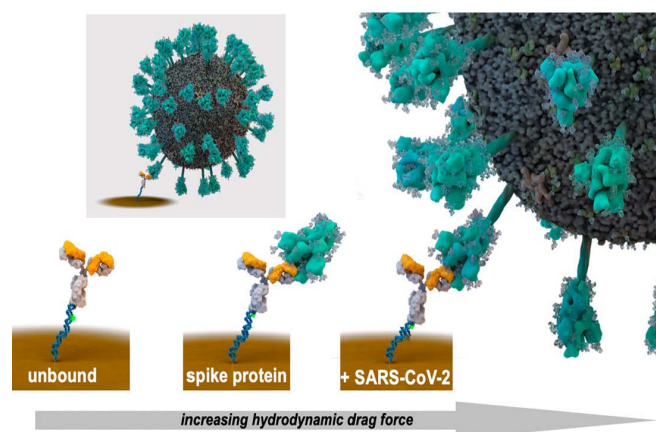


Fig. 7. Complex sensor binding to the SARS-CoV-2 viral particles. Reprinted with permission from [75]. Copyright © 2021 American chemical society.

immunocomplexes on paper by labeling antibody receptor binding domain of the SARS-CoV-2 spike protein (S-dAb) to Co-Fe@hemin nanozyme chemiluminescence probes. Then, nanozyme probe CLIAs would produce the chemiluminescence signals. This signal was detected by CCD or smartphone camera and then Image-Pro Plus software was utilized to analyze the signal [73]. Surface plasmon resonance (SPR) was also reported to detect SARS-CoV-2 antigen based on Kretschmann configuration incorporating layers of Silicon and BaTiO₃ on the top of a metal layer (Ag). Ag was used as the substrate layer to enhance the sensitivity due to its higher SPR ratio. Thus, with this architecture for SARS-CoV-2 detection, the SPR sensor achieved 7.6 times higher sensitivity than the basic Kretschmann configuration [61].

Nevertheless, SPR is not affordable to most research and clinical institutions, thus SPR is rarely implemented in clinical and point-of-care applications. As an alternative to this, a low-cost nanoplasmonic sensor was developed for the COVID-19 biosensor. Nanostructure design allowed the removal of any external coupling optics. Intensity changes and plasmon resonance wavelength change since the recognition events can be simply observed by transmission light spectroscopy or imaging. With this approach, the detection time was within 15 min and the detectability limit of 370 viral particles/mL was achieved [74].

Still utilizing the photonics architectures, terahertz (THz) plasmonic biosensor, detecting SARS-CoV-2 spike protein based on toroidal dipole-resonant metamolecules that has extreme sensitivity, has also been reported [63]. Toroidal dipole-resonant metasurfaces allow low-radiative losses, low mode volumes, and ultranarrow spectral line shapes through strong electromagnetic field confinement.

Electrochemical and reagent-free detection approach has been studied by utilizing the field-induced transport of a sensor complex on electrodes and the modulation of the kinetics of transport by the binding of viral components. The sensor will obtain a large change in hydrodynamic diameter in the presence of the spike protein and a viral particle. This change tends to affect the time required for the sensor to contact

the surface of the electrode (Fig. 7). The sensor complex is made from the S-protein specific antibody bound to double-strand DNA with redox probe ferrocene. The electric field force between the electrode and the complex is opposed by the hydrodynamic drag. The kinetic is measured as change of current versus time in a chronoamperometry setup [75].

However, SARS-CoV-2 diagnostic tools which rely on biological recognition elements tend to decrease sensor shelf life and increase the cost. One of the potential approaches to replace biological recognition is the use of molecularly imprinted polymers (MIPs) – materials mimicking antibodies' ability to bind among molecules. Gold-based thin-film electrodes (Au-TFE) were modified with MIP-endowed selectivity for SARS-CoV-2 nucleoprotein (ncovNP-MIP) film as a recognition element in the ncovNP sensor. This sensor was examined as having excellent long-term stability. On the other hand, the presence of other proteins of SARS-CoV-2 in COVID-19 positive sample might disturb the response ability of the sensor towards ncovNP. Moreover, the sample needs to be vortexed for 30 min before testing [76].

Several commercially available rapid antigen tests have been evaluated, including BIOCREREDIT COVID-19 Ag test. The sensitivity of this was 30.2%, which is 10⁵ fold less sensitive than RT-qPCR [77]. Other rapid antigen tests showed slightly higher sensitivity, such as Panbio™ COVID-19 AG rapid test evaluation showed an overall sensitivity of 73.3% [78]. The STANDARD™ F COVID-19 Ag FIA had an overall sensitivity of 45% and selectivity of 97.8% and the SARS-CoV-2 Rapid Antigen Test obtained sensitivity and selectivity of 50.3% and 97.7%, respectively [79].

Nevertheless, SARS-CoV-2 detection using antigen-based tests could be done most reliably within 1-3 days before symptom onset and 7 days after the onset of the symptoms [80] and might not be able to detect SARS-CoV-2 afterwards. The antibody-based test result can be considered at least two weeks after the onset of symptoms [68]. Nucleic acid-based tests, such as RT-LAMP, have the same sensitivity as RT-qPCR within 9 days after symptoms onset [81]. Whereas RT-qPCR can even detect the SARS-CoV-2 before development of symptoms [82] (Fig. 8).

The time progression of SARS-CoV-2 cases may have different periods among people. Generally, the incubation period takes 4 to 6 days after exposure for most cases, but it can be up to 14 days. The incubation period defines the time duration from being infected by the virus until the onset of symptoms. Whereas the infectious period may start 1 to 3 days before and the first 7 days after the symptoms appear. The infectious period is the range of times during which the infected people may spread the virus to someone else. The symptoms, such as fever, fatigue, and cough appear mostly for about 9 to 10 days but it could be longer. Then, if the COVID-19 patients have no symptoms for 3 days, it means they are no longer infectious (Fig. 8) [83].

VI. OTHER APPROACHES

Nucleic acid-based, antigen-based, antibody-based, and CT-scan are relatively expensive. Another promising approach, therefore, was developed by relying on gaseous molecules

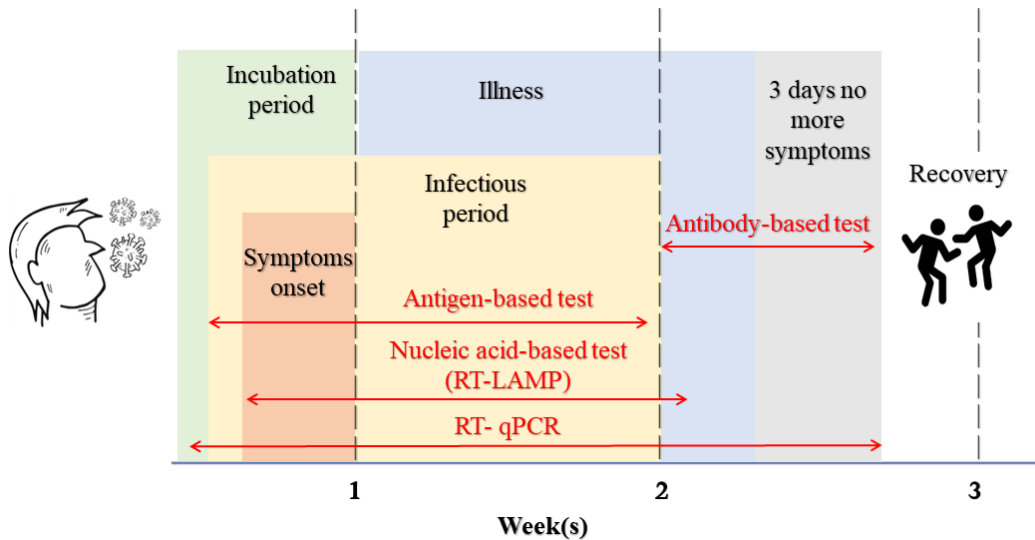


Fig. 8. Coronavirus progression in majority of cases and recommended diagnostic tools in general cases, adapted from the concept presented in [83].

called volatile organic compounds (VOCs). Pathological processes alter the metabolites' composition in the body and produce VOCs as a degradation product of metabolic processes. These VOCs can then be surrogate biomarkers that indicate the infection of SARS-CoV-2. Electronic nose (e-nose) that can detect these VOCs surrogate biomarkers have been reported [84]. It consists of three micro hotplate metal-oxide sensors, such as carbon monoxide (AS-MLC), nitrogen dioxide (AS-MLN), and VOC (AS-MLX) sensors. The participants were required to breathe for 5 min through a disposable mouthpiece consisting of a carbon filter and a high-efficiency particulate air (HEPA) filter to avoid contamination of the internal tubing. The breath analysis was assessed to discriminate COVID-19-positive participants by artificial intelligence (AI). They reported that this electronic nose has a sensitivity of 0.86. However, so far the electronic nose has only been utilized as a screening tool, and further RT-qPCR test is required to confirm the positive prediction. Moreover, alcohol in the vicinity of the device interferes with the sensor, thus generating uninterpretable data [84]. In Indonesia, an electronic nose, called GeNose, was also developed as an alternative to screening people who are infected by SARS-CoV-2 (Fig. 9). Interestingly, GeNose showed high accuracy of 97% obtained from testing 600 sample data and has been now made available in some public areas for screening purposes [85].

The application of AI has been explored in another COVID-19 diagnosis method, such as lung detection images, including computerized tomography (CT) images, X-ray images, and ultrasound images which can visualize pneumonia. The image of the lung can show the patient with suspected SARS-CoV-2 infection. CT AI-assisted screening is demanded by the radiologists who are less expertise in chest imaging. AI systems will improve the accuracy of the clinical diagnosis. However, in some cases, COVID-19 patients still have normal lung images even though they have been infected by SARS-CoV-2 already. Therefore, the negative predictive value of the lung image is limited and does not clearly



Fig. 9. Photograph of GeNose device. Reprinted from [117] with permission from Gadjah Mada university press.

indicate infection. Consequently, the accuracy of single AI diagnostics is still challenged. Thus, multiple AI algorithms are required to combine chest imaging or lung imaging with clinical symptoms, exposure history, and laboratory tests in the diagnosis of COVID-19 [86].

VII. SAMPLE COLLECTION TECHNIQUES

Sampling technique is also important for SARS-CoV-2 detection. The sample type used for the biosensor determines the sampling method and protocol for the COVID-19 biosensor (see Table IV). Detection of virus in sputum samples, obtained by nasal swabs is an ideal technique in the first 14 days after onset, whereas throat swabs might lead to false-result 8 days after the onset of symptom [3]. While saliva samples are effective to be used before 10 days after onset (see Table V) [87].

Priya and Prabakaran [88] conducted a study to detect SARS-CoV-2 from different sites, such as blood, urine,

TABLE IV
DIAGNOSTIC TECHNIQUES

Ref.	Sample used	Diagnostic technique	Target
[57]	Blood	ELISA	Antibody
[116]	Blood and Saliva	Electrochemical detection	Spike glycoprotein
[65]	Blood	Optical detection	Spike protein antibody
[64]	Serum sample	EIS	Antibodies
[103]	Pharyngeal swab	RT-LAMP Colorimetry	ORF8 and N SARS-CoV-2 genes
[105]	Nasopharyngeal (NP) swabs	RT-LAMP Colorimetry	S-gene and NA-dependent RNA polymerase (RdRP) of SARS-CoV-2
[108]	Saliva	RT-LAMP Colorimetry, spectrophotometry, and real time fluorescence	Nucleocapsid (Gene N) and Orf1ab regions

DPV = Differential pulse voltammetry; OCP-EIS = open circuit potential-electrochemical impedance spectroscopy

TABLE V
COMPARISON VIRAL LOAD PEAK AT DIFFERENT SERIAL SAMPLES

Ref.	Serial samples	Target	Viral load effective measurement
[118] [119]	Sputum	Nucleic acid	<15 days post-symptom onset (peak at 5-6 days post-symptom onset)
[118] [119]	Throat swab	Nucleic acid	<8 days post-symptom onset (peak at 5-6 days post-symptom onset)
[119]	Nasal swab	Nucleic acid	<14 days post-symptom onset
[80]	Nasal swab	Antigen	1-3 days pre-symptom onset and 5-7 days post-symptom onset
[87], [120]	Saliva	Nucleic acid	<10 days post-symptom onset
[68]	Blood	Antibody	≥14 days post-symptom onset
[121]	Urine	Nucleic acid	At day 12 and day 24 post-symptom onset
[122]	Feces	Nucleic acid	11 (7-13) days post-symptom onset

sputum, feces, and nasal samples. The result revealed that bronchoalveolar lavage fluid has the highest virus load, followed by sputum, nasal swab, fibrobronchoscope brush biopsy,

pharyngeal swabs, feces, and blood. However, the timeline for positivity of urine samples is varying among the reports [89]. Another study revealed that antibody was low or undetectable in the early infection. However, antibodies load may increase with time, while virus molecular load may decrease [90].

VIII. FUTURE PERSPECTIVE

The latest reports reported that ageusia (loss of taste) is one of the early symptoms of COVID-19. Saliva plays a major role in the oral chemosensory perception of taste sensation. Saliva is a complex isotonic substance. It consists of 99% water and 1% other constituents [91]. The constituents are proteins, inorganic constituents, enzymes, hormones along with salivary flow rate, and pH playing an important role in taste perception. Salivary constituents are possibly changed due to SARS-CoV-2 infection which might be associated with ageusia [92]. One of the potential approaches to detect the changes of constituents in saliva was electronic tongue. This approach offers low-cost and convenient detection of surrogate biomarkers associated with COVID-19-related ageusia. Electronic tongue (ET) consists of multiple sensors (sensor arrays). Most electronic tongues were designed of macroscopic solid supports coated with nanostructured films [93] or membranes [94]. The analytical methods of ET mostly used potentiometry and impedance spectroscopy [95]. ET has to be able to analyze the output from each sensor which is then being classified using machine learning [96]. Each sensor will detect the alteration of each constituent. The salivary constituents that might alter due to SARS-CoV-2 infection have already been discussed in reference [92]. The study of ET on detecting bacteria possessed an accuracy of 98.8% [97].

Several studies have developed COVID-19 biosensors using paper as a substrate, offering cheap and sustainable devices. However, there are some disadvantages of paper-based devices, such as poor delivery capability because of low retention in the channels, decreasing mechanical strength of the paper as aqueous solution wet the channels and could lead to damage by the excess solution. To overcome the aforementioned limitation, cotton cloth can be used as an alternative to paper since it provides excellent absorbing properties and better physical and chemical properties [16], [17], [98], [99].

Microfluidic fabric-based electronic tongue has potential to recognize SARS-CoV-2 infection, the application of microfluidics will allow the use of small sample volume [100]. To assess the constituents, membrane can be coated on the microfluidic fabric-based device [94]. Then the outputs of the sensors array can be controlled by a multiplexer to enter a measurement technique, such as EIS [100].

Another possibility of developing a portable COVID-19 biosensor with high specificity is by utilizing pyrrolidiny peptide nucleic acid (acpcPNA) as a probe. It provides antiparallel/parallel binding to the target and a low tendency for self-hybridization. It could reach an LOD of 1.24 nM for *Mycobacterium tuberculosis* (MTB) detection [101].

IX. CONCLUSION

There have been various approaches to develop portable, low-cost, and non-invasive COVID-19 biosensors based on

the nucleic acid, antibody, antigen, and metabolic products related to SARS-CoV-2. However, detecting the low viral load amount, non-invasively, without amplification is still a major challenge. The accuracy and sensitivity of these solutions also depend a lot on the correct protocol related to the time progression of SARS-CoV-2 viral infection. A promising approach for portable, sensitive and non-invasive sensor would be antigen-based electrochemical detection. However, the cost is high and the versatility is limited due to the need of specific antibody production for the specific variant antigen. Another alternative would be to use biomimetic binding molecule to replace the expensive antibody. Finally, an emerging solution based on the combination of non-selective sensing array and artificial intelligence algorithm has been presented. This last option may be increasingly developed in the future with the increasing power of computation.

REFERENCES

- [1] S. Erensoy, "SARS-CoV-2 and microbiological diagnostic dynamics in COVID-19 pandemic," *Mikrobiyol. Bul.*, vol. 54, no. 3, pp. 497–509, 2020.
- [2] L. Y. Hsu, P. Y. Chia, and J. F. Lim, "The novel coronavirus (SARS-CoV-2) pandemic," *Ann. Acad. Med. Singapore*, vol. 49, no. 3, pp. 105–107, Mar. 2020.
- [3] B. Udugama *et al.*, "Diagnosing COVID-19: The disease and tools for detection," *ACS Nano*, vol. 14, no. 4, pp. 3822–3835, Apr. 2020.
- [4] F. Li, "Structure, function, and evolution of coronavirus spike proteins," *Annu. Rev. Virol.*, vol. 3, no. 1, pp. 237–261, Sep. 2016.
- [5] R. H. Silverman, "COVID-19: Coronavirus replication, pathogenesis, and therapeutic strategies," *Cleve. Clin. J. Med.*, vol. 87, no. 6, p. 321, 2020.
- [6] Z. Qin, R. Peng, I. K. Baravik, and X. Liu, "Fighting COVID-19: Integrated micro-and nanosystems for viral infection diagnostics," *Matter*, vol. 3, pp. 628–651, Jul. 2020.
- [7] A. Basiri *et al.*, "Microfluidic devices for detection of RNA viruses," *Rev. Med. Virol.*, vol. 31, no. 1, pp. 1–11, Jan. 2021.
- [8] A. Kovács, P. Palásti, D. Veréb, B. Bozsik, A. Palkó, and Z. T. Kincses, "The sensitivity and specificity of chest CT in the diagnosis of COVID-19," *Eur. Radiol.*, vol. 31, no. 5, pp. 1–6, 2020.
- [9] E. A. Oblath, W. H. Henley, J. P. Alarie, and J. M. Ramsey, "A microfluidic chip integrating DNA extraction and real-time PCR for the detection of bacteria in saliva," *Lab Chip*, vol. 13, no. 7, pp. 1325–1332, 2013.
- [10] OECD. (2020). *Testing for COVID-19: How to Best Use the Various Tests?* OECD Policy Responses to Coronavirus (COVID-19). Accessed: Mar. 21, 2021. [Online]. Available: <http://www.oecd.org/coronavirus/policy-responses/testing-for-covid-19-how-to-best-use-the-various-tests-c76df201/>
- [11] M. You *et al.*, "Ultrafast photonic PCR based on photothermal nanomaterials," *Trends Biotechnol.*, vol. 38, no. 6, pp. 637–649, Jun. 2020.
- [12] J. Cheong *et al.*, "Fast detection of SARS-CoV-2 RNA via the integration of plasmonic thermocycling and fluorescence detection in a portable device," *Nature Biomed. Eng.*, vol. 4, no. 12, pp. 1159–1167, Dec. 2020.
- [13] H. Yin *et al.*, "Ultrafast multiplexed detection of SARS-CoV-2 RNA using a rapid droplet digital PCR system," *Biosensors Bioelectron.*, vol. 188, Sep. 2021, Art. no. 113282.
- [14] S. Malhotra, A. Verma, N. Tyagi, and V. Kumar, "Biosensors: Principle, types and applications," *Int. J. Adv. Res. Innov. Ideas Educ.*, vol. 3, no. 2, pp. 3639–3644, 2017.
- [15] R. Kazemi-Darsanaki, A. Azizzadeh, M. Nourbakhsh, G. Raeisi, and M. Azizollahiabi, "Biosensors: Functions and applications," *J. Biol. Today's World*, vol. 2, no. 1, pp. 53–61, 2013.
- [16] S. Bagherbaigi, E. P. Córcoles, and D. H. B. Wicaksono, "Cotton fabric as an immobilization matrix for low-cost and quick colorimetric enzyme-linked immunosorbent assay (ELISA)," *Anal. Methods*, vol. 6, no. 18, pp. 7175–7180, 2014.
- [17] M. Alafeef, K. Dighe, P. Moitra, and D. Pan, "Rapid, ultrasensitive, and quantitative detection of SARS-CoV-2 using antisense oligonucleotides directed electrochemical biosensor chip," *ACS Nano*, vol. 14, no. 12, pp. 17028–17045, 2020.
- [18] G. Sandoval and E. J. Herrera-López, "Lipase, phospholipase, and esterase biosensors," *Lipases Phospholipases*, vol. 1835, pp. 391–425, Aug. 2018.
- [19] M. Fani, M. Zandi, S. Soltani, and S. Abbasi, "Future developments in biosensors for field-ready SARS-CoV-2 virus diagnostics," *Biotechnol. Appl. Biochemistry*, vol. 68, no. 4, pp. 695–699, Aug. 2021.
- [20] N. Bhalla, Y. Pan, Z. Yang, and A. F. Payam, "Opportunities and challenges for biosensors and nanoscale analytical tools for pandemics: COVID-19," *ACS Nano*, vol. 14, no. 7, pp. 7783–7807, Jul. 2020.
- [21] T. Leichlé, L. Nicu, and T. Alava, "MEMS biosensors and COVID-19: Missed opportunity," *ACS Sensors*, vol. 5, no. 11, pp. 3297–3305, Nov. 2020.
- [22] M. Asif *et al.*, "The role of biosensors in COVID-19 outbreak," *Curr. Opin. Electrochem.*, vol. 23, pp. 174–184, Sep. 2020.
- [23] P. Asrani *et al.*, "Diagnostic approaches in COVID-19: Clinical updates," *Expert Rev. Respiratory Med.*, vol. 15, no. 2, pp. 197–212, Feb. 2021.
- [24] I. El Jaddaoui *et al.*, "A review on current diagnostic techniques for COVID-19," *Expert Rev. Mol. Diagn.*, vol. 21, no. 2, pp. 141–160, 2021.
- [25] S. Suleman *et al.*, "Point of care detection of COVID-19: Advancement in biosensing and diagnostic methods," *Chem. Eng. J.*, vol. 414, Jun. 2021, Art. no. 128759.
- [26] R. Dubey and R. Bhushan, "Specificity versus selectivity: Twin aims of aptasensors in bioanalysis," *Bioanalysis*, vol. 10, no. 19, pp. 1549–1551, Oct. 2018.
- [27] W. J. Peveler, M. Yazdani, and V. M. Rotello, "Selectivity and specificity: Pros and cons in sensing," *ACS Sens.*, vol. 1, no. 11, pp. 1282–1285, Nov. 2016.
- [28] D. N. Carvajal and P. C. Rowe, "Sensitivity, specificity, predictive values, and likelihood ratios," *Pediatrics Rev.*, vol. 31, no. 12, pp. 511–513, 2010.
- [29] W. Zhu, N. Zeng, and N. Wang, "Sensitivity, specificity, accuracy, associated confidence interval and ROC analysis with practical SAS implementations," in *Proc. NESUG Health Care Life Sci.*, vol. 19, 2010, p. 67.
- [30] S. Ghoneim, "Accuracy, recall, precision, F-score & specificity, which to optimize on," *Obtenido Towar. Data Sci.*, 2019. [Online]. Available: <https://towardsdatascience.com/accuracy-recall-precision-f-score-specificity-which-to-optimize-on-867d3f11124>
- [31] D. Lozano and M. Cantero, "Difference between analytical sensitivity and detection limit," *Amer. J. Clin. Pathol.*, vol. 107, no. 5, p. 619, 1997.
- [32] G. Seo *et al.*, "Rapid detection of COVID-19 causative virus (SARS-CoV-2) in human nasopharyngeal swab specimens using field-effect transistor-based biosensor," *ACS Nano*, vol. 14, no. 4, pp. 5135–5142, 2020.
- [33] D. L. Massart, A. Dijkstra, and L. Kaufman, *Evaluation and Optimization of Laboratory Methods and Analytical Procedures*. Elsevier, 1978.
- [34] M. Sokolova, N. Japkowicz, and S. Szpakowicz, "Beyond accuracy, F-score and ROC: A family of discriminant measures for performance evaluation," *Proc. Aust. Conf. Artif. Intell.*, vol. 2006, pp. 1015–1021.
- [35] K. J. van Stralen, V. S. Stel, J. B. Reitsma, F. W. Dekker, C. Zoccali, and K. J. Jager, "Diagnostic methods I: Sensitivity, specificity, and other measures of accuracy," *Kidney Int.*, vol. 75, no. 12, pp. 1257–1263, Jun. 2009.
- [36] T. Julian, S. N. Hidayat, A. Rianjanu, A. B. Dharmawan, H. S. Wasisto, and K. Triyana, "Intelligent mobile electronic nose system comprising a hybrid polymer-functionalized quartz crystal microbalance sensor array," *ACS Omega*, vol. 5, no. 45, pp. 29492–29503, Nov. 2020.
- [37] G. Caruana *et al.*, "Diagnostic strategies for SARS-CoV-2 infection and interpretation of microbiological results," *Clin. Microbiol. Infection*, vol. 26, no. 9, pp. 1178–1182, Sep. 2020.
- [38] C.-M. Chang, W.-H. Chang, C.-H. Wang, J.-H. Wang, J. D. Mai, and G.-B. Lee, "Nucleic acid amplification using microfluidic systems," *Lab Chip*, vol. 13, no. 7, pp. 1225–1242, 2013.
- [39] S. Neidler, "What are the differences between PCR, RT-PCR, qPCR, and RT-qPCR," *Enzo*, 2018.
- [40] P. Fozzouni *et al.*, "Direct detection of SARS-CoV-2 using CRISPR-Cas13a and a mobile phone," *MedRxiv*, 2020, doi: [10.1016/j.cell.2020.12.001](https://doi.org/10.1016/j.cell.2020.12.001).
- [41] Y. Zhao, F. Chen, Q. Li, L. Wang, and C. Fan, "Isothermal amplification of nucleic acids," *Chem. Rev.*, vol. 115, no. 22, pp. 12491–12545, Nov. 2015.
- [42] V. L. D. Thi *et al.*, "A colorimetric RT-LAMP assay and LAMP-sequencing for detecting SARS-CoV-2 RNA in clinical samples," *Sci. Transl. Med.*, vol. 12, no. 556, Aug. 2020, Art. no. eabc7075.

- [43] B. Schermer *et al.*, "Rapid SARS-CoV-2 testing in primary material based on a novel multiplex RT-LAMP assay," *PLoS ONE*, vol. 15, no. 11, Nov. 2020, Art. no. e0238612.
- [44] J. Rodriguez-Manzano *et al.*, "Handheld point-of-care system for rapid detection of SARS-CoV-2 extracted RNA in under 20 min," *ACS Central Sci.*, vol. 7, no. 2, pp. 307–317, Feb. 2021.
- [45] E. K. Rames and J. Macdonald, "Rapid assessment of viral water quality using a novel recombinase polymerase amplification test for human adenovirus," *Appl. Microbiol. Biotechnol.*, vol. 103, no. 19, pp. 8115–8125, Oct. 2019.
- [46] A. A. Nassir *et al.*, "RPA-based method for the detection Of SARS-CoV2," *medRxiv*, 2020, doi: [10.1101/2020.09.17.20196402](https://doi.org/10.1101/2020.09.17.20196402).
- [47] M. J. Kellner, J. G. Koob, J. S. Gootenberg, O. O. Abudayyeh, and F. Zhang, "SHERLOCK: Nucleic acid detection with CRISPR nucleases," *Nature Protocols*, vol. 14, no. 10, pp. 2986–3012, Oct. 2019.
- [48] R. Nouri, Z. Tang, M. Dong, T. Liu, A. Kshirsagar, and W. Guan, "CRISPR-based detection of SARS-CoV-2: A review from sample to result," *Biosensors Bioelectron.*, vol. 178, Apr. 2021, Art. no. 113012.
- [49] J. P. Broughton *et al.*, "CRISPR–Cas12-based detection of SARS-CoV-2," *Nature Biotechnol.*, vol. 38, no. 7, pp. 870–874, 2020.
- [50] Z. Ali *et al.*, "ISCAN: An RT-LAMP-coupled CRISPR-Cas12 module for rapid, sensitive detection of SARS-CoV-2," *Virus Res.*, vol. 288, Oct. 2020, Art. no. 198129.
- [51] Y. Zou, M. G. Mason, and J. R. Botella, "Evaluation and improvement of isothermal amplification methods for point-of-need plant disease diagnostics," *PLoS ONE*, vol. 15, no. 6, Jun. 2020, Art. no. e0235216.
- [52] P. Subsoontorn, M. Lohitnavy, and C. Kongkaew, "The diagnostic accuracy of isothermal nucleic acid point-of-care tests for human coronaviruses: A systematic review and meta-analysis," *Sci. Rep.*, vol. 10, no. 1, pp. 1–13, Dec. 2020.
- [53] A. Ghaffari, R. Meurant, and A. Ardakani, "COVID-19 serological tests: How well do they actually perform?" *Diagnostics*, vol. 10, no. 7, p. 453, Jul. 2020.
- [54] F. Xiang *et al.*, "Antibody detection and dynamic characteristics in patients with coronavirus disease 2019," *Clin. Infectious Diseases*, vol. 71, no. 8, pp. 1930–1934, Nov. 2020.
- [55] Z. Li *et al.*, "Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis," *J. Med. Virol.*, vol. 92, no. 9, pp. 1518–1524, 2020.
- [56] J. Zhao *et al.*, "Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019," *Clin. Infect. Dis.*, vol. 71, no. 16, pp. 2027–2034, 2020.
- [57] S. Kasetsirikul, M. Umer, N. Soda, K. R. Sreejith, M. J. A. Shiddiky, and N.-T. Nguyen, "Detection of the SARS-CoV-2 humanized antibody with paper-based ELISA," *Analyst*, vol. 145, no. 23, pp. 7680–7686, 2020.
- [58] S. K. Elledge *et al.*, "Engineering luminescent biosensors for point-of-care SARS-CoV-2 antibody detection," *medRxiv*, 2020, doi: [10.1038/s41587-021-00878-8](https://doi.org/10.1038/s41587-021-00878-8).
- [59] Y. Liu *et al.*, "Reciprocating-flowing on-a-chip enables ultra-fast immunobinding for multiplexed rapid ELISA detection of SARS-CoV-2 antibody," *Biosensors Bioelectron.*, vol. 176, Mar. 2021, Art. no. 112920.
- [60] A. Yakoh, U. Pimpitak, S. Rengpipat, N. Hirankarn, O. Chailapakul, and S. Chaiyo, "Based electrochemical biosensor for diagnosing COVID-19: Detection of SARS-CoV-2 antibodies and antigen," *Biosensors Bioelectron.*, vol. 176, Mar. 2021, Art. no. 112912.
- [61] S. M. A. Uddin, S. S. Chowdhury, and E. Kabir, "Numerical analysis of a highly sensitive surface plasmon resonance sensor for SARS-CoV-2 detection," 2020, *arXiv:2008.10354*. [Online]. Available: <http://arxiv.org/abs/2008.10354>
- [62] A. Djailab *et al.*, "A rapid and quantitative serum test for SARS-CoV-2 antibodies with portable surface plasmon resonance sensing," *ChemRxiv*, vol. 15, pp. 10–26434, Apr. 2020.
- [63] A. Ahmadiyand, B. Gerislioglu, Z. Ramezani, A. Kaushik, P. Manickam, and S. A. Ghoreishi, "Femtomolar-level detection of SARS-CoV-2 spike proteins using toroidal plasmonic metasensors," 2020, *arXiv:2006.08536*. [Online]. Available: <http://arxiv.org/abs/2006.08536>
- [64] M. Z. Rashed *et al.*, "Rapid detection of SARS-CoV-2 antibodies using electrochemical impedance-based detector," *Biosensors Bioelectron.*, vol. 171, Jan. 2021, Art. no. 112709.
- [65] R. Funari, K.-Y. Chu, and A. Q. Shen, "Detection of antibodies against SARS-CoV-2 spike protein by gold nanospikes in an opto-microfluidic chip," *Biosensors Bioelectron.*, vol. 169, Dec. 2020, Art. no. 112578.
- [66] B. Zhao, C. Che, W. Wang, N. Li, and B. T. Cunningham, "Single-step, wash-free digital immunoassay for rapid quantitative analysis of serological antibody against SARS-CoV-2 by photonic resonator absorption microscopy," *Talanta*, vol. 225, Apr. 2021, Art. no. 122004.
- [67] S. E. Turbett *et al.*, "Evaluation of three commercial SARS-CoV-2 serologic assays and their performance in two-test algorithms," *J. Clin. Microbiol.*, vol. 59, no. 1, Dec. 2020, Art. no. e01892.
- [68] J. Watson, A. Richter, and J. Deeks, "Testing for SARS-CoV-2 antibodies," *BMJ*, vol. 370, p. m3325, Sep. 2020.
- [69] F. M. Liotti *et al.*, "Performance of a novel diagnostic assay for rapid SARS-CoV-2 antigen detection in nasopharynx samples," *Clin. Microbiol. Infection*, vol. 27, no. 3, pp. 487–488, Mar. 2020.
- [70] H.-Y. Kim *et al.*, "Development of a SARS-CoV-2-specific biosensor for antigen detection using scFv-fc fusion proteins," *Biosensors Bioelectron.*, vol. 175, Mar. 2021, Art. no. 112868.
- [71] S. Mavrikou, G. Moschopoulou, V. Tsekouras, and S. Kintzios, "Development of a portable, ultra-rapid and ultra-sensitive cell-based biosensor for the direct detection of the SARS-CoV-2 S1 spike protein antigen," *Sensors*, vol. 20, no. 11, p. 3121, May 2020.
- [72] D. Murugan, H. Bhatia, V. V. R. Sai, and J. Satija, "P-FAB: A fiber-optic biosensor device for rapid detection of COVID-19," *Trans. Indian Acad. Eng.*, vol. 5, no. 2, pp. 211–215, Jun. 2020.
- [73] D. Liu *et al.*, "Nanozyme chemiluminescence paper test for rapid and sensitive detection of SARS-CoV-2 antigen," *Biosensors Bioelectron.*, vol. 173, Feb. 2021, Art. no. 112817.
- [74] L. Huang *et al.*, "One-step rapid quantification of SARS-CoV-2 virus particles via low-cost nanoplasmonic sensors in generic microplate reader and point-of-care device," *Biosensors Bioelectron.*, vol. 171, Jan. 2021, Art. no. 112685.
- [75] H. Yousefi *et al.*, "Detection of SARS-CoV-2 viral particles using direct, reagent-free electrochemical sensing," *J. Amer. Chem. Soc.*, vol. 143, no. 4, pp. 1722–1727, Feb. 2021.
- [76] A. Raziq, A. Kidakova, R. Boroznjak, J. Reut, A. Öpik, and V. Syritski, "Development of a portable MIP-based electrochemical sensor for detection of SARS-CoV-2 antigen," *Biosensors Bioelectron.*, vol. 178, Apr. 2021, Art. no. 113029.
- [77] G. C. Mak *et al.*, "Evaluation of rapid antigen test for detection of SARS-CoV-2 virus," *J. Clin. Virol.*, vol. 129, Aug. 2020, Art. no. 104500.
- [78] M. Linares *et al.*, "Panbio antigen rapid test is reliable to diagnose SARS-CoV-2 infection in the first 7 days after the onset of symptoms," *J. Clin. Virol.*, vol. 133, Dec. 2020, Art. no. 104659.
- [79] A. Osterman *et al.*, "Evaluation of two rapid antigen tests to detect SARS-CoV-2 in a hospital setting," *Med. Microbiol. Immunol.*, vol. 210, pp. 65–72, Feb. 2021.
- [80] *Antigen-Detection in the Diagnosis of SARS-CoV-2 Infection Using Rapid Immunoassays: Interim Guidance*, World Health Org., Geneva, Switzerland, Sep. 2020.
- [81] M. Inaba *et al.*, "Diagnostic accuracy of LAMP versus PCR over the course of SARS-CoV-2 infection," *Int. J. Infectious Diseases*, vol. 107, pp. 195–200, Jun. 2021.
- [82] T. R. Mercer and M. Salit, "Testing at scale during the COVID-19 pandemic," *Nature Rev. Genet.*, vol. 22, no. 7, pp. 415–426, Jul. 2021.
- [83] T. Housen, A. E. Parry, and M. Sheel, "How long are you infectious when you have coronavirus," *Conversat. April*, vol. 13, pp. 6–20, Apr. 2020.
- [84] A. G. W. E. Wintjens *et al.*, "Applying the electronic nose for pre-operative SARS-CoV-2 screening," *Surgical Endoscopy*, pp. 1–8, Dec. 2020.
- [85] Satria. (Accessed: Feb. 16, 2020). *Breath of Swab Test Class for Covid-19 Detection: GeNose by UGM*. Gajah Mada University. Accessed: 2020. [Online]. Available: <https://ugm.ac.id/id/berita/20051-genose-deteksi-covid-19-cepat-mudah-dan-akurat-hanya-dengan-hembusan-nafas>
- [86] S. Huang, J. Yang, S. Fong, and Q. Zhao, "Artificial intelligence in the diagnosis of COVID-19: Challenges and perspectives," *Int. J. Biol. Sci.*, vol. 17, no. 6, p. 1581, 2021.
- [87] A. L. Wyllie *et al.*, "Saliva or nasopharyngeal swab specimens for detection of SARS-CoV-2," *New England J. Med.*, vol. 383, no. 13, pp. 1283–1286, 2020.
- [88] B. Priya and R. Prabakaran, "Salivary diagnostics and its implementation in diagnosis of COVID19," Thai Moogambigai Dental College Hospital, India, Tech. Rep., 2020.
- [89] A. H. Kashi, M. Fallah-karkan, E. Amini, and M. Vaezjalali, "The presence of COVID-19 in urine: A systematic review and meta-analysis of the literature," *medRxiv*, 2020, doi: [10.22037/uj.v16i7.6248](https://doi.org/10.22037/uj.v16i7.6248).
- [90] W. Zhang *et al.*, "Molecular and serological investigation of 2019-nCoV infected patients: Implication of multiple shedding routes," *Emerg. Microbes Infections*, vol. 9, no. 1, pp. 386–389, Jan. 2020.
- [91] M. A. Eltahir, "Saliva: In relation to COVID19," Qassim Univ., KSA, Saudi Arabia, Tech. Rep., 2020.

- [92] T. Abduljabbar, R. S. Alhamdan, M. Al Deeb, K. A. Alaali, and F. Vohra, "Association of salivary content alteration and early ageusia symptoms in COVID-19 infections: A systematic review," *Eur. J. Dentistry*, vol. 14, no. S 01, pp. S152–S158, Dec. 2020.
- [93] P. H. B. Aoki *et al.*, "Molecularly designed layer-by-layer (LbL) films to detect catechol using information visualization methods," *Langmuir*, vol. 29, no. 24, pp. 7542–7550, Jun. 2013.
- [94] L. I. Immohr, R. Turner, and M. Pein-Hackelbusch, "Impact of sodium lauryl sulfate in oral liquids on e-tongue measurements," *Int. J. Pharmaceutics*, vol. 515, nos. 1–2, pp. 441–448, Dec. 2016.
- [95] E. Richards, C. Bessant, and S. Saini, "Multivariate data analysis in electroanalytical chemistry," *Electroanalysis*, vol. 14, no. 22, pp. 1533–1542, Nov. 2002.
- [96] A. N. Z. Rowa'Al Ramahi and N. Abu-Khalaf, "Evaluating the potential use of electronic tongue in early identification and diagnosis of bacterial infections," *Infect. Drug Resist.*, vol. 12, p. 2445, Aug. 2019.
- [97] J. R. Carey *et al.*, "Rapid identification of bacteria with a disposable colorimetric sensing array," *J. Amer. Chem. Soc.*, vol. 133, no. 19, pp. 7571–7576, May 2011.
- [98] J. Adkins, K. Boehle, and C. Henry, "Electrochemical paper-based microfluidic devices," *Electrophoresis*, vol. 36, no. 16, pp. 1811–1824, 2015.
- [99] E. V. Heriawan, "Microfluidic fabric-based electrochemical device for glucose monitoring in blood," M.S. thesis, Swiss German Univ., Tangerang, Indonesia, 2018.
- [100] C. M. Daikuzono, C. Delaney, A. Morrin, D. Diamond, L. Florea, and O. N. Oliveira, "Paper based electronic tongue—A low-cost solution for the distinction of sugar type and apple juice brand," *Analyst*, vol. 144, no. 8, pp. 2827–2832, 2019.
- [101] P. Teengam, W. Siangproh, A. Tuantranont, T. Vilaivan, O. Chailapakul, and C. S. Henry, "Electrochemical impedance-based DNA sensor using pyrrolidinyl peptide nucleic acids for tuberculosis detection," *Analytica Chim. Acta*, vol. 1044, pp. 102–109, Dec. 2018.
- [102] W. E. Huang *et al.*, "RT-LAMP for rapid diagnosis of coronavirus SARS-CoV-2," *Microb. Biotechnol.*, vol. 13, no. 4, pp. 950–961, 2020.
- [103] L. Mautner *et al.*, "Rapid point-of-care detection of SARS-CoV-2 using reverse transcription loop-mediated isothermal amplification (RT-LAMP)," *Virology*, vol. 17, no. 1, pp. 1–14, Dec. 2020.
- [104] W. Yang *et al.*, "Rapid detection of SARS-CoV-2 using reverse transcription RT-LAMP method," *MedRxiv*, 2020.
- [105] A. N. Mohon *et al.*, "Development and validation of direct RT-LAMP for SARS-CoV-2," *Medrxiv*, 2020.
- [106] V. L. Fowler *et al.*, "A highly effective reverse-transcription loop-mediated isothermal amplification (RT-LAMP) assay for the rapid detection of SARS-CoV-2 infection," *J. Infect.*, vol. 82, no. 1, pp. 117–125, 2021.
- [107] Y. H. Baek *et al.*, "Development of a reverse transcription-loop-mediated isothermal amplification as a rapid early-detection method for novel SARS-CoV-2," *Emerg. Microbes Infect.*, vol. 9, no. 1, pp. 998–1007, 2020.
- [108] M. A. Lalli *et al.*, "Rapid and extraction-free detection of SARS-CoV-2 from saliva by colorimetric reverse-transcription loop-mediated isothermal amplification," *Clin. Chem.*, vol. 67, no. 2, pp. 415–424, Jan. 2021.
- [109] Q. Yang *et al.*, "Saliva TwoStep: An RT-LAMP saliva test for SARS-CoV-2 and its assessment in a large population," *medRxiv*, 2020.
- [110] T. Chaibun *et al.*, "Rapid electrochemical detection of coronavirus SARS-CoV-2," *Nature Commun.*, vol. 12, no. 1, pp. 1–10, Dec. 2021.
- [111] H. Zhao *et al.*, "Ultrasensitive supersandwich-type electrochemical sensor for SARS-CoV-2 from the infected COVID-19 patients using a smartphone," *Sens. Actuators B, Chem.*, vol. 327, Jan. 2021, Art. no. 128899.
- [112] A. Ganguli *et al.*, "RT-LAMP assay for ultra-sensitive detection of SARS-CoV-2 in saliva and VTM clinical samples," *medRxiv*, 2020.
- [113] C. Adrover-Jaume *et al.*, "Paper biosensors for detecting elevated IL-6 levels in blood and respiratory samples from COVID-19 patients," *Sens. Actuators B, Chem.*, vol. 330, Mar. 2021, Art. no. 129333.
- [114] L. M. Pandey, "Design of engineered surfaces for prospective detection of SARS-CoV-2 using quartz crystal microbalance-based techniques," *Expert Rev. Proteomics*, vol. 17, no. 6, pp. 425–432, Jun. 2020.
- [115] S. Yadav, A. Gedam, and S. Tirkey, "A dielectric modulated biosensor for SARS-CoV-2," *IEEE Sensors J.*, vol. 21, no. 13, pp. 14483–14490, Jul. 2021.
- [116] S. A. Hashemi *et al.*, "Ultra-sensitive viral glycoprotein detection NanoSystem toward accurate tracing SARS-CoV-2 in biological/non-biological media," *Biosensors Bioelectron.*, vol. 171, Jan. 2021, Art. no. 112731.
- [117] Satria. (Accessed: Mar. 13, 2021). *GeNose UGM Dapatkan Izin Edar dan Siap Dipasarkan*. Universitas Gadjah Mada. Accessed: 2020. [Online]. Available: <https://ugm.ac.id/id/berita/20551-genose-ugm-dapatkan-izin-edar-dan-siap-dipasarkan>
- [118] Y. Pan, D. Zhang, P. Yang, L. L. M. Poon, and Q. Wang, "Viral load of SARS-CoV-2 in clinical samples," *Lancet Infectious Diseases*, vol. 20, no. 4, pp. 411–412, Apr. 2020.
- [119] Y. Yang *et al.*, "Laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections," *MedRxiv*, 2020, doi: 10.1016/j.xinn.2020.100061.
- [120] R. Cheema and D. A. Blumberg, "Understanding laboratory testing for SARS-CoV-2," *Children*, vol. 8, no. 5, p. 355, Apr. 2021.
- [121] J. Sun *et al.*, "Isolation of infectious SARS-CoV-2 from urine of a COVID-19 patient," *Emerg. Microbes Infect.*, vol. 9, no. 1, pp. 991–993, 2020.
- [122] Y. Chen *et al.*, "The presence of SARS-CoV-2 RNA in the feces of COVID-19 patients," *J. Med. Virol.*, vol. 92, no. 7, pp. 833–840, 2020.



Elga F. Saki is pursuing the degree with the Biological Engineering Department, Swiss German University (SGU), Tangerang, Indonesia.

In 2019, she conducted her internship at the Universiti Teknologi Malaysia, developing wearable electrocardiography (ECG) circuit, under the supervision of Dr. Fauzan Che Harun. Then in 2020, she conducted her second internship at the University of Basel, Switzerland, conducting intern research on various bio-phonic projects under the supervision of Prof. Azhar Zam. She

also presented her research on thread-based electrode biosensor during the 13th Asian Conference on Chemical Sensors (ACCS) 2019, Bali, Indonesia.



Samuel A. Setiawan received the B.E. and S.T. degrees in biomedical engineering from Swiss German University (SGU), Tangerang, Indonesia, in December 2020.

He was with the Department of Biomedical Engineering, SGU. His research was on wearable electrocardiography (ECG) under the supervision of Mr. Aulia A. Iskandar. From 2020 to 2021, he was a Research Assistant at the Biomedical Engineering Laboratory and had been conducting various preliminary research

on portable diagnostic tool for COVID-19 diagnostic. Since April 2021, he works with PT AP&M Indonesia.



Dedy H. B. Wicaksono (Member, IEEE) received the bachelor's degree in engineering (engineering physics) from Institut Teknologi Bandung, Indonesia, in 1998, the M.E. degree in biological information engineering from Tokyo Institute of Technology in 2002, and the Ph.D. degree in microelectronics from Delft University of Technology in 2008.

From 2008 to 2010, he worked at Delft University of Technology as a Postdoctoral Researcher, developing dental drill-bit integrated optical imaging and sensing. From 2010 to 2016, he had been working as a Lecturer at the Faculty of Biosciences and Medical Engineering, Universiti Teknologi Malaysia (UTM), where he pioneered fabric-based flexible microfluidic devices. He worked as an Assistant Professor and the Head of the Department of Biomedical Engineering at Swiss German University (SGU), Indonesia. His research interest was in textile-based biomedical devices.