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# Nanobioengineering: A promising approach for early detection of COVID-19

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## 9.1 Introduction

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Unique pneumonia due to an unknown source emerged in December 2019 in the city of Wuhan, China [1,2]. Consequently, the World Health Organization (WHO) declared this condition as a new coronavirus disease-19 also known as COVID-19 on February 11, 2020, which on March 13, 2020 was declared as a pandemic [3]. The virus that causes COVID-19 was found to have a similar genome (80% similarity) with the previously known acute respiratory syndrome also known as SARS-CoV. The novel virus was later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4–6]. SARS-CoV-2 falls in the family of *Coronaviridae* which is further divided into *Nidovirales* and another subfamily called Orthocoronavirinae.

The four generations of the coronaviruses belongs to the *Orthocoronavirinae* family that consists of alpha, beta, gamma and delta coronavirus, which are denoted as  $\alpha$ -CoV,  $\beta$ -CoV,  $\gamma$ -CoV,  $\delta$ -CoV respectively [7,8]. The  $\alpha$ -CoV and  $\beta$ -CoVs are mainly known to infect mammals whereas  $\gamma$ -CoV and  $\delta$ -CoV are generally found in birds. The  $\beta$ -CoVs also comprise of SARS-CoV and also include another virus that was found in the Middle East called the Middle East respiratory syndrome virus (MERS-CoV) and the cause of current pandemic SARS-CoV-2. These viruses initially cause the development of pneumonia in the patients and further development of a severe case of acute respiratory distress syndrome (ARDS) and other related symptoms that can be fatal leading to death [9].

Insights into the origin of SARS-CoV-2 and its transmission from one species to another are aiding in finding ways and means to prevent COVID-19 from further spreading. The natural host of SARS-CoV-2 has been suggested to be pangolins and bats [10]. The transmission takes place from animals to humans. Further, the virus also has the ability to spread from human to human with ease which creates a life-threatening disease [11]. The research to find the precise host for COVID-19 is still ongoing and novel diagnostic and strategies are paramount in early detection that can prevent the spread of the disease.

The genomic sequencing of the COVID-19 virus was performed and assisted in identifying the host and the evolutionary relationship between SARS-CoV and SARS-CoV-2. It has been found through phylogenetic analysis that SARS-CoV-2 and SARS-CoV share a highly conserved domain in nsp1 amino acid linkage [12]. Further studies confirmed that SAR-CoV-2 had 77.2% and 82.3% amino acid similarity profiles with coronaviruses in bat, i.e. SARS-CoV and SL-CoVZC45 respectively [13,14]. Other studies depicted that the RNA-binding domain of SARS-CoV-2 is an amino acid longer than SARS-CoV. These outputs provided insights into the ability of SARS-CoV-2 to use angiotensin converting enzyme 2 (ACE2) receptors to enter the cells, unlike SARS-CoV. Another study confirmed that SARS-CoV-2 possessed a spike(S) that had a furin-like cleavage site, which is generally not found in SARS-like CoVs [6]. The research for further understanding the genome pathology of SARS-CoV-2 is still going on all around a more effective treatment and sensitive diagnostic strategies are being reported as more research for disease progresses.

Following the outbreak and the spread of the COVID-19 pandemic has called for diagnostic systems that are; cost-effective, highly sensitive and have a short period between the testing and getting results tests for the masses worldwide. Several methods of molecular tests and immunoassays were rapidly developed. Nanoengineering has been at the forefront to bring to life sensitive nano-based diagnostic and biosensors systems [15]. This chapter covers the biomarkers of COVID-19 that have been employed to engineer diagnostic systems. Furthermore, we explore different

nanosystems that have been developed for the diagnosis of COVID-19, and try to define future and emerging nanoengineered and the need for continuous development of accurate diagnostic testing is vital for quicker patient detection at the point of care in order to improved prevention and treatment, based on the information available to date .

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## 9.2 Biomarkers

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For effective management, prevention of and curbing the spread of COVID-19, accurate detection, and well-timed diagnosis are needed. For this to happen, biomarkers play a paramount role in the early detection of disease etiology, diagnosis, treatment, and prognosis. Several markers have been identified that have made the detection of the COVID-19 disease possible. This section of the book chapter will discuss those biomarkers and their application in the detection, treatment, and prevention of COVID-19.

### 9.2.1 C-reactive protein (CRP)

Inflammation has been a hallmark for COVID-19 and proinflammatory biomarkers have played a key in developing diagnostic systems for the disease. C-reactive protein (CRP) is a plasma protein produced in response to inflammatory mediators by the liver. CRP being a nonspecific protein is used as a biomarker for clinical evaluation of inflammatory conditions, and an increase in CRP level is directly proportional to the disease severity [16]. CPR was used as a biomarker in a study conducted in Wuhan, China, where the majority of nonsevere cohort patients demonstrated lower levels as compared to the severe cohort (33.2 mg/L vs. 57.9 mg/L  $P < .001$ ) [17]. Another study found that patients with CPR level  $>41.8$  mg/L could lead to fatal results due to COVID-19 infection [18]. These studies depicted that CPR can be used as an important marker to determine the severity of infection in the patients.

### 9.2.2 Interleukin-6

Interleukin 6 (IL-6) is an interleukin that is a pro-inflammatory cytokine and is considered one of the most important cytokines that are produced during infection. Moreover, IL-6 undergoes systemic upregulation during the acute phase of most viral infections [19]. Cytokine release syndrome (CRS) results in an extra release of the inflammatory mediators (like IL-6) and which also underlies the pathological process of acute respiratory distress syndrome (ARDS) [20]. ARDS has been associated with SARS, MERS, and infections from SARS-CoV-2 [21]. Therefore, this leads to the association of IL-6 to the severity of COVID-19 infection [22]. Several

studies of Wuhan SARS-CoV-2 infected patients showed that there was an increase in the IL-6 concentration. Moreover, a comparison between severe COVID-19 patients and nonsevere patients there were up to 2.9 times higher in IL-6. Therefore, IL-6 has been concluded as a potential biomarker for the progression of the COVID-19 disease [23,24].

### 9.2.3 White cell count

White blood cells (WCC) are divided into two wide groups: agranulocytes and granulocytes. Granulocytes are subdivided into; basophils, neutrophils (NC), and eosinophils, whereas agranulocytes are subdivided into; monocytes and lymphocytes (LC). The ratio of these respective WBCs and the white cell count (WCC) sheds light on various infections inside the patient's body. A recent study illustrated that WCC had a difference between nonsevere COVID-19 and severe COVID-19 patients [17]. It was seen that the levels of monocytes basophils, eosinophils, and lymphocytes were lower which resulted in a higher neutrophil to lymphocyte ratio (NLR). NLR is considered as a biomarker that shows the inflammatory severity in the patient due to the disease. But there is a need to carry out an extensive study to check the effectiveness of NLR as a COVID-19 biomarker. It is seen that lymphoid tissue and disruption in IL-6 mechanisms by the virus can cause low LC count, which too should be studied [25].

### 9.2.4 Lactate dehydrogenase

Various biomarkers are being investigated for their role in prognosis COVID-19. Lactate dehydrogenase (LDH) is one such biomarker as its elevated levels have been associated progression of viral infections in patients before [26,27]. LDH is known to convert pyruvate into lactate during the glucose metabolism pathway. The secretion of the enzyme is kick started by the necrosis in the cell membrane, which shows either the damage in the lungs or viral infection like pneumonia caused by SARS-CoV-2 [28]. The evidence suggests that high levels of LDH in patients with COVID-19 are associated with a severe form of the disease [29]. The higher levels of LDH were associated with individuals in ICU as compared to non-ICU patients. Isozyme 3 of LDH is present in lung tissue and it has been reported, patients having COVID-19 infections release higher amounts of LDH in the circulation up to 6 fold, due to interstitial pneumonia, which causes acute respiratory distress syndrome (ARDS). ARDS is the hallmark of severe COVID-19 [30,31].

### 9.2.5 D-dimer

Fibrin Degradation Fragment (D-dimer) is one of the protein fragments produced due to the breakdown of blood clots. When cross-linked fibrin

undergoes lysis D-dimers concentrations increase which indicates that fibrinolysis and coagulation have been activated [32]. The activation of the coagulation cascade has been associated with disseminated intravascular coagulation and adverse clinical outcomes in COVID-19 disease [33]. Initial observations in patients with hemostatic abnormalities suffering from COVID-19 had higher levels of D-dimer as compared to patients who survived [34]. A recent study with 191 patients concluded that D-dimer ( $>1.0 \mu\text{g/mL}$ ) levels and deaths were directly proportional. Further, the study concluded that patients with D-dimer levels equal to  $2.0 \mu\text{g/mL}$  or higher when admitted, predicted the mortality rate due to COVID-19 in hospitals [35]. Finally, studies reported that 90% of patients suffering from pneumonia had high coagulation, marking a rise in the D-dimer concentrations [36].

### 9.2.6 Platelet count

Previous studies revealed that COVID-19 led to hematological change causing thrombocytopenia. An analytical study consisting of 1799 individuals revealed a measurable decrease in the platelet counts of the patients [37]. It was observed that nonsurvivors had a reasonably lower amount of platelet count when mortality was considered as an endpoint. Even though the definition for the severity of the disease varies and thrombocytopenia has an impact on results, but platelet count still could be used as an indicator to clinically suggest the severity of the infection.

### 9.2.7 Cardiac troponin

Patients with cardiovascular disorders have a higher mortality rate when infected with COVID-19 as recently observed by various researchers [[38–40]]. Cardiac troponin (cTn) as a biomarker that may aid in classification and stratifying the risk for myocardial injury among patients with COVID-19. An increase in cardiac troponin is an indication of myocardial injury which is associated with COVID-19 prognosis [41]. A study was carried out in China with patients with positive COVID-19 infection, unveiled univariable odds with the death ratio at 80.1 for high-sensitive cardiac troponin (hs-TnI) (95% CI 10.3–620.4,  $P < .0001$ ) [42]. The analysis of this marker is a risky task as compared to other biomarkers for COVID-19 and downstream analysis could put the life of the patient at a risk.

### 9.2.8 Renal markers

It has been also been seen that severe COVID-19 cases and chronic kidney infections have been related [43]. Several studies indicated a significant increase in the levels of renal biomarkers like creatinine and

serum urea in severe COVID-19 cases [44]. High serum creatinine levels of patients co-related with the severity of COVID-19 was found in a study carried out by researchers involving 701 patients [45]. This study also concluded that these patients had more probability to need a mechanical ventilators. Additionally, another study depicted that urinalysis could also aid in the determination of disease severity [46]. Therefore, it suggested that urinalysis was more convenient as compared to kidney serum renal biomarkers. The effect of changes in biomarkers concentrations in patients is summarized in [Table 9.1](#).

### 9.3 Detection techniques for COVID-19

Large-scale testing and contact tracing are vital in controlling Covid-19. Therefore rapid, reliable, and scalable detection assays are crucial for sensitive, specific, and large-scale surveillance of SARS-CoV2. Thus, rapid sensitive and effective are paramount in combating the COVID-19 pandemic. The current section discusses the existing molecular detection techniques for SARS-CoV2 as illustrated in [Fig. 9.1](#).

#### 9.3.1 PCR-based detection

The PCR program has three basic steps; the first step is denaturation, at a high temperature (around 90–95°C) the unwinding of the two strands of DNA takes place which is essential for the annealing of the oligonucleotide primers in presence of DNA polymerase enzyme start the replication of DNA (multiplication of copy number of the target sequence). The annealing usually takes place at a temperature ranging from 45 to 65°C depending upon the G-C content of the target sequence. Since Guanine (G) joins the Cytosine (C) with three hydrogen bonds (triple bond) compared to two hydrogen bonds (double bond) that forms between Adenine (A) and Thymine (T), therefore, the pair of GC rich oligonucleotide primers may require a relatively higher annealing temperature than an AT-rich oligonucleotide primer. The third step of a PCR reaction is an extension which prepares the amplified target sequence for the repetition of the PCR cycles. The extension takes place at 72°C. Each PCR reaction consists of a mixture of oligonucleotide primers, DNA template (target gene or sequence), dNTPs, PCR buffer, MgCl<sub>2</sub>, and DNA polymerase enzyme. Agarose gel electrophoresis is used to detect the amplified product using a fluorescent dye (ethidium bromide) at the end of the various steps [47,48].

The PCR-based amplification provides more sensitive and targeted detection of the microbial pathogens compared to the serological or immunological assays. Several variations of the PCR assays have been in regular use for applications in forensics, biological research, archaeology,

TABLE 9.1 Summarizes changes observed of biomarkers during COVID-19.

Biomarker	Function	Presentation in COVID-19	References
CRP	Proinflammatory protein that triggers the classical innate immunological pathway by binding to microorganisms' polysaccharides such as phosphocholine (PCh)	Concentration increases in COVID-19 infections. Can be employed to classify severe from nonsevere presentation of the disease.	Qin et al. [17]; Sproston and Ashworth [231]
IL-6	A proinflammatory cytokine that is produced during an infection	Upregulation during acute viral infections. Underlies the pathological process of ARDS. Up to 3-fold higher in severe COVID-19 patients. Can be used to classify severity of the disease.	Coomes and Haghbayan [23]; Mahajan et al. [20]; Ulhaq and Soraya [24]; Velazquez-Salinas et al. [19]
LDH	Convert pyruvate into lactate in the glucose metabolism pathway. It reduces NAD <sup>+</sup> to NADH and H <sup>+</sup> through the oxidation of lactate to pyruvate. Employed to measure apoptotic and necrotic cell death.	Elevated hallmark for progression of viral infections in the body. Indicative of the damage in lungs or viral infection like pneumonia associated with COVID-19. Up to 6-fold higher in severe cases linked to interstitial pneumonia, that ARDS. Isoenzyme 3 found only in lungs used to detect ARDS and severe COVID-19	Ferrari et al. [29]; Henry et al. [30]; Mo et al. [31]
D-dimer	Protein fragments produced as a result of fibrinolysis.	Adverse clinical outcomes in COVID-19 disease are associated with disseminated intravascular coagulation. A predictor of COVID-19 mortality.	Milbrandt et al. [36]
Cardiac troponin	Found in skeletal and cardiac muscle fibers. They regulate muscular contraction. Elevated levels in blood are a measure of myocardial injury.	Sensitive biomarker assay in recognition of myocardial injury in acute illnesses. Used in testing and classification of pathogenesis in patients with myocardial injury. Aid in classification and stratifying the risk for myocardial injury among patients with COVID-19. Positive test COVID-19 patients may indicate prognosis of myocardial injury due to SARS-CoV-2 effects.	Chapman et al. [226]; Zhou et al. [42]

CRP = C-reactive protein; IL-6 = interleukin 6; LDH = lactate dehydrogenase.



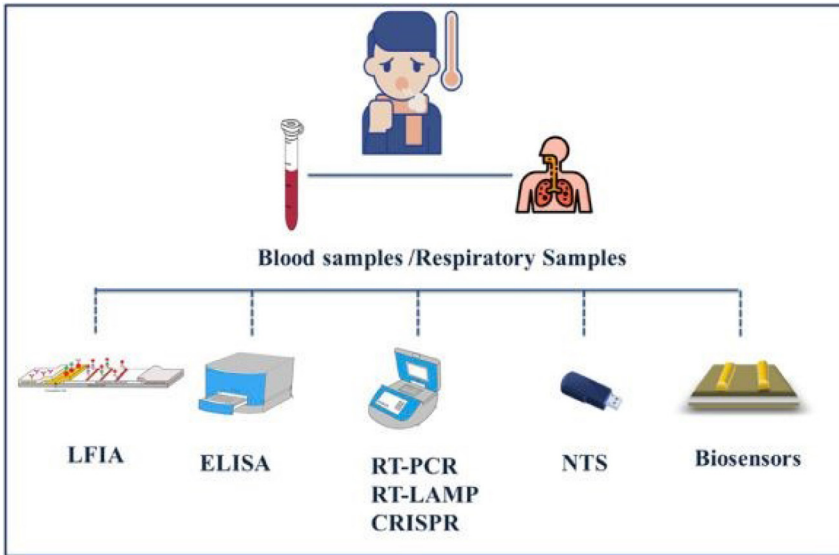


FIGURE 9.1 Diagnostic techniques for COVID-19 and new developments. Representation of different diagnostic methods for the detection of SARS-CoV-2 from respiratory and serum samples (permission granted) [226,227]. *Talanta*. 2020;220(1):121392. doi:10.1016/j.talanta.2020.121392.

anthropology, and, food technology [49,50]. There are several factors that may determine the sensitivity of a PCR assay including PCR protocol, target gene(s), oligonucleotide primer sequences, quality of nucleic acid template, and of course the handling. Since SARS-CoV2 has an RNA genome, therefore, the amplification of the target sequence for the detection of SARS-CoV2 requires an additional step of reverse transcription before the amplification step. The reverse transcriptase is an enzyme that converts RNA into DNA which can then be amplified to produce multiple copies of the target sequence required for the detection in the PCR assay.

The real time RT-PCR is based on fluorescent signaling amplification which is much faster and more specific due to the application of a TaqMan probe than the conventional RT-PCR assay. Nested RT-PCR is another version that is used for the detection of complicated target DNA to avoid false results due to mutation using two sets of primers [51]. For SARS-CoV-2 detection, several genes have been targeted such as N-gene (nucleocapsid), E gene, RdRP gene, ORF1ab gene, and S gene (spike protein) [52]. Research conducted by Chu et al. described two different one step real-time RT-PCR attempts to detect ORF1ab and N genes of the SARS-CoV-2 genome which showed a range of 0.0002–20 with 50% tissue culture infective dose (TCID<sub>50</sub>) per reaction and detection limit below 10 RNA copies per reaction [53].

The Charité University Hospital developed an RT-PCR based protocol for SARS-CoV-2 detection [54]. Additionally, the Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA have developed a SARS-CoV-2 detection protocol along with nucleic acid extraction kits and the set of primers for SARS-CoV-2 detection [55]. Further, TaqMan chemistry has designed a single step real-time RT-PCR assay for SARS-CoV2 detection using N or ORF1b gene-based detection. Several other manufacturers have also developed SARS-CoV-2 detection assays targeting different genes (N gene, E gene, RdRp gene, ORF-1a gene, ORF-1b gene, etc.) in the SARS-CoV2 genome, with varying sensitivity [52]. The SYBR green-based real-time RT-PCR assay has also been introduced primarily to reduce the detection cost, with 91.7 % specificity [56].

### 9.3.2 ELISA-based detection

Enzyme-linked immunosorbent assays (ELISA) are based on antibody-antigen interaction to provide specific and reproducible results. This technique is cost-effective and easy to handle in comparison to RT-PCR assay. Several immunoassay kits have been developed for SARS-CoV-2 detection in recent months [57]. Currently numerous manual and automated immuno-test kits are available using fluorescence immunoassays, chemiluminescence enzyme immunoassays, lateral flow immunoassays for SARS-CoV2 detection. All these assays are based on SARS-CoV-2 nucleocapsid protein as an antigen and their respective antibodies (IgG, IgA, and IgM). The major challenge with ELISA kits is the lack of specificity as it has cross responsiveness of SARS-CoV-2 antibodies with other coronaviruses. The cross reactivity of S protein based antibodies of SARS-CoV-2 have been studied in 15 patients of SARS-CoV2 and observed the high frequency of cross reactivity with SARS-CoV [58]. Zhang and coworkers used Rp3 nucleocapsid protein of SARS-CoV-2 to detect the COVID-19 in patients, this protein resembles upto 80 % with SARS-CoV protein. Using IgG and IgM antibodies in sandwich ELISA, a study successfully detected SARS-CoV-2 [59]. The SARS-CoV2 consists of four proteins viz., S, M, E, and N, which have epitopes to bind with the paratope of antibody. ELISA exhibits high sensitivity with a relatively longer ( $\geq 1.5$  h) period of detection. The level of other protein biomarkers like C-protein, D-dimer, lymphocytes, leukocytes, and blood platelets also have been elevated in COVID-19 patients [38] but the level of these protein biomarkers may become abnormal in several other health conditions too, therefore, may not offer a reliable diagnosis.

There have been several approaches to detect SARS-CoV2 in blood, mucosal swabs, urine, etc. Several companies prepared immunoassays, for example, BioMedomics rapid test, Surescreen rapid test, Assay Genie POC kit, etc for reliable detection which is still unsure. The new diagnostic

assays will have to find novelty related to the material, process, specificity, and sensitivity. The ELISA kits based on N, and S proteins- IgG interaction are available for SARS-CoV with 94.7% and 58.9% sensitivity, respectively [60]. The IgG and IgM antibodies were measured in the SARS-CoV-2 patients, the antibody concentration effected after 5–7 days of infection [61]. The multiplex digital detection of SARS-CoV-2 can be a fast and smart detection method using an optical reader [62]. Since a large number of SARS-CoV2 strains are in circulation ( $n = 104$ ) therefore, maintaining the sensitivity of the immunoassays is quite challenging. There is a need to create an effective way to get an accurate diagnosis of COVID-19 that addresses sensitivity, specificity as well as cost implications.

### 9.3.3 CRISPR-based detection

The “Clustered regularly interspaced short palindromic repeats” (CRISPR) is the combination of two distinct characteristics of DNA, which has a repeated sequence of nucleotide and spacer. CRISPR is a genome-editing technique but has also been utilized in Covid-19 detection, for which the CRISPR-based SHERLOCK (Specific High Sensitivity Enzymatic Reporter UnLOCKing) technique has been developed. This uses a synthetic RNA fragment of SARS-CoV-2 which can detect 10–100 copies per microliter. It follows three steps and provides the results within an hour, following the 25 minutes of amplification of extracted nucleic acid then 30 minutes of incubation-detection of viral RNA sequence using Cas 13, and finally 2 minutes for reading the results with paper dipstick [63,61]. One advantage of the SHERLOCK technique is that this does not require skilled personnel and produces the result in less than one hour with the dipstick method.

Mammoth Biosciences have developed a CRISPR-DETECTOR (DNA endonuclease targeted CRISPR trans reporter) based lateral flow strip for the detection of SARS-CoV2. In this, Cas12 enzyme is used for E gene, N gene, and P gene RNA as a control for SARS-CoV-2, following the same protocol as in SHERLOCK, but the results can be visualized in lateral flow strip in 30 minutes with the range of 70–300 copies/ $\mu\text{L}$  [64,65]. Lucia and the group have used Cas12 enzyme with RdRp and ORF1ab genes for the detection of SARS-CoV-2 on the paper strips with labeled fluorescein ssDNA and WH-human1 sequence (as control). The detection limit of this assay is  $\sim 10$  copies/ $\mu\text{L}$  [66].

### 9.3.4 Lateral flow-based detection

Lateral flow immunoassay (LFA) attracts interest due to its user-friendliness, portability, and cost-effectiveness. Most of the LFA assays are paper-based and immobilize with either nucleotides or antibodies. There

have been several LFA kits available in the market for the detection of SARS-CoV2. The major drawback of LFA kits is that this assay detects the target only in the postsymptomatic patients, which means those individuals who are asymptomatic but infected may not get detected using LFA kits. However, immunoassays are rapid and cost-effective compared to the RT-PCR, but they have less specificity and low sensitivity in comparison to nucleic acid-based detection methods.

Blood and saliva tests based on LFA have been developed to detect anti-SARS-CoV2 antibodies [67–69]. LFA assays have the advantage of rapidity, no requirement of an experiment protocol, and no sample preparation. Many immunoglobulin antibodies (A, M, and G) based testing for SARS-CoV2 have been applied in clinical laboratories [67,68]. An elaborate study on LFA for SARS-CoV2 is required on different stages of the disease. These immunoassay kits can't be used at an early stage of the disease, which is one of the major disadvantages of these assays [11]. In the current COVID-19 pandemic, the LFA kits have been utilized for Sars-Cov-2 detection in patients with serious health conditions. One week after the appearance of symptoms, patients were tested with LFA kits which yielded 95–98% sensitivity [70]. Recently, a two-dimensional paper-based lateral immune assay has been developed [71]. The present LFA for detection of COVID-19 is based on IgG or IgM antibodies. The nucleotide sequence-based LFA assays are more sensitive than the immuno-based LFA assays. It has been reported that the labeling of capture probe with gold nanoparticles or other luminescent material may help to enhance the signal amplification in lateral flow assays during the detection of the target [72].

### 9.3.5 Biosensors: State-of-the-art biosensing devices

A biosensor is a device that consists of three parts: a bioreceptor, transducer, and detector. The bioreceptor loaded with biomolecules like antibodies, peptides, and DNA, which interact with their specific target(s). After the interaction, the signal is produced and read by the transducer, the signal is amplified and processed to the detector. Based on detectors, biosensors are classified into three classes: electrochemical, piezoelectric, and colorimetric. The bioreceptor plays an important role in a biosensor. Based on bioreceptor, the biosensors can be characterized into two categories: immunosensor and aptasensor. The immunosensors rely on antibody and antigen interaction while aptasensors rely on the aptamers (synthetic single-strand DNA complementary to the target). The following biosensing techniques have been utilized to detect SARS-CoV2:

#### 9.3.5.1 Immunosensor for SARS-CoV-2 detection

In immunosensor the interaction of antibody and antigen is read by electrochemical, piezoelectrical, colorimetric, or impedimetric technique

[73–77]. It is observed that electrochemical immunosensors for influenza A virus subtype H5N1 have shown a higher sensitivity, selectivity toward the virus and appeared to be economically affordable than the conventional detection methods [78]. The signal amplification of immunosensor can determine sensitivity, based on two factors (a) electrochemical-chemical redox cycling, (b) enzyme reduction-electrochemical, which play a major role in signal amplification [79].

The major advantages offered by an immunosensor over other detection techniques are rapidity, portability, user-friendliness, and cost-effectiveness. Though immunosensor has some drawbacks like it requires the availability of a specific monoclonal antibody; shelf-life of assay and antigen variation makes it difficult to generate a similar type of antibody. During the ongoing COVID-19 pandemic the US- FDA has approved various immune kits for the detection of SARS-CoV2 [57]. Since the SARS-CoV2 has more than 100 different strains and each virus contains multiple proteins with unique epitopes over the surface, more research is required to develop a highly specific and sensitive immunosensor for SARS-CoV2 detection [80]. An ACE2 receptor based impedimetric biosensor has been developed for the detection of SARS-CoV2 [81] using human blood. To further improve the signal amplification, the redox active molecules (alkalanthiol) and metal nanoparticles have been used [82].

### 9.3.5.2 Aptasensor for SARS-CoV2 detection

Aptamers are small peptides or oligonucleotides of RNA/DNA that act as the receptors for target DNA. The aptamers are synthesized using single-stranded RNA/DNA with 10–100 nucleotides in length. The nucleotides sequence for the aptamer is selected via the Systematic Evolution of Ligands by Exponential Enrichment (SELEX) process to get a specific RNA/DNA sequence toward a broad spectrum of the target. Aptamers are nanoscale in size and can detect up to nano- and picogram levels, therefore aptasensors are considered as the nanobiosensor [83,84].

Aptasensors are user-friendly, cost-effective, and stable analytical tools for rapid detection of viruses [85,86]. These nanosensors have great potential to detect the virus with various modifications at the electrode surface [87–90]. At present, there is no aptasensor for the detection of SARS-CoV2. In principle, oligonucleotide sequences of aptamer are specific for identifying the viral sequence via the hybridization process. The aptamers can be functionalized easily with fluorescence labels or any other redox material in order to improve the sensitivity and specificity of the aptasensor. The aptasensors have advantages over self-life and cost-effectiveness over immunosensors. Due to these properties, aptasensors are suitable for commercialization in the form of a device with the incorporation of other technologies for the rapid detection of SARS-CoV2.

Biosensors have the edge over other detection techniques like PCR, ELISA, and CRISPR due to portability, scalability, cost-effectiveness, and rapidity [91]. In recent days, several innovated hands-on biosensing devices have been developed using nanomaterials to overcome the drawbacks of lengthy protocols of other detection techniques. The use of nanomaterials enhances the surface to volume ratio and the tunneling property which helps in improving the sensitivity and signal amplification of the biosensing device [92,93].

### 9.3.6 Computed tomography (CT) scan

During the COVID-19 pandemic, the computed tomography (CT) of the chest of the patients has appeared to be one of the rapid and reliable diagnostic techniques with high sensitivity. It can give the results at the infection phase before the appearance of clinical symptoms. The CT scan measures cross-sectional images of the patient's chest from many angles using X-rays [94,95]. These images are then examined by a radiologist for establishing the diagnosis. The image features vary among the stages of infection. The thick lobular septa, multi-lobar ground glass opacity in the posterior and peripheral region have been observed in COVID-19 patients in chest CT images [96,97]. A study reported CT images (56%) at the initial two days of disease progression with a follow up till the appearance of the clinical symptoms (~10 days) which found hazy opacity in the peripheral region of the lungs [98].

A few studies reported that the imaging feature of CT shows a higher sensitivity up to 86-98% in comparison to other detection techniques [38,99-101]. Unfortunately, the CT imaging features have a major limitation of low specificity (25%), which may collapse with the other viral infections (pneumonia, etc.) or in an event of lung disease [100]. Another limitation of the CT scanning technique is that it requires an expensive instrument and expert technician, and the cost is higher than the other detection techniques. The CT scans are primarily conducted to eliminate the false-negative results of the assay kits. Due to the overwhelming numbers of infected people and limited numbers of available test kits, the CT scans have been useful for the screening of the serious as well as the mild COVID-19 cases with the objective to streamline the life-threatening cases as earliest as possible.

## 9.4 Role of nanomaterials in biosensing of COVID-19

The COVID-19 pandemic has ravaged the globe, unlike previous pandemics the outbreak was met with the advancement in technology. Nano-based technologies have been at the forefront in fighting the pandemic.

Different studies are being carried out to find an effective drug, sensitive detection methods, and vaccines against SARS-Cov2 infection. In both scenarios, this is still a dream in the pipeline. For effective treatment of SARS-Cov2 infection prevention and contact tracing, it is essential to have diagnostic tools that are rapid, cost-effective, sensitive, selective, reproducible, multiplexing, disposable, and easy to use. Different diagnostic tools such as reverse transcription polymerase chain reaction (RT-PCR), serological testing, and chest computed tomography (CT) scan are used. However, some of these methods contain drawbacks; the high cost of CT scan diagnosis and its inability to differentiate between SARS-Cov2 and other viruses' infections limit its application. RT-PCR is time-consuming and requires sophisticated equipment. Also, during the earlier stages of the outbreak, many false negative and false positive results were reported from the RT-PCR method [102,103].

Nanomaterials, such as silver or gold, polymeric, and silica nanoparticles (NPs), carbon nanotubes, and quantum dots, are being employed in the detection of viruses [104]. In these types of nanosystems, their surfaces were modified with biomolecules (such as DNA, RNA, antigen, antibody, peptide) obtained from the virus [105]. It is also important to note that the high surface and volume ratios of nanomaterials improve the interactions between the sensor and analyte, thus increasing the detection limit and decreasing the detection time [106]. Nano-based probes are widely used for the assembly of biosensors and they improve the sensor's response, either by obtaining electrical, optical or catalytic properties, thus offering superior analytical sensitivity for diagnosis [107]. Amongst the nanosystems utilized as detection tools, gold nanoparticles have stood out thanks to their photonic, electrical, and catalytic properties [108]. The gold NPs have been functionalized with probes modified with thiol on the surface, that hybridize with the target, inhibiting the aggregation of the NPs by salts and this results in a color change; therefore this type of system can be easily modified for COVID-19 diagnosis [109]. Other diagnostic systems have incorporated gold nanoparticles fused with antibodies against SARS-CoV-2 IgG/IgM. These systems have showed the potential for application as a rapid symptomatic and asymptomatic screening for COVID-19 [110]. Field-effect transistors (FET) supported graphene have previously reported to detect the viral load of SARS-CoV-2 from nasopharyngeal swab specimens using specific antibodies from the virus [111]. Selected antibody against SARS-CoV-2 spike protein coated graphene sheets of a FET were employed to fabricate the biosensor. SARS-CoV-2 spike antibody was then immobilized onto the fabricated device through 1-pyrenebutanoic acid succinimidyl ester, an efficient interface coupling agent used as a probe linker. The sensor was found to sensitive enough to differentiate the SARS-CoV-2 and MERS-CoV proteins. Moitra et al. also reported a gold NPs capped with thiol-modified antisense oligonucleotides (ASO) biosensor



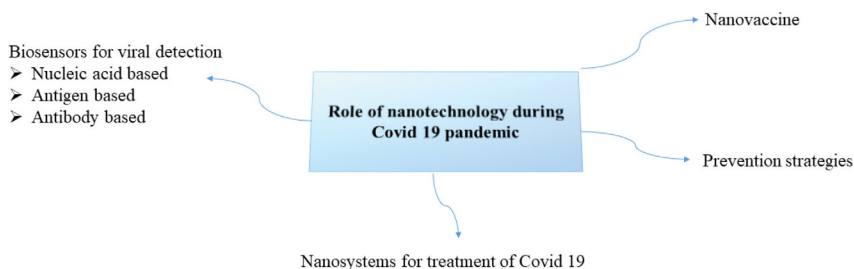


FIGURE 9.2 Role of nanotechnology during the COVID 19 pandemic.

system with specificity for the N-gene (nucleocapsid phosphoprotein) of SARS-CoV-2. The reported system could provide diagnostic results for COVID-19 in a couple of minutes [112]. Furthermore, Baker et al., have also reported gold nanoparticles that had been polymer-stabilized multi-valent bearing sialic acid derivatives and that interacted with SARS-CoV-2 spike glycoprotein [113]. From the study  $\alpha$ , N-acetylneuraminic acid binds strongly with the spike glycoprotein and functioned as a prototype for the lateral flow diagnostic device detection unit.

As the world continues to fight the SARS-Cov2 pandemic and the number of cases increases at an alarming rate, testing kits' availability has not been sufficient; this has resulted in under-reporting of the actual active SARS-Cov2 cases worldwide. Different studies are being conducted to fabricate diagnostic tools from nanomaterials such as gold, magnetic, and polymeric nanoparticles to solve this challenge. It is important to note that nanomaterials' morphology and size play a crucial role in their application. Nanomaterial-based diagnostic tools are known to have several advantages compared to conventional methods. Fig. 9.2 shows the role of nanotechnology during the COVID 19 pandemic. This section will discuss various nanomaterial-based diagnostic tools that have been reported so far in the literature.

### 9.4.1 Gold nanostructure-based biosensors

In recent years, the application of nanotechnology in the fight against different diseases has increased. Gold nanoparticles are among the frequently used nanomaterials to fabricate biosensors for SARS-CoV2 infection. This is mainly due to their stability, high surface chemistry, biocompatibility, and surface molecular biochemical conjugation. A biosensor is a device made up of a biological recognition component (anti-bodies, enzymes, nucleic acids, organic and biological receptors) and a transducer. A transducer's function is to transform the interaction between the analytes and biological components into a measurable signal. Qiu et al [114] developed a dual functional plasmonic photothermal biosensor for



detection of SARS-CoV2. Gold nanoislands factionalized with complementary DNA receptors were used to detect SARS-CoV2 through nucleic acid hybridization. A detection limit of 0.22 pM was obtained. This method is highly sensitive, fast, and reliable. Moitra et al. [112] reported the development of a colorimetric biosensor using gold NPs capped with thiol modified Antisense oligonucleotides specific for N-gene of SARS-CoV2. The presence of SARS-CoV2 was detected within 10min. The biosensor showed selectivity toward SARS-CoV2 in the presence of MERS-Cov viral RNA with a low limit of detection of 0.18 ng/uL. This method is cost-effective and eliminates the need for sophisticated instruments. Also, detecting the presence of SARS-CoV2 in 10 min from the total RNA isolated from infected biosamples is an added advantage.

Ventura et al [115] developed a colorimetric biosensor for fast detection of SAR-CoV2 in nasal and throat swabs. Colloidal gold nanoparticles (20 nm) functionalized with antibodies targeting three surface proteins of SARS-CoV2 (spike, envelope, and membrane) were used. A low limit of detection, which was close to that of real-time PCR was obtained. This method can be used for mass screening of SARS-CoV2 since only the interaction between the functionalized gold nanoparticles and virions is required. Therefore, this eliminates the pretreatment step, such as RNA extraction and amplification required in other methods. Mahari et al [116] reported the fabrication of two biosensors for the detection of SARS-Cov2. The first sensor was fabricated using a fluorine-doped tin oxide electrode with gold nanoparticles (FTO/AuNPs). This electrode was immobilized with nCovid 19 monoclonal antibody. The second sensor used a screen-printed carbon electrode (SPCE) immobilized with nCovid 19 monoclonal antibodies. These two biosensors were used to detect nCovid antigen in spiked saliva samples. The detection limit was found to be 90 fM and 120 fM for the first and second sensors, respectively. A colorimetric sensor that is based on gold nanoparticles was reported by Kumar et al [117]. In this study, the detection of RNA polymerase (RdRp) gene of SARS-CoV2 was achieved in less than 30 min with a detection limit of 0.5 ng. Recent studies on the application of gold nanoparticles to fabricate biosensors for SARS-Cov2 detection are shown in [Table 9.2](#).

#### 9.4.2 Graphene-based biosensors

Carbon-based materials such as graphene and its derivatives (graphene oxide and reduced graphene oxide) are frequently used in sensing and drug delivery systems. These materials have a high surface area, high conductivity, and excellent mechanical, thermal, and electrical properties [118,119]. G3raphene is used in optical sensors because of its ability to quench photoluminescence. Its high electrocatalytic activity makes it useful in electrochemical sensors as illustrated in [Fig. 9.3](#). While graphene's

**TABLE 9.2** Recent gold nanoparticles based biosensors for detection of SARS-CoV2.

Biosensor description	Nanoparticles	Detection limit	Time	Benefits	Ref.
Plasmonic fiber-optic absorbance biosensor	Gold nanoparticles	–	15 min	Rapid, cost-effective, sensitive, and selective	Kumar et al. [232]
Rapid IgM-IgG combined antibody test	Gold nanoparticles (40 nm in diameter)	–	15 min	Minimal sample preprocessing, fast and sensitive. No additional equipment is required.	Whitman et al. [69]
Opto-microfluidic sensing platform with gold nanospikes	Gold nanospikes	0.08 ng/mL	30 min	Cost-effective, easy to use, rapid, and feasible for mass production.	Murugan et al. [233]
Colloidal gold nanoparticles based lateral-flow assay	Gold nanoparticles (30 nm in diameter)	–	15 min	Small sample used (10–20 uL), excellent specificity, stability, low cost, easy operation, and less time-consuming.	Funari, Chu, and Shen [234]
Nanomaterial-based optical sensing platform	Gold nanoparticles (10 nm)	0.5 ng	30 min	Fast sensitive and selective, No sophisticated equipment	Mahari et al. [117]
FTO/AuNPs/nCovid-19 Ab SPCE/nCovid-19 Ab	Gold nanoparticles	120 fM 90 fM	10–30 s	Onsite application, cheap, no sophisticated laboratory set up, the device is potable	Ventura et al. [116]
Colorimetric biosensor based on gold nanoparticles	Gold nanoparticles (20 nm)	–	–	Pretreatment is not required, relies on its sensitivity to the virion rather than to its content (RNA)	Qiu et al. [115]
A colorimetric assay based gold nanoparticles capped with thiol modified antisense oligonucleotides	Gold nanoparticles	0.18 ng/uL	10 min	Rapid, selective, and visual ‘naked eye’ detection, no sophisticated laboratory equipment.	Seo et al. [112]
Dual-functional plasmonic photothermal biosensor	Gold nanoislands	0.22 pM	–	Highly sensitive, fast, and reliable.	Baker et al. [114]

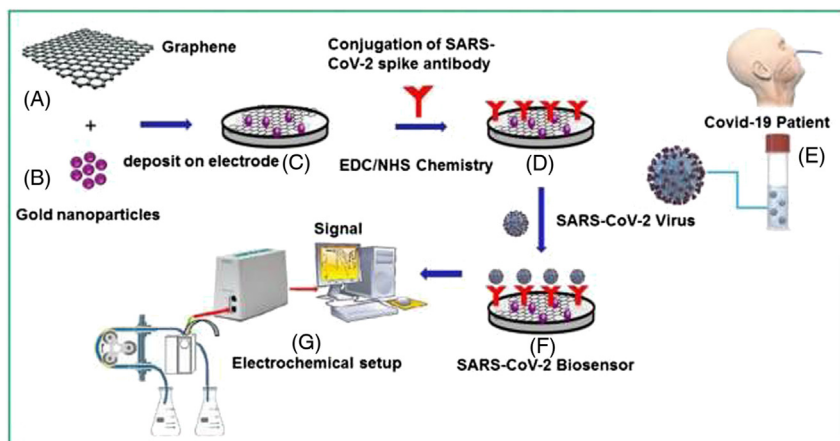


FIGURE 9.3 Potential of graphene-based materials to combat COVID-19: properties, perspectives, and prospects. Illustrations of how electrochemical graphene-based biosensors can be employed for the detection of the SARS-CoV-2 virus. Adapted with permissions from [119,228]. *Materials Today Chemistry*. 2020;18:100385. doi:10.1016/j.mtchem.2020.100385.

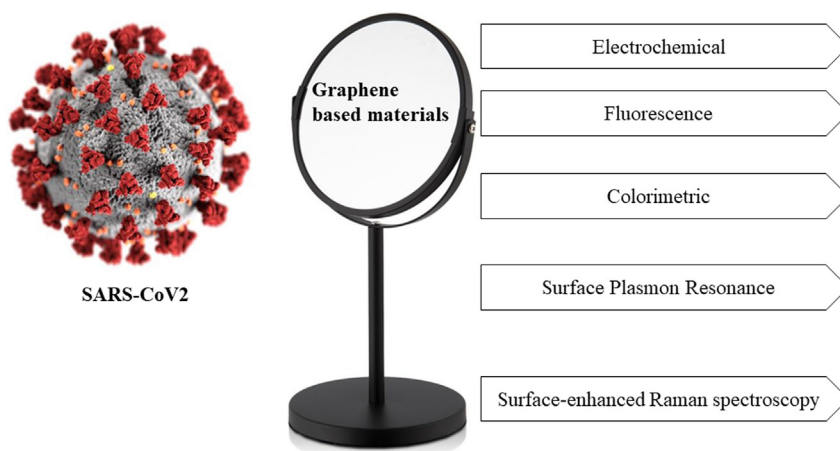


FIGURE 9.4 Typical graphene-based biosensors.

ability to adsorb guest molecules on its surface is advantageous for biosensors, as shown in Fig. 9.4.

However, graphene's application is limited by its hydrophobic nature and lack of chemically reactive functional groups that could be used to immobilize different biological molecules. To overcome these drawbacks, covalent and noncovalent functionalization, synthesis of graphene-based nanomaterials, doping with metal and metal oxide nanoparticles, and

the introduction of defects are among the commonly used strategies. Graphene oxide (GO) and reduced graphene oxide (rGO) are the most used graphene-based materials in biosensors. Graphene oxide has many oxygen-containing functional groups such as hydroxyl, epoxy, and carbonyl groups. These functional groups make the attachments of biological recognition elements and surface functionalization easy. However, the presence of these oxygenated groups decreases its electrical conductivity. Therefore, reduced graphene oxide is synthesized as an alternative using various methods (hydrothermal, chemical, electrochemical, and thermal). Torrente-Rodríguez et al [120] developed an electrochemical graphene-based sensor for simultaneous detection of different SARS-CoV2 biomarkers. Viral antigen nucleocapsid proteins, IgM and IgG antibodies, and inflammatory biomarkers were used. The sensor showed high sensitivity and selectivity due to graphene's unique properties and the specificity and sensitivity of the immune-sensing strategies.

A field-effect transistor biosensor for SARS-CoV2 detection in clinical samples was reported by Seo et al [111]. The antibody specific for SARS-CoV2 was coated on the graphene sheet. A limit of detection of 1 fg/mL and 100 fg/mL was obtained for SARS-CoV2 in spike phosphate-buffered saline and clinical transport medium, respectively. This method is selective and sensitive; also, no sample pretreatment and labeling were required. A graphene oxide decorated Au/fiber Bragg grating probe was used to detect COVID-19 in human saliva by Samavati et al [121]. An ultrasensitive super sandwich-type electrochemical sensor for SARS-CoV2 was developed using calixarene functionalized graphene oxide Zhao et al [122]. This sensor is based on the RNA measurement of SARS-CoV2. a limit of detection of 200 copies/mL was obtained. In this method, a small sample of 10  $\mu$ L per assay was required. The sensor works as a portable electrochemical smartphone; thus, nucleic acid amplification and reverse transcription are not needed.

### 9.4.3 Magnetic nanomaterial-based biosensors

With the increasing demand for SAR-CoV2 testing worldwide, several studies have reported the potential use of magnetic nanoparticles (iron oxide, ferrites of manganese, nickel, cobalt, and magnesium) based biosensors such as magnetic resonance, electrochemical, fluorescence, and rolling circle amplification [119]. Iron oxide nanoparticles are commonly used because of their biocompatibility and superparamagnetic properties. Magnetic biosensors are designed by modifying the magnetic tags with magnetic nanoparticles that are later functionalized with various biological components that are selective to the target analytes. These biosensors' main advantages include low sample matrix and low background noise since most of the biological environments are nonmagnetic.

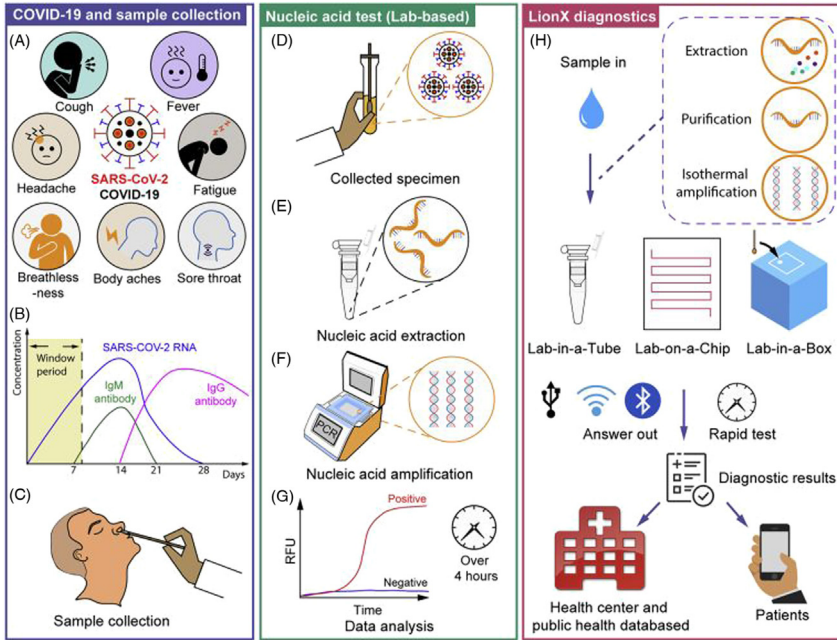


FIGURE 9.5 COVID-19 diagnosis with laboratory-based and POC tests (with permission) [229,177]. Fighting COVID-19: Integrated Micro- and nanosystems for viral infection diagnostics. *Matter*. 2020;3(3):628-651. doi:10.1016/j.matt.2020.06.015.

## 9.5 Emerging diagnostic techniques for COVID-19

This pandemic has caused researchers to begin to revamp conventional and novel systems in order to curb its global reach. Coronavirus treatment requires both restricting viral proliferation and the limitation of inappropriate immune reaction [123]. At present, numerous diagnostic kits and methods to test for COVID-19 are accessible, and repurposing strategies for COVID-19 have demonstrated to be clinically viable (Fig. 9.5; [124,125]). As the worldwide interest for diagnostics and therapeutics keeps on rising, it is important to quickly create different procedures to effectively distinguish and contain the infection. With the infection rates of COVID-19 rising exponentially, precise and quick diagnostic methods are needed to detect and control the virus. Confirmed identification and detection of the virus followed by nonpharmaceutical interventions are the primary measures to curb the spread of SARS-CoV-2 [126,127]. In spite of the fact that there are a number of strategies available for virus diagnosis, these conventional strategies and techniques have their own drawbacks. Right now, the World Health Organization (WHO) has recommended different

analytic instruments and recommended the collection of upper respiratory specimen utilizing NP swabs [128,129]. The CDC and WHO also suggest the collection of Oropharyngeal (OP) specimens, sputum, endotracheal aspirate, bronchoalveolar lavage, blood, stool, and postmortem material and tissue from the lungs [130]. As of late, the WHO has affirmed the utilization of qSARS-CoV-2 IgG/IgM quick serological tests, in which venepuncture blood gathered by clinical experts can be utilized [131,132]. Be that as it may, the utilization of this test is restricted to approved research facilities. This test distinguishes the IgM and IgG antibodies created by the patient in light of SARS-CoV-2 contamination. Furthermore, the tests accessible check for the presence of viral nucleic acid through RT-PCR. For diagnosis confirmation, at least two targets must be picked on the SARS-CoV-2 genome, with one being specific for SARS-CoV-2. Another downside is that the development of antibodies only occurs a few weeks after infection which inevitably increases the possibility of false negatives [133]. Until further notice, the utilization of RT-PCR as a diagnostic tool for covid-19 is recommended. As the worldwide interest for real-time diagnostic tools keeps on rising, it is of utmost importance to hasten the development of novel diagnostic systems at the point of care. COVID-19 diagnosis is a critical step in tracing the virus to understand its epidemiology [134]. The usual tests for pathology are gathered from upper and lower respiratory tracts (throat, oropharyngeal, nasopharyngeal, bronchoalveolar liquid, and sputum) through swabs for RT-PCR test [135,136]. Urine and blood samples are not considered useful specimens due to the fact that that the virus is still absent at the time of detection in the upper and lower respiratory tracts [137]. Reports of irregularity in RT-PCR test results for CoV-SARS-2 in different tissues indicates a huge gap in research in the relationship between the viral load and its bio-distribution in different tissues [138]. Therefore, novel methods are necessary to galvanize the detection and diagnosis of SARS-CoV-2 viral infection in order to halt their propagation. To date, numerous diagnostic tools and assays have been commercialized and approved for COVID-19 diagnosis and others are currently at their respective phases of development. In this section, we will discuss some novel methods used for Covid-19 detection.

### 9.5.1 Nano-based automated systems

Nanotechnology innovation has gotten a lot of attention in biomedical applications and diagnostics [104,139]. One of the most significant applications of advanced nanomaterials is the probability of employing multiple probes concurrently with biological and nonbiological labels in virus detection [140,141]. The advantage of using nanobiosensors in detecting SARS-CoV-2 is due to their small size, fast response, high sensitivity as well as portability which is possible to use in point-of-care settings [142,143]. Since

SARS-CoV-2 mutation is expected to potentially produce more virulent strains globally [144,145], it is, therefore, essential to provide diagnostic nano-biosensors especially at the point of care for rapid detection in order to halt the possibility of mutations and further outbreaks.

### 9.5.2 Point of care diagnostics for personalized health

Rapid diagnosis is an important control measure for effective management of Covid-19 propagation [146]. Currently, RT-PCR is the gold standard for diagnosis [147], however central lab facilities are needed. Point of Care (POC) testing provides results within minutes of the test being conducted, thereby providing on-time decision making regarding patient care [148]. POC testing is also applicable in community settings and regions where rapid diagnosis is not readily available [149]. POC testing can be used for SARS-CoV-2 diagnosis in settings such as doctors' rooms, clinics, pharmacies, schools, nursing homes, as well as in drive-through sites managed by different organizations [150,151]. A point-of-care test for acute coronavirus 2 in hospitalized adults is possible, accurate, and improves the duration of outcomes compared with laboratory PCR [152]. This type of testing is associated with advances in the use of infection control methods, patient flow, and patient enrolment in clinical trials. At this juncture, it is important to direct efforts toward personal testing as well as medical care center testing in preparation for the second wave of COVID-19 [153]. WHO has emphasized on rapid point-of-care diagnostics for detection of SARS-CoV-2 as vital strategy in tackling the pandemic [154,155]. The Foundation for Innovative Diagnostics has identified over 90 point-of-care near-patient or mobile diagnostic tests for SARS-CoV-2 detection [156]. However, most of these tests require the handling of samples, which limits their use at the point-of-care. Point-of-care tests decentralizes testing and this strategy helps to reduce the work load of the centralized laboratories, thereby increasing overall testing capacity (Fig. 9.5; [157]). Another important factor in point-of-care diagnostics is their ability to accelerate clinical decision making, thus enabling effective and timely infection and control measures [158]. Conversely, point-of-care diagnostics may still need some extend of sample handling and processing, which impacts their efficiency [159]. The SARS-CoV-2 symptoms are nonspecific and during this scenario of viral detection, a point-of-care (POC) device can be used onsite and within the field, and an added advantage is that these devices do not necessarily require a trained technician to work [2].

In order to circumvent the present time-consuming detection procedures which uses RT-qPCR, an alternate molecular amplification technique should be deployed. The Loop-mediated isothermal amplification (LAMP) reaction may be a novel technique that amplifies DNA with high specificity and speed under isothermal conditions [160]. Specially designed primers



are used in this method and a DNA polymerase is also employed with strand displacement activity to synthesize target DNA up to 10<sup>9</sup> copies in an hour and at a 65°C [161]. The ultimate products are stem-loop DNAs with multiple inverted repeats of the target, bearing structures with a cauliflower-like appearance. LAMP is specific, sensitive, and is straightforward as consequently, it became very popular after its initial development as a pathogen detection tool [162]. The US Food and Drug Administration has also issued an emergency authorization of use for the American company, Cepheid's POC COVID-19 diagnostic device named Xpert Xpress SARS-CoV-2 [163]. The tests detect the virus within 45 minutes, using specimens collected from nasopharyngeal swabs and nasal wash/aspirate. Another POC diagnostic tool, Xpert Xpress SARS-CoV-2 test cartridge is devoted to detecting the virus using RT-qPCR without the use of reagents [164].

With the amount of COVID-19 positive cases and infections rising exponentially, mass public testing is vital for speed detection, identification, and treatment of infected persons. At present, the varied RT-PCR tests and immunoassays present limitations in terms of accessibility and in rapid diagnosis [125,165]. After the patient's samples are collected, transport logistics derail the delivery of samples for analysis. Current turnaround times for standardized tests can take up to 2 weeks [166]. This lack of rapid testing for a large number of infected individuals has been a great limiting factor in halting the virus propagation. POC diagnostic devices can help control the spread of SARS-CoV-2 because they supply a rapid and easy way for broad-spectrum testing in community settings [167]. The design of POC diagnostic tests is in such a way that they can be user friendly without the necessity for a skilled professional. They also do not require complicated facilities and machinery and therefore may be ideal for usage in at-home settings by consumers [168].

Several POC tests have been developed and received Emergency Use Authorization (EUs) to be used under the patient-care settings (Table 9.3). Among these tests is Cepheid's Xpert Xpress SARS-CoV-2 test mentioned earlier, except for use on Cepheid's GeneXpert Xpress System compact and simplified system utilized in physician offices and clinics [169]. The other tests are the Abbott Diagnostic's ID NOW COVID-19 Test, Mesa Biotech's Accula SARS-CoV-2 Test, and the Cue Health's Cue COVID-19 Test [170,171]. The ID NOW COVID-19 test relies on isothermal macromolecule amplification, targeting a singular region of the RNA-dependent RNA polymerase (RdRP) gene of SARS-CoV-2 [172] which has a shorter diagnostic time (19 tests in 13 minutes). The system also has high analytical sensitivity of 125 copies/mL [4,173]. The Mesa Biotech's Accula SARS-CoV-2 Test employs a combinatorial approach of RT-PCR and lateral flow immunoassay and targets the N gene of SARS-CoV-2 from nasal and throat samples [174]. The test is performed on the Accula Dock or Silaris Dock



TABLE 9.3 Emergency Use Authorization (EUA) for use at the point of care (POC).

Product	Manufacturer	Sample type	FDA approval	Type	Target	Reference
Xpert SARSCoV-2	Cepheid (USA)	Nasopharyngeal swab, nasal aspirate	Yes	RT-PCR	SARS-CoV-2 RNA	Qin et al. [235]
VitaPCR COVID-19 assay	Credo (Singapore)	Nasopharyngeal or oropharyngeal swabs	Pending	RT-PCR	SARS-CoV-2 RNA	Lauxmann, Santucci, and A.M.J.I.b.j.u., [236]
RapiPrep COVID-19	Microsens Dx (London)	Sputum or swabs	Yes	LAMP amplification technology	SARS-CoV-2 RNA	Fournier et al. [237]
ePlex SARSCoV-2	GenMark Diagnostics (United States)	Nasopharyngeal swab	Yes	RT-PCR	SARS-CoV-2 RNA	Green et al. [238]
Accula SARSCoV-2	Mesa Biotech (United States)	Throat and nasal swabs (in same collection tube)	Yes	RT-PCR + lateral flow	SARS-CoV-2 RNA	Younes et al. [239]
ID NOW COVID-19	Abbott Diagnostics	Throat, nasal, nasopharyngeal and oropharyngeal swabs	Yes	Isothermal nucleic acid amplification	SARS-CoV-2 RNA	Sidiq et al. [240]
GT-100 SARS- CoV-2 IgG/IgM kit	Goldsite Diagnostic Inc. (China)	Human serum and plasma (20 uL)	Yes	Time- resolved fluorescence immunoassay	IgG/IgM	Fournier et al. [237]
Rapid POC kit	Assay Genie (Acro Biotech, Inc) (Ireland)	Blood, serum and plasma	Yes	Colloidal gold immuno-chromatography	IgG/IgM	Green et al. [238]

(continued on next page)

COVID- 19 IgM- IgG Rapid Test	BioMedomics, BD (United States)	Finger prick/venous blood	Yes	Lateral flow immunoassay	IgG/IgM	Fournier et al. [237]
COVID- 19 Rapid Test Cassette	SureScreen Diagnostics (England)	Finger prick	Yes	Lateral flow immunoassay	IgG/IgM	Harrington et al. [241]
VivaDiag COVID- 19 IgG - IgM test	VivaChek (China)	10uL volume - finger prick / venous blood, plasma or serum	Yes	Colloidal gold immune-chromatography	IgG/IgM	Leightley et al. [242]
BioFire Respiratory Panel 2.1-EZ (RP2.1-EZ)	BioFire Diagnostics, LLC	Nasopharyngeal swab	Yes	RT, Nested multiplex PCR, Multianalyte	SARS-CoV-2 RNA	Cassaniti et al. [243]
Xpert Xpress SARS-CoV-2 test	Cepheid	Nasopharyngeal swab, nasal swab or nasal wash/aspirate	Yes	Real-time RT-PCR, multianalyte	SARS-CoV-2 RNA	Paret et al. [244]
Cobas SARS-CoV-2 & Influenza A/B Nucleic Acid Test for use on the Cobas Liat System	Roche Molecular Systems, Inc.	Nasopharyngeal and nasal swabs and self-collected nasal swabs	Yes	Real-time RT-PCR, Multi-analyte	SARS-CoV-2 RNA	McCormick-Baw et al. [245]
ID NOW COVID-19	Abbott Diagnostics Scarborough, Inc.	Direct nasal, nasopharyngeal or throat swabs	Yes	RT, Isothermal amplification	SARS-CoV-2 RNA	Sidiq et al. [240]
Accula SARS-CoV-2 Test	Mesa Biotech Inc.	n throat swab and nasal swabs	Yes	RT and amplification	SARS-CoV-2 RNA	Hansen et al. [246]
Cue COVID-19 Test	Cue Health Inc.	Nasal swabs	Yes	RT, Isothermal amplification	SARS-CoV-2 RNA	Wong et al. [163]

and is comparatively straightforward to use. The swab from the sample is dipped into a buffer vial and transferred into a test cassette which has all of the reaction reagents [163]. The test cassette sits within the dock for about half-hour, and afterwards results are optically interpreted. The test comprise of the interior positive process control line, the SARS-CoV-2 test line, and therefore the internal negative process control line. The observation of any shade of blue at the SARS-CoV-2 test line indicates a positive result. However, any appearance of blue at the negative process control line indicates an invalid test, and therefore the test must be performed again. Cue Health's Cue COVID-19 Test also uses isothermal amplification on nasal swabs and also targets the N gene of SARS-CoV-2 [163]. Moreover, Cue's disposable POC test cartridge forms a connected diagnostic platform with a mobile device that permits a patient to possess their health status. All 4 tests are quite sensitive and specific however, Abbott and Cue Health's tests both use isothermal amplification and are therefore easier to use, have shorter turnaround times, and consume less power compared to Mesa Biotech and Cepheid's tests that use RT-PCR. From this we can deduce that isothermal amplification may be the preferred detection technique for POC SARS-CoV-2 detection compared to RT-PCR [175]. An advantage of using the RT-PCR based Cepheid's Xpert Xpress Test is that it is the sole diagnostic POC tool that has been approved by the FDA-EUA for usage in patient care settings and can detect both the N2 and E gene of SARS-CoV-2, thus offering a further assurance of accuracy [176]. In the case of Cue Health's test for POC application, it is portable, simple to use, and connect to mobile devices to supply patients' health status at their fingertips [177].

### 9.5.3 AI supported POC diagnostic systems

The management of the COVID-19 pandemic requires an amalgamation of approaches from various fields to ensure rapid, selective, and sensitive diagnosis at its early stages of infection. The application of artificial intelligence (AI) is important for the efficient and smart diagnosis of SARS-CoV-2. There is a huge scope in research for the development of smart sensors employing AI for rapid detection of SARS-CoV-2 proteins at the picomolar level. Due to the nature of COVID-19 infection and transmission, its diagnosis requires point-of-care techniques to eliminate the burden of specialized labs and expert personnel. Researchers have indicated that big data, data banks and vast bioinformatics collection associated with the COVID-19 pandemic are required for effective control of the spread of the pandemic [178,179]. A number of AI-based diagnostic systems have been designed and developed to predict the probability of which population groups or patients can become critically ill [180,181]. The consequences of SARS-CoV-2 are population dynamics related and the usage of smart technology is required to characterize those aspects for accurate prediction,

surveillance, and diagnosis. AI-supported deep learning, machine learning algorithms, and internet of things (IoT) techniques have recently emerged as tool to halt the propagation of SARS-CoV-2 [182]. Wang et al. [105] reported that Taiwan employs such technology at the battlefield to explore big data analysis, new technologies, and proactive testing [183]. This research reported on the identification of pandemic zones, optimization of resources, and understanding of emergency and timely diagnosis decisions. Bai et al. [184] reported that IoT-based methods were very useful to medical personnel to establish the full spectrum of COVID-19 and allowed for intelligent processing and accurate diagnosis [185].

BlueDot, a Canadian company specializing in communicable disease forecasting revealed the importance of AI application toward COVID-19 [184]. Using an AI engine that continuously gathers disease data from various sources globally, the company was ready to predict the COVID-19 outbreak and alert its users even before the WHO did. In Singapore, an AI-powered Chabot (SGDormBot) has been used for the mass screening of COVID-19 symptomatic migrant workers [186]. Another fully automated 3D deep-learning framework developed for the detection of COVID-19 (COVNet) has been designed and developed to extract relevant patient information from 2D and 3D images obtained from a CT scan images in order to differentiate patients with COVID-19 from patients with non-COVID-19 community-acquired pneumonia [187]. The AI-system also identifies COVID-19 features in CT scans of patients with false-negative RT-PCR results [188]. Even with the great prospects of AI to be implemented within the fight against COVID-19, such systems are still at the early stages of development. A drawback to AI algorithms usage is the access needed to massive datasets and this raises ethical considerations regarding the privacy of patients [189]. Efficacy for COVID-19 detection also can be increased by usage of the smart city data network which employs a terminal tracking system and data sharing for better urban management and therefore the location of sporadic occurrences might be predicted [190]. The usage of smartphones for self-screening and surveys can help identify population groups under quarantine [191].

Machine learning algorithms are also important in the processing of COVID-19 patient symptoms [192]. The symptoms are evaluated by asking basic questions from infected patients. Using that information and that from emergency care admission exams, the algorithm is then employed to diagnose covid-19 [193]. An ensemble of machine learning algorithms has been utilized in a variety of works to diagnose the disease. These approaches include logistic regression, Support Vector Machine, Decision Tree, and Random Forest and call all process patient data and diagnose covid-19 cases [194]. Other approaches include K-Nearest Neighbour (KNN), artificial Neural Networks (ANN) and Naive Bayes algorithms and can also be used to diagnose the disease [195]. In the case of smart

devices, they can provide a good platform for developing AI methods for diagnosis. They're widely available, they will collect an excellent deal of knowledge from people from symptoms to behavior and travel patterns, and that they can inform people of any risk they'll face [178]. An AI-based algorithm linked to a mobile App that monitors people's cough has been proposed to spot potential COVID-19 cases [28]. In these devices, an end-to-end portable system supported machine learning records cough data from patients and uses them to coach a classifier for diagnosing the disease.

The application of Deep Learning algorithms is also of great importance in order to accelerate the method of COVID-19 diagnosis. Some of these approaches include Generative Adversarial Networks (GANs), Extreme Learning Machine (ELM), and Long /Short Term Memory (LSTM) [196]. These approaches have the ability to put together a continuum of structured and unstructured data sources. A framework called CovidDeep has also been proposed and employs the usage of DNN with wearable medical sensors for pervasive testing of the virus and therefore the disease [197]. The algorithm functions on the info collected from wearable devices and a few easy-to-answer questions during a questionnaire.

Another machine learning-based method has been proposed to research blood exams as input and find the suspected cases of COVID-19 [198]. Another approach proposed uses white blood cell counts, and therefore the platelets and plasma levels as features for machine learning algorithms to detect COVID-19 infection [199]. In another study, it was found that COVID-19 patients tend to possess higher plasma fibrinogen levels, low platelet counts, and around 25% of patients showing outright thrombocytopenia [200]. This information was then fed to a neural network-powered extraction system for the analysis and diagnosis of COVID-19 infection. Text analytics and processing also allow for the extraction of tons of knowledge around the disease and more text-based algorithms should be developed [201]. In this method, a web questionnaire is developed to gather data about COVID-19 patients [202]. The information is then provided to a predictive machine learning algorithm such as SVM, Logistic Regression, and MLP for the accurate prediction of possible Covid-19 infected persons based on specific descriptors, indications, and symptoms identified.

#### 9.5.4 Nano-based therapies for COVID-19

Recently, broad-based antiviral drugs and conventional dosage forms have been seen to be prone to resistance, and the rise of newer strains poses an even greater danger [203]. Nanotechnology has been recently explored as therapeutic use toward COVID-19 [204]. Within the medical

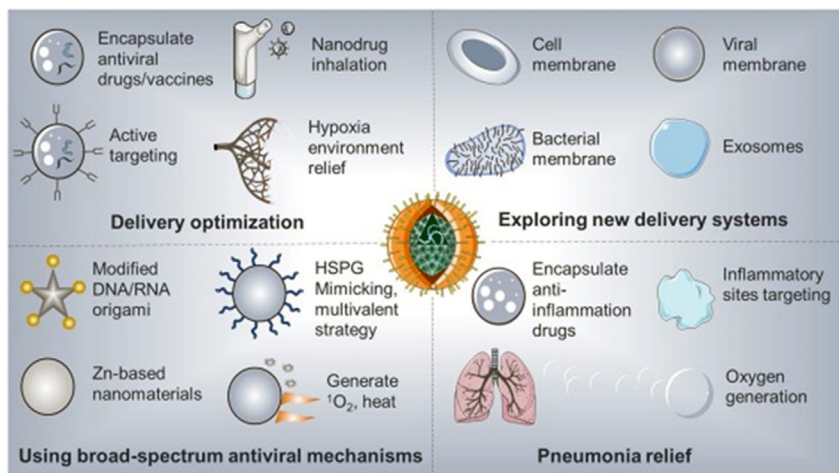


FIGURE 9.6 Application of nanotechnology against COVID-19 (permission granted) [230,212]. Insights from nanotechnology in COVID-19 treatment. *Nanotoday*. 2020;36:101019. doi:10.1016/j.nantod.2020.101019.

field, it incorporates the utilization of nanomaterials for diagnosis, treatment, control, and prevention of diseases [205]. This technology holds great potential as a diagnostic and therapeutic tool for the prevention of COVID-19. Different nano-based approaches could be taken to curb the spread of COVID-19. The design and development of highly specific and sensitive nano-based sensors for quick identification of infection and/or immunological response [206], nano-based vaccination to enhance the immune response [207] and nano-based formulations with targeted delivery antivirals [208,209,[210]] could be the trinity that could assist in the elimination of the disease; the development of nano-based vaccines using differing [211–213]. The application of nanotechnology in combating COVID-19 has marked potential, ranging from delivery optimization, and exploration of novel delivery systems to using broad-spectrum antiviral mechanisms (Fig. 9.6). Two nano-based vaccines have successfully passed phase III clinical trials and one of them has been approved in the United Kingdom, Canada United States of America and the manufacturers are seeking approval in the European Union. Therefore, much research is still required for the optimization of antiviral drugs and vaccines in nanosystems for the prevention of COVID-19 infections.

Similar to other viruses, SARS-CoV-2 requires rapid response testing and operational simplicity. It is quite a difficult task to sanitize surfaces and other inanimate objects all the time, and there's no guarantee that the surface won't be contaminated again. Coating surfaces with virus

active molecules is also a strategy. In this regard, nanotechnology can function as a useful tool for the design and prevention of contamination of the equipment. A study by Jorge et al. (2020) [247] reported that metal-loaded and metal embedded copper nanoparticles in polymer matrices are very effective against viral pathogens and consequently can be employed toward COVID-19 [214]. Furthermore, it has also been reported that the mixture of copper nanoparticles with quaternary ammonium shell that have exhibited potential antiviral activity [215]. Other studies have reported that various metal and metal oxide nanoparticles such as zinc nanoparticles (ZnONPs), cuprous oxide nanoparticles (CuONPs), silver nanoparticles (AgNPs), nanosized copper (I) iodide particles (CuINPs), gold nanoparticles (AuNPs), silica nanoparticles (SiONPs) and quaternary ammonium cations commonly called QUATs are capable of deactivating SARS-CoV-2 [216–218]. Bhattacharjee et al., study showed that graphene oxide grafted metal nanoparticles can be employed to surface coat private protective equipment (PPE) [219] for killing and prevention of viral transmission. Balagna et al., evaluated also studied the antiviral effect of silver nanocluster/silica composite by depositing the on the filtering facepiece-3 (FFP3) facial mask SARS-CoV-2 transmission prevention [220]. The co-sputtering process was employed in depositing silver nanocluster/silica on the PEE thus adding an antiviral surface coat on the face mask due to the antiviral effect of the silver NPs [221]. The study demonstrated that the silver nanocluster/silica coating deposited on the facial mask possessed virucidal activity [222]. Surface-coated copper nanoparticles also can also effectively block the viral infection. Polymer-based copper nanoparticles and other metal nanoparticles are often used as an antiviral coating which may be applied or sprayed on surfaces [222,223]. These nanosystems release metal ions on the coated surface and these ions act as antiviral agents [224]. This coating technique can very well limit the spread of COVID-19 and the metallic ions contained in them have varied properties which makes them ideal candidates to destroy SARS-CoV-2 [225].

It is envisaged that these emerging diagnostic approaches to tackle COVID-19 will bring about new perspectives and overhaul to current dosage forms and treatment regimens. Moreover, more studies are needed to elucidate the SARS-CoV-2 inhibition by nanosystems in order to provide a rational approach in target-based therapy. Undoubtedly, the COVID-19 would need to involve a myriad of novel approaches from different scientific fields in order to probe further on its pathogenesis. The application of Nanotechnology should be the hegemonic strategy of researchers coupled with biosensors and POC systems in order to ease the burden on medical personnel and healthcare facilities. With the combinatorial approaches of biosensors, AI can very well provide rapid communication between hospitals, patients, and the wider community in order to timeously respond to future possibilities of outbreaks.



## 9.6 Future perspectives

COVID-19 a pandemic has affected the global healthcare and economy. Overcoming the pandemic has become a matter of urgency. The design, development, validation, verification, and implementation of diagnostic tests have been rapidly developed by manufacturers and approved by regulatory authorities while several are waiting for clinical approval. This chapter has summarized the important biomarkers for the detection and classification of the COVID-19 disease. Standard systems being employed for detection of COVID-19 have successfully assisted in early detection control of the disease have also been discussed. However, their disadvantages such as longer time taken for detection vs. the rapid spread of the disease, lack of sensitivity and universal tests for different strains of the virus have resulted to the need of better alternatives. Due to the dire need for faster, reliable, and sensitive diagnostic systems which are being developed with the aid of nanotechnology. Systems such as point of care diagnostics for personalized health and artificial intelligence-based systems are revolutionizing the detection of COVID-19. The designs of nanotherapeutics that are target specific, effective, and safe to treat COVID-19 are also required. The development of novel nanomedicines that target the virus are showing potential to be potent, effective and at the same time they could overcome possible SARS-CoV-2 resistance. Nanotechnology has provided the two effective vaccines against the virus that have been approved in some markets. This indicates the coming of age of nanomedicine. However, as the advancement of nanotechnology continues there is also a need for continuous global improvement in diagnostic tests and nanotherapeutics that provide rapid detection and treatment of patients, possibly at the point of care. Moreover, these diagnostic tests and treatment options need to be developed so that they can be sensitive and cost-effective and can be applied in both industrialized and resource-limited countries.

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### Conflict of interest

Authors declare no conflict of interest.

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## Non-Print Items

### Abstract

Unique pneumonia due to an unknown source emerged in December 2019 in the city of Wuhan, China. Consequently, the World Health Organization (WHO) declared this condition as a new coronavirus disease-19 also known as COVID-19 on February 11, 2020, which on March 13, 2020 was declared as a pandemic. The virus that causes COVID-19 was found to have a similar genome (80% similarity) with the previously known acute respiratory syndrome also known as SARS-CoV. The novel virus was later named Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 falls in the family of *Coronaviridae* which is further divided into *Nidovirales* and another subfamily called *Orthocoronavirinae*. The four generations of the coronaviruses belongs to the *Orthocoronavirinae* family that consists of alpha, beta, gamma and delta coronavirus which are denoted as  $\alpha$ -CoV,  $\beta$ -CoV,  $\gamma$ -CoV,  $\delta$ -CoV respectively. The  $\alpha$ -CoV and  $\beta$ -CoVs are mainly known to infect mammals whereas  $\gamma$ -CoV and  $\delta$ -CoV are generally found in birds. The  $\beta$ -CoVs also comprise of SARS-CoV and also include another virus that was found in the Middle East called the Middle East respiratory syndrome virus (MERS-CoV) and the cause of current pandemic SARS-CoV-2. These viruses initially cause the development of pneumonia in the patients and further development of a severe case of acute respiratory distress syndrome (ARDS) and other related symptoms that can be fatal leading to death.

### Keywords

COVID-19; ARDS; SARS-CoV-2; Biomarkers; C-reactive protein; Diagnosis