Chapter

Current Status of COVID-19 Diagnostics

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Abstract

In December 2019, an unexpected outbreak was caused by novel corona virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The lung disease caused by SARS-CoV-2 was given the name of the novel coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) on February 11, 2020. Since its origin in the Hubei province of Wuhan city in China, now it has spread to 218 countries worldwide. Panic situation created by COVID-19 has compelled researchers and doctors to work collaboratively. To combat with the disease, every control measures are under consideration from drug discovery to vaccine development. In the management of disease, rapid diagnosis is equally important as development of vaccine and drug. At present, various diagnostic kits are available for COVID-19. With the disease progression, global demand for diagnostics is raising. So, this chapter will include the updates on efficient diagnostic assays and future of diagnostic.

Keywords: novel corona virus, COVID-19, SARS-CoV-2, diagnosis, COVID-19 management

1. Introduction

COVID-19 is now a global health emergency as the number of confirmed COVID-19 cases worldwide exceeds 75 million, while the number of global deaths exceeds 1 million. WHO has already declared COVID-19 as a public health emergency of international concern (PHEIC) on January 30, 2020 and a pandemic on March 11, 2020. New COVID-19 cases and deaths are continuously rising. Globally, there have been 106,797,721 confirmed cases and 2,341,145 deaths as per a WHO report on February 11, 2021, since the pandemic started [1, 2]. At the start of pandemic, the regions of the America and Europe were affected badly, contributed 85% of new cases and 86% of new deaths globally. The USA and India are top two countries with more than 10 million confirmed cases and 313,748 and 145,810 deaths, respectively [3]. The infection starts to spread from the seafood wholesale market in Wuhan, China, while the exact origin of the first case remains unclear. Initially, COVID-19 spread, from china to other countries, was due to travelers who got infected in China and then moved outside of the China [4]. Countries who have reported travel-associated spread were Singapore, Japan, Republic of Korea, Malaysia, Vietnam, Australia, the United States of America, Germany, etc. [4, 5]. Current, corona virus outbreak is third after the SARS and MERS corona virus outbreaks. SARS-CoV-2 virus evolved in such a manner that the spread of COVID-19 is more severe than that of the previous severe acute respiratory syndrome (SARS)

and the middle east respiratory syndrome (MERS) [6]. Currently, the COVID-19 pandemic has reached to a threatening new phase. New strains from UK with more infectivity are being reported. SARS-CoV-2 belongs to family *Coronaviridae* and order *Nidovirales*. SARS-CoV-2 stands together with two highly pathogenic viruses, SARS-CoV and MERS-CoV as belongs to Betacoronavirus genera [7]. Corona viruses are enveloped, positive-sense, single-stranded RNA viruses. Transmission of SARS-CoV-2 was initiated first from infected animals to humans and then spread rapidly throughout the world via human to human. It spreads via contact to respiratory droplets or aerosols through nosocomial transmission from an infected to uninfected [8]. As COVID-19 causes enormous human casualties and serious economic loss, we are in the urgent need of efficient vaccine and drug development against this dreadful virus. Globally, various serious efforts are being made in this direction. Governments of many countries have taken immediate action and precautionary measures against the virus. Countrywide lockdown were imposed to minimize human contact at public places. Social distancing, hygiene, and self-quarantine limit social interactions and spread of the disease. To control and manage the present pandemic situation the entire world is working and taking necessary steps. To propagate research in this field, governments are providing enough funds for scientists and institutions. To combat with the disease, both preventive and curative approach is considered. We have many potential vaccine candidates that are yet to be approved. Recently in mid November, four groups have reported about the efficacy of their vaccines. Vaccination has been started in many countries like USA, India. Pfizer-BioNTech COVID-19 vaccine and Moderna's COVID-19 vaccine have been approved by FDA recently [9].

To cure the infected patient, several drugs are being tested and used. Drugs that are currently in clinical trials are repurposed drugs, which were designed for other disease including antiviral and antimalarials [10–13]. Other natural product-based formulations are also tested in the management of the disease, for example, Indian giloy (*Tinospora cordifolia*) and ashwagandha [14, 15]. Because of continued spread of COVID-19, accurate diagnosis of people becomes necessary. Rapid screening of an infected person before transmission onto others is essential to curb the disease. Delay and inaccurate diagnosis will give patient a chance to spread the virus. Present pandemic has enforced researchers to work at breakneck speed. As a major contribution toward diagnostic of COVID-19, various detection methods have been developed. Primarily we have molecular-based approaches to confirm suspected cases. Real-time reverse transcription-polymerase chain reaction (RT-PCR)-based testing is the main technique for laboratory diagnosis. Virus antigen- or serological antibody-based assays are also available with the advantage of a short turnaround time for the detection of novel corona virus infection. In this chapter, we will discuss and review the available COVID-19 detection methods and future prospectus of the same.

2. Disease biology

SARS-CoV-2 is a novel corona virus. It is spherical and enveloped. SARS-CoV-2 spans 50–200 nM in diameter. It also contains a typical crown like appearance of coronaviruses due to the presence of 20 nM long spikes like structure on its surface (**Figure 1**). Corona viruses are divided into four genera: alpha-coronavirus (α-CoV), betacoronavirus (β-CoV), gamma-coronavirus (γ-CoV), and delta-coronavirus (δ-CoV). SARS-CoV-2 belongs to β-CoV genera. SARS-CoV-2 is a positive-sense, single-stranded RNA virus with large 29 Kb genome size [16, 17]. Genome wide study demonstrates that SARS-CoV-2 has sequence similarity with the human and bat corona viruses with 82% and 89% sequence homology, respectively [18]. Protein

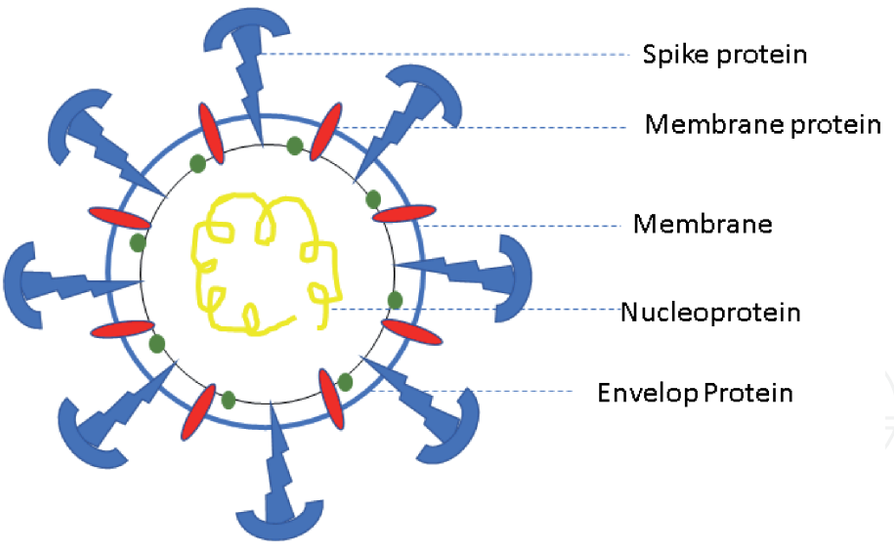

Figure 1.
Schematic diagram showing SARS-CoV-2 structure.

mapping reveals the common protein interaction networks among three CoVs (SARS-CoV-1, MERS-CoV, and SARS-CoV-2) in humans, hence identified molecular mechanisms and potential therapeutic interventions [19]. Genome organization includes sequences for leader region, UTRs, replicase, Spike, Envelope, Membrane, Nucleocapsid protein, 3′UTR, and poly (A) tail sequence [20]. The spike (S), membrane (M), envelope (E), and nucleocapsid (N) are the main four structural proteins of SARS-CoV-2 (**Figure 2**). Spike protein is a club-shaped protein present on the surface of virus and also capable of inducing neutralizing antibodies. It plays a major role in pathogenesis of SARS-CoV-2. M protein is the conserved and abundant protein, which helps virus to maintain its shape. It is also important during budding of viral particles from host cells. Role of E protein is important in viral pathogenesis. Like M protein, E is also a conserved one. Spike, E, and M together form the envelope of SARS-CoV-2. Viral RNA and N protein construct the nucleocapsid of virus [21, 22]. SARS-CoV-2 infects the upper respiratory tract in humans and cause common cold and flu-like infections. Patients suffer from influenza, sore throat, fever, cough, fatigue, and shortness of breath; in few cases, patients also experience gastrointestinal issues, such as diarrhea and vomiting. Severity leads to multiorgan failure and thus causes death [23, 24]. Old age people and individuals suffering from diabetes, hypertension, pulmonary disease, asthma, bronchitis, and cardiovascular disorders are at high risk of severe case of corona disease [24]. It has been reported that bats are the natural reservoir of SARS-CoV-2 like for other human CoVs. SARS-CoV-2 was initially transmitted to humans from infected

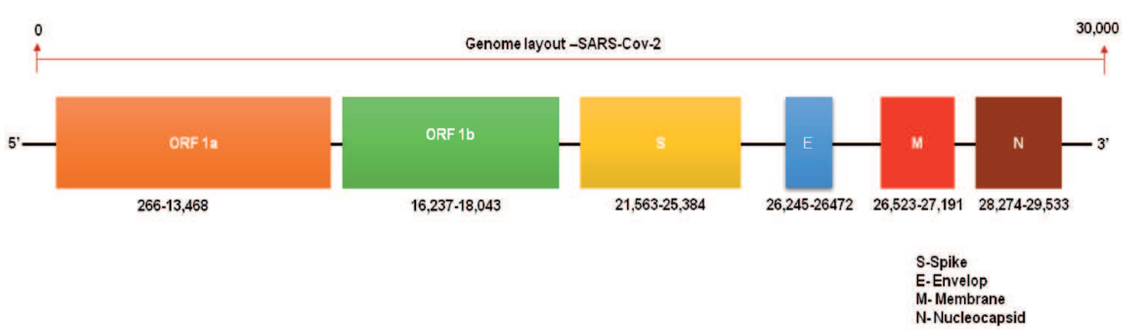

Figure 2.
Genome organization of SARS-CoV-2.

animals in the Wuhan market and then spread globally when human-to-human contact occurs via respiratory droplets or aerosols of infected [16].

At molecular level, when the receptor binding domain of spike protein interacts with human-ACE2 (angiotensin-converting enzyme 2) receptor, it facilitates the binding and subsequent entry of viral particles into host cells. The spike is a heavily glycosylated protein and made up of two subunits, the S1 and the S2. The S1 subunit is again divided into two domains, that is, an N-terminal (S1 NTP) and a C-terminal domain (S1 CTP). RBD is present in C terminal S1 CTP. The RBD shows genomic variability. RBD determines the cellular tropism and host range to be infected by virus [25–27]. Different strains of Corona viruses have variation in binding affinity or human ACE2, thus differ in infection ability, transmission rate, and pathogenicity. In comparison to SARS-CoV (~31 nM) and MERS-CoV (~16.7 nM), SARS-CoV-2 binding affinity (~4.7 nM) is very high [28].

3. Available diagnostic assays

The severity of the disease varies in diagnosed patients ranging from asymptomatic or mild cases to severe cases. The former can be cured by supportive care but the latter depends upon extracorporeal membrane oxygenation. Once patients reached to symptomatic stage, they become contagious and start to shed and spread the virus. Mass screening and accessible diagnostics always play a vital role to constrain the transmission and spread of the virus thus in reduction of mortality rate. Proper infection tracing is needed in the assessment of overall health impacts and statistics. Till now, there are various strategies for diagnosing COVID-19, which are mainly based on viral nucleic acid or antigen detection, and detection of the host's immunological responses. Description about the available test is below:

3.1 Molecular test

Till now, confirmatory diagnosis for COVID-19 is based on molecular approaches only. These are considered to be first-line methods. Nucleic acid testing based on real-time reverse transcription-polymerase chain reaction (RT-PCR) is the main technique for laboratory diagnosis. It involves nucleic acid amplification test to detect unique sequences within SARS-CoV-2 genome. RT-PCR is a two step process. In the first step, viral RNA is converted to cDNA using a reverse transcriptase enzyme, and the second step involves the amplification of only the selected region using gene-specific primers and further quantification is carried out as fluorescently labeled hydrolysis probe produces fluorescent signals [29]. Since the release of entire genome sequence of the virus from scientists of China, many countries, such as England, Germany, South Korea, Turkey, Russia, the USA, India, and China, launched their clinical-grade RT-PCR kits for SARS-CoV-2 detection. For RT-PCR kits, samples are taken from various infected parts of the body, including nasopharyngeal, oropharyngeal, or nasal swabs, upper and lower respiratory tract aspirates, bronchoalveolar lavage, and the sputum [30]. Main components in RT-PCR-based Kits are the reverse transcription and amplification enzymes, specific primers and probes for amplification of the selected viral genome regions, and authorized reagents for negative, positive, and internal controls, target genes, corresponding primer, and probe sequences used in RT-PCR kits so far for SARS-CoV-2 detection. Various research groups have been proposed the use of different set of target genes, corresponding primer, and probe sequences. Generally, the commercial kits based on the RT-PCR are only operated in well-equipped laboratory conditions and require skilled persons [31]. Pixel by

LabCorp COVID-19 Test Home Collection Kit made home collection possible. It contains a specimen biohazard bag, pre-labeled return FedEx envelope, saline tube, insulated specimen pouch, nasal specimen collection, swab gel pack (for sample cooling), shipping box, and the user guideline [32].

Other molecular-based technologies like LAMP, RT-LAMP, and rRT-LAMP amplify nucleic acid isothermally without any use of a thermocycler. DNA polymerase along with multiple primers, six or four as inner and outer primers, is used to amplify the target sequence. In RT-LAMP, analysis of results is done by the change of color, fluorescence, or turbidity in the PCR tubes, which makes it a simple and practical technique. Use of multiple primers gives specificity in results. RT-LAMP is a fast and specific method which completes detection of SARS-CoV-2 in 1–2 h without any need of a trained molecular biologist [33].

Another isothermal nucleic acid amplification based assay is SHERLOCK assay, which also employs the clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated system (Cas) enzymology for the detection of the target nucleic acid. Upon the binding of CRISPR RNA to the target sequence, the nonspecific endonuclease activity of Cas13 or Cas12 starts, leading to the cleavage of nearby reporter RNAs which generates signal for detection. SHERLOCK is a very specific and sensitive assay for diagnosis as Cas13 does not get activated if two or more mismatches are present in the target RNA, and it can easily discriminate between SARS-CoV-2 and other similar viruses [34].

Advantages:

- RT-PCR is the gold standard for SARS-CoV-2 because it can directly measure the viral genomic parts.
- It is most reliable method for SARS-CoV-2 detection.

Disadvantages:

- It is a tedious, time-consuming protocol.
- When infection of the virus starts to move toward the lower respiratory track, sample collected from throat may give us false negative results.
- It requires laboratories with biosafety level II facility so not suitable for rapid testing.
- Limited number of assay can be performed.
- Sensitivity is low at early stage of infection.
- It can detect the active infection in a patient, not the recovered.

3.2 Antibody test

In an antibody test, existence and concentration of IgG and IgM antibodies is measured in the blood/serum/plasma samples of infected patients. It can determine if the body encounters with a pathogen like SARS-CoV-2 virus. Common antibody tests are based on lateral flow type assays (LFA) and enzyme-linked immunosorbent type assays (ELISA) [35]. An antibody LFA test detects the presence of the specific antibodies in the patient's blood sample. A SARS-CoV-2 antigen(s) is already immobilized on a sample pad. The sample is loaded onto the sample pad at end port

where Colloidal gold (CG) or quantum dot (QD)-labeled detection antibodies are present. Sample along with labeled antibodies moves through the strip by capillary action to the test line and control line [36]. If SARS-CoV-2 antibodies are present in the sample, they will be captured by the labeled detection antibody and will bind to the immobilized antigen at test line. Even if the SARS-CoV-2 antibodies are absent in the sample, the gold-labeled antibodies will still be captured at the control line and a band on the strip will appear due to the accumulation of CG or QD.

ELISA tests are performed in multi-well plates coated with the recombinant viral antigen. If antibodies (IgG or IgM) against the SARS-CoV-2 antigen are present in the sample, a binding between coated antigen and SARS-CoV-2 antibodies occurs. Then, secondary anti-human antibodies are added to bind with SARS-CoV-2 Ag-Ab complex. Secondary antibodies are enzyme labeled (usually horseradish peroxidase). Upon addition of an enzyme substrate, a color-changing reaction happens. In the absence of the antibody of interest, no color is generated. In a modified version of ELISA, that is, chemiluminescent immunoassays (CLIA), the binding of the secondary antibody is confirmed by a chemiluminescent substrate [37]. ELISA test is a multistep process that demands a well-equipped lab, but LFA can be used at home without any training [38, 39].

3.3 Antigen test

An antigen is a non-self particle/fragment/molecule that can induce the immune system to produce antibody against pathogens, hence protects the body. The antigen test is also an immunoassay which detects viral components (i.e., S glycoprotein, M protein, or released N protein) or directly virus. Unlike the antibody-based methods, antigen tests detect the active viral infection, not the recovery situation. Because antigens precede antibodies, antigen test could be more reliable than antibody tests. Antigen tests can also be operated on LFA strips for rapid detection or in ELISA plates for increased sensitivity, and high throughput uses [29, 40].

Advantages:

- Antigen tests completes in 15–20 minutes.
- Antigen tests do not require well-equipped labs and highly trained personnel.
- It is cost-effective for both mass screening and application.
- Specificity is higher as it detects direct viral antigen.

Disadvantages:

- Low sensitivity as it requires high level of viral load for testing.

3.4 Other methods

Several other methods for diagnosis have been proposed. Some of them are novel and at research stage and some are based on conventional technology, for example, computed tomography (CT) scans. Aptamers functionalized with quantum dots (Qds), paper-based assays, semiconductor-based binding assays, surface plasmon resonance-based assays, piezoelectric immune sensors, and electrochemical sensors have been developed. A CT scan reveals about the possible abnormalities due to the viral infection in the chest [41]. Other detection

Method	Developer company	References
RT-PCR	Viractor Erofins	[46]
RT-PCR	Bosch	[47]
RT-LAMP	Abbott Laboratories	[48]
SHERLOCK	Howard Hughes Medical Institute	[34]
CMIA	Abbott Laboratories	[49]
Lateral flow assay	Pharmact AG	[50]
Lateral flow assay	ChemBioDiagnostic Systems	[51]
ELISA	Bio-Rad	[52]
Antigen test N protein LFA	Quidel Corporation	[53]

Table 1.
Developed kits for COVID-19 diagnosis.

technologies developed for the identification of SARS-CoV-2 are based on the presence of different biomarkers in bio-fluids. Increased concentrations of C-reactive protein, D-dimer, lymphocytes, leukocytes, and blood platelets and elevated levels of serum urea, creatinine, and cystatin C can be utilized for diagnosis. Biosensors based on plasmonic sensing and field effect transistor (FET) have been developed for mass screening. Localized surface plasmon resonance (LSPR) sensor detects the SARS-CoV-2 nucleic acid with combined use of photo-thermal effect and plasmon sensing [42]. In FET-based biosensors, biological molecules modify the charge distribution of the surface, or they generate a surface potential by binding to the surface, which is further measured as a conductance value [43]. For mass screening of such pandemic, we need a global e-platform to control the spread of the virus which is now possible with emergence of data science and advancement in mobile telecommunications. In this view, mHealth is a useful development, which is an application of mobile devices like smarphones, onboard optics/sensor based patient monitoring devices, and wireless/Bluetooth technology. Such advancements lead to easy collection of large epidemiological data based on contact tracing, automation of inventory mangement, digital, and fast reporting of the new cases. It can also help further in supply chain management of limited resources for affected areas and also help government in policy making [44]. Indian government has also launched "Aarogya setu" app during COVID-19 pandemic [45]. Information about some of the COVID-19 diagnostic kits based on above discussed methods are listed in **Table 1**.

4. Future of diagnostic and conclusion

COVID-19 has emerged as the most severe and terrifying viral infection encountered by us. Considering present pandemic situation, researchers from all around the globe have put strenuous efforts to develop test for COVID-19 diagnosis. They aim to develop a test that shows fast and accurate results, without compromising on the sensitivity and selectivity of the assay. Although present vaccine regime against COVID-19 has lessen the burden on health sector still, we are not aware of the long-term effects of COVID-19. Early medical interventions are only possible if diagnosis of the diseases is done at earlier stages. Many diagnostic tests have been developed which differ from sensitivity to specificity. Every test has disadvantages and advantages over the other methods (**Figure 3**).

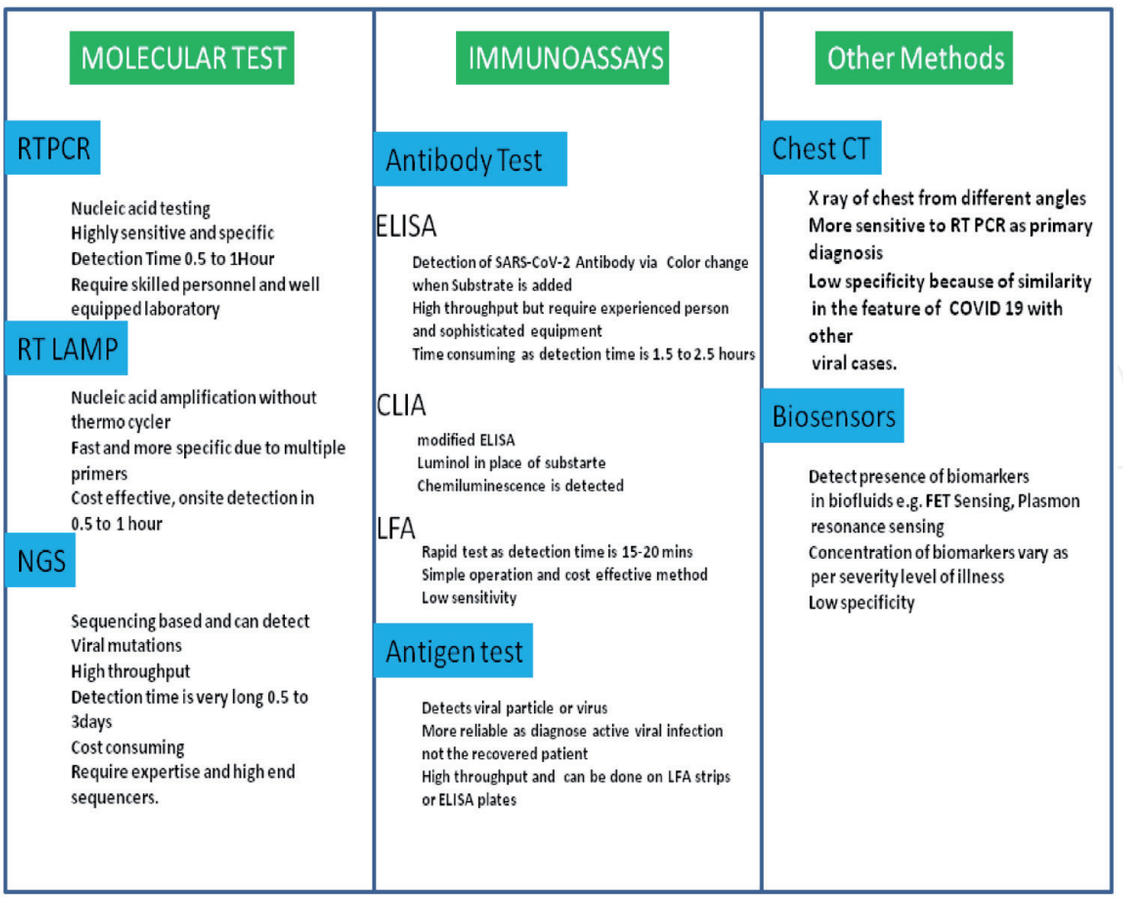

Figure 3.
Comparison of different COVID-19 diagnostic assay.

The genome-based detection of SARS-CoV-2 is solely relied on the RT-PCR method. Existing RT-PCR-based assays are not sensitive enough to detect the COVID-19 in the early stages of infection. Serology tests are rapid and apt for vast screening but they cannot confirm the presence of the active infection. Antigen-based test are also very promising but need development. Despite the excellent effort put by researchers globally, we are still in the need of developing an assay which can detect the SARS-CoV-2 in individuals at the initial stage. For this purpose, early stage biomarkers of COVID-19 should be identified and utilized for development of new assays. In severe conditions, CT scan can be used as complementary diagnostic tool along with RT-PCR [54]. It is reported that physicians took help of CT SCAN to effectively detect COVID-19 infection in RT-PCR false-negative cases. Antigen tests can also be performed along with RT-PCR to support present diagnostics and accelerate the detection speed worldwide. Different manufacturers and laboratories are using various parameters and conditions for testing. We do not have any universal standard for testing. Specimen and collection time needs to be optimized. Such standardization will give consistency in test results [55]. More effort toward research is required for further understanding of the influence of diagnostics. There is still scope in exploring about SARS-CoV-2 virus biology and COVID-19 pathology. Understanding of virus will help in developing more accurate diagnostic and effective treatment. Further research is required in the field of COVID-19 diagnostics to develop a rapid and automated diagnostic test with more sensitivity and specificity. In light of this, the government of India has also announced the call for various research projects for funding. In this direction public, clinicians, industries, and government all should work in coordination to fight against SARS-CoV-2. Global coordination between them is in high demand.

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Conflict of interest

The authors declare no conflict of interest.

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