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Chapter 3

# Biomarkers, tools, and test kits for COVID-19

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## Chapter outline



## 3.1 Introduction

Toward the end of 2019, all of a sudden, the city of Wuhan in Hubei Province belonging to China became the epicenter of unaccountable cases of pneumonia. At the outset of 2020, Chinese scientists found the cause of the severe pneumonia and reported the causative organism as a novel coronavirus, transiently known as severe acute respiratory syndrome coronavirus 2 abbreviated as SARS-CoV-2. The World Health Organization (WHO) modified its name as coronavirus disease 2019 (COVID-19) in February 2020 as the disease spread across the entire globe. Since its diagnosis in China, it has spread to each and every part of the world rapidly. SARS-CoV-2 is reported to be the

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seventh human coronavirus and found to be the highest pathogen to human being in the history of infectious diseases [1].

SARS-CoV-2 is reported to be easily transmitted from human to human. Based on recent hypothesis, the first case of transmission started among bats, although the intermediate host from bats to human is yet to be investigated. A person infected with SARS-CoV-2 may infect approximately three new persons as reported. The common symptoms of COVID-19 are fever, cough, sore throat, and fatigue, but the others may have variable symptoms whereas some hosts may be asymptomatic. Generally, the symptoms of COVID-19 are found to be similar to that of the common cold or flu or influenza. The common mode of transmission of the novel coronavirus at this stage is reported to be through direct contact or droplet infection by coughing or sneezing [2]. The National Institute of Health recently reported that novel coronavirus can stabilize for days on plastic and stainless steel and even last up to an entire day on cupboard.

Currently, there is neither effective therapy nor promising preventive measure available for COVID-19, but scientists of different countries have been investigating a plethora of drugs and vaccines that may be repurposed to fight COVID-19 pandemic. However, currently, there is no drug or vaccine fully approved by the United States Food and Drug Administration (US-FDA) for treatment of COVID-19 disease caused by novel coronavirus [3]. Proper diagnostics can play a very crucial role breaking the contamination chain of COVID-19. The diagnostics can enable the quick implementation of control measures that minimize the spread through case identification, isolation, and contact tracing, i.e., identifying the person that may have come in contact with an infected one. The present diagnostic system for COVID-19 is portrayed in Fig. 3.1. The current episode plans to explore the ongoing known diagnostic kits, tools, and biomarkers for detecting SARS-CoV-2, emerging diagnostics, and surveillance technology to curb the spread.

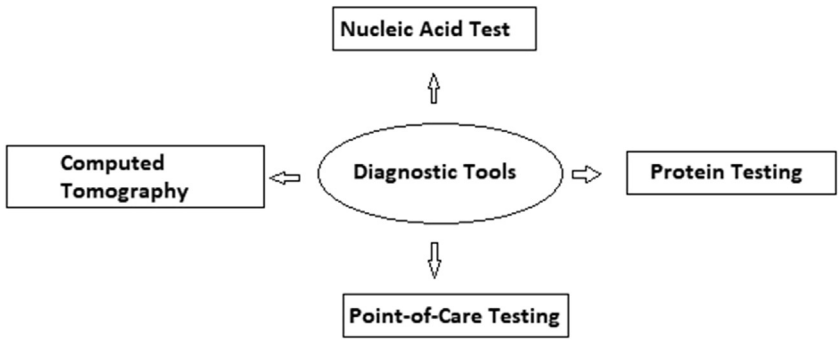


**FIGURE 3.1** Diagnostics based on different technologies.

## 3.2 Biomarker

High-risk patients related to COVID-19 disease progression can be easily stratified by using suitable and reliable biomarkers. Hence, scientists are making frantic efforts in order to find reliable biomarkers. To slowdown the progression of this pandemic, it is necessary to categorize the patients into high-risk groups. Novel biomarkers are needed to identify the high-risk groups with chances of rapid disease progression to severe consequences, even death. Testimony of innovative biomarkers is stringently associated with deep perceiving of viral pathogenetic mechanisms and damage of cells and organs. Effective biomarkers would be of paramount importance for initial screening, effective clinical management, and prevention of serious complications. Preliminary investigation indicates vasculitis processes underlying organ damage in seriously ill patients, induced by the activation of inflammatory cascades, complement activation, and proinflammatory cytokines, i.e., interleukin-6 [4]. Vasculitic damage leads to edema and severe respiratory acute syndrome in the lung and cardiovascular damage and also cerebral injuries. Currently, the available biomarker, i.e., D-dimers or prothrombin time/activated partial thromboplastin time, is not able to predict the severity of cardiovascular damage. The identification of patients at risk of fatal complications is required to estimate IL-6, D-dimer, lactate dehydrogenase (LDH), and transaminases along with routine laboratory test as suggested by current clinical practice.

It is observed epidemiologically that cardiovascular damage causes problem in the mortality of COVID-19 patients. However, as costly, cytokine analysis is not routinely performed in most laboratories; surrogate markers of infection (ferritin, C-reactive protein [CRP]) correlated to IL-6 will be of increasing interest for prognostic value. Beyond D-dimer, prothrombin time, and fibrin degradation product [5], there are no specific predictive parameters of severe ischemic and thromboembolic disease. For this reason, it is not easy to cluster patients in risk categories for an appropriate early anticoagulant or fibrinolytic therapy. The positive cases of COVID-19 are classified into mild, severe, and critical cases on the basis of prevailing diagnosis and treatment program 2019 [6]. Some hematological parameters, including white blood cell, lymphopenia, CRP, and some biochemical parameters, such as LDH, creatine kinase, and troponin, were reported to be associated with COVID-19 severity [7]. Based on the prevailing research statistics, homocysteine (Hcy), age, MLR (monocyte−lymphocyte ratio), and time from appearance of symptoms to hospitalization were found to be the key indicators as observed by computed tomography (CT) scan in the course of first week of COVID-19 infection without involving other organs.

## 3.3 Current diagnostic tools for COVID-19

The symptoms of COVID-19 patients are variable and also in some cases remain as asymptomatic; hence they cannot be a benchmark of diagnosis.

According to statistical data presented by Guan et al. [8], out of total 1099 COVID-19 patients from China, 44% of patients had fever at the time of admission to hospital and 89% of patients acquired fever during treatment in hospital. Their report also revealed that about 68% of patients suffered from cough, 38% of patients felt fatigue, 34% of patients produced sputum, and 19% of patients had shortness of breath. The symptoms of novel coronavirus presented above were found to be almost similar to any other diseases of respiratory tract. Emerging diagnostic techniques currently being used for novel coronavirus are portrayed in Table 3.1.

### 3.3.1 Nucleic acid testing

Developing nucleic acid test for detecting SARS-CoV-2 virus is the fundamental method of diagnosing COVID-19. Genetically, a huge number of reverse transcription polymerase chain reaction (RT-PCR) kits have been designed for the detection of SARS-CoV-2. RT-PCR is a laboratory technique which involves reverse transcription of SARS-CoV-2 RNA into complementary DNA (cDNA); and then the specific region of cDNA is amplified. It consists of basically two steps: the first step involves the alignment of the viral genome sequence and design of primer, while the second step involves the optimization of the assay as well as testing. In order to develop a set of primers and probes, Corman et al. [10] reported that they had aligned and analyzed a number of SARS-related viral genome sequences. They revealed the three regions that had hoarded sequences of SARS-related viral genomes: (1) RNA-dependent RNA polymerase gene (RdRP gene) in the open reading frame ORF1ab region, (2) the envelope protein gene (E gene), and (3) the nucleocapsid protein gene (N gene). The technical limits for analytical sensitivity of RdRP and E genes are 3.6 and 3.9 copies per reaction, respectively, whereas the N gene possessed analytical sensitivity of 8.3 copies per reaction [9]. Two-target system-based assay can be accomplished in which one primer cosmically identifies numerous coronaviruses including COVID-19 virus, i.e., SARS-CoV-2, and a second primer set exclusively detects SARS-CoV-2. Designing the primers and probes, followed by the optimization of assay conditions, i.e., reagent conditions, incubation times, and temperatures, is again followed by PCR testing; RT-PCR can be executed in either single-step or double-step assay. In a single-step assay, reverse transcription and amplification of PCR are developed into single reaction. This assay can provide rapid and reproducible results for high-throughput analysis.

### 3.3.2 Computed tomography

The Hubei Province, China, the source of COVID-19, used CT scans temporarily instead of RT-PCR for clinical diagnosis of COVID-19 due to scarcity of kits and false-negative results. CT scans are noninvasive and

**TABLE 3.1** Emerging diagnostic techniques currently being used for novel coronavirus [9].

| Sl. No. | Techniques | Biomarkers | Technology | Working principle | Sample type |
|---|---|---|---|---|---|
| 1. | CRISPR | Nucleic acid | RPA | The sequences of CRISPR "spacer" are reproduced into short sequences of RNA, capable of guiding the system to matching sequences of DNA. On getting the targeted DNA, the enzyme produced from CRISPR system, i.e., cas9, ties to DNA followed by cutting and blocked off the gene | Serum |
| 2. | CRISPR | Nucleic acid | RT-RPA | RPA, SHERLOCK multiplexed signal detection via fluorescence | Nasopharyngeal swabs |
| 3. | LAMP | Nucleic acid | LAMP | Isothermal DNA synthesis using self-recurring strand displacement reactions; positive detection leads to increased sample turbidity | Throat swabs |
| 4. | RPA | Nucleic acid | RPA | Forward and reverse primars blind to DNA and amplify strands at 37°C | Fecal and nasal swabs |
| 5. | RCA | Nucleic acid | RCA | DNA polymerase used to extend a circular primer and repeatedly replicate the sequence | Serum |
| 6. | RT-LAMP | Nucleic acid | LAMP | RT-LAMP reaction for RNA targets | Nasopharyngeal aspirates |
| 7. | Magnetic bead | Nucleic acid | Magnetic | Magnetic beads isolate bacteria for PCR detection | Stool |
| 8. | Paramagnetic bead | Protein | Magnetic biosensor | Magnetic separation of protein targets | Serum |
| 9. | ELISA | Protein | ELISA | Enzymatic reaction to produce colored product in presence of target | Serum |
| 10. | Rapid antigen test | Protein | Lateral flow | Gold-coated antibodies produce colorimetric signal on paper in presence of target | Serum |

painless tests. It involves taking many X-ray measurements at different angles across a patient's chest to produce cross-sectional images. It implicates to invent cross-sectional icons by hauling many X-ray measurements at different angles across a patient's chest. The images are subjected to analysis by radiologists to investigate any abnormalities for proper diagnosis.

The imaging characteristics of COVID-19 are distinct. They deduce on the phase of flu following onset of action. The CT scan findings of Bemheim et al. [11] revealed that the imagings were quite normal within 0−2 days of onset of symptoms, but after 10 days maximum lung involvement occurred. The CT scan findings of Bernheim et al. [11] revealed that the imagings are quite normal within 0−2 days followed by ultimate crisis of lungs showing highest on 10 days after appearance of first symptoms. The most common indications of COVID-19 include bilateral and areas of hazy opacities as well as fluid or solid material in compressible lung tissue. Pan et al. [12] reported that after 0−4 days of onset of action, the ground-glass opacities become most prominent and with the progress of COVID-19 infection, in addition to ground-glass opacities, irregular-shaped paved stone pattern develops, followed by increasing coalition of the lungs. Based on these imaging features, several recollective investigations revealed that CT scans have a higher sensitivity (86−98%) and improved false negative rates compared to RT-PCR. The main drawback of using CT for COVID-19 is that the specificity is low (25%) because the imaging features overlap with other viral pneumonia. COVID-19 is currently diagnosed with RT-PCR and has been screened for with CT scans.

### 3.3.3 Antigen−antibody testing

COVID-19 can be diagnosed by using viral protein antigens as well as antibodies that are developed with regards to a SARS-CoV-2 infection. It is difficult to detect viral proteins as the viral load changes with progression of infection. Lung et al. [13] reported that salivary viral loads are high at the appearance of first symptom which gradually decreases with time. On the other hand, antibodies produced in response to viral proteins may offer better chance for detecting SARS-CoV-2 indirectly. Antibody tests can be particularly useful for detection of COVID-19. One of the major challenges with developing accurate serological tests is the potential cross-reactivity of SARS-CoV-2 antibodies with antibodies produced against other coronaviruses. Lv et al. [14] reported that there is a high rate of cross-reactivity by testing plasma samples from 15 COVID-19 patients against the S protein of SARS-CoV-2 and SARS-CoV. Currently, serological tests are under development. Zhang et al. [15] assayed immunoglobulin G and M, i.e., IgG and IgM, from human serum of COVID-19 patients using enzyme-linked immunosorbent assay. They adopted the SARS-CoV-2 Rp3 nucleocapsid protein, which has 90% similar amino acid sequence as that of other SARS-related viruses. The recombinant proteins are adsorbed onto the surface of 96-well plates. The excess protein is

washed away. After adding the diluted human serum for 1 h, the well dish is subjected to cleaning followed by addition of antihuman IgG functionalized with horseradish peroxidase and subjected to attachment to the target. The well plate is cleaned again and the substrate 3,3′,5,5′-tetramethylbenzidine is added. The reaction between the substrate and the peroxidase leads to a change in color which can be detected by using a plate reader. The presence of antiprotein of SARS-CoV-2, i.e., IgG, will be impregnated between the adsorbed nucleoprotein and the antihuman IgG probe, which will result in a positive signal. The IgM test by Xiang et al. [16] has reported a similar test as that of Zhang et al. [15], but they have used antihuman IgM adsorbed to the plate and an anti-Rp3 nucleocapsid probe. By analyzing samples from 16 COVID-19 positive cases confirmed by RT-PCR, they found that antibodies corresponding to SARS-CoV-2 increased within initial 5 days after onset of symptoms. COVID-19 positive cases were found to possess 50% IgM and 81% IgG on initial day which were found to be gradually increased to 81% and 100%, respectively, on the fifth day. On analysis of blood, respiratory, and fecal samples, antibodies were found.

### 3.3.4 Point-of-care testing

To detect infected patients with COVID-19, point-of-care tests are employed to diagnose patients without sending samples to testing laboratories. The example of point-of-care approach is lateral flow antigen dig out for SARS-CoV-2 which is in the process of development for the diagnosis of COVID-19 cases. Commercially available lateral flow antigens are reported to possess a membrane similar to a paper with two lines of coatings: one line with gold nanoparticle−antibody conjugates and the other line with captured antibodies. The urine or blood sample of patients is subjected to deposition on the membrane, and the proteins are drawn across the strip by capillary action. As the sample crosses the first line, the antigens attach to the gold nanoparticle−antibody conjugates, and the complex as a whole flows together through the membrane. When they approach to the second line, the complex is immobilized by the capture antibodies, resulting in a visible red or blue line. Individually gold nanoparticles appear red in color, but assembled gold nanoparticles in solution are found to be blue in color as a result of coupling to band of plasmon.

#### *3.3.4.1 Rapid diagnostic tests based on antigen detection*

Rapid diagnostic test (RDT) based on antigen detection is used to detect the presence of viral proteins, i.e., antigens expressed by the COVID-19 virus in a sample from the respiratory tract of a person within 30 min. When the sample contains sufficient concentrations of target antigens, they will attach to specific antibodies fixed to one line of paper strip present in a plastic covering and show a visually detectable signal, within half an hour in general. When the

virus actively replicates, the viral antigens are expressed and detected by RDT. This test is best used to identify acute or early infection.

The accuracy of the test depends on many factors such as the time from start of infection, the viral loads, the quality of sample collection, processing, and the optimization of reagents within the test kits. As COVID-19 is also a respiratory disorder like influenza, in which infected patients have comparable concentrations of influenza virus in respiratory sample as seen in COVID-19, the sensitivity of this test might be expected to vary from 34% to 80%. Based on this literature, half or more of COVID-19 infected patients might show false negative by such tests, based on the group selected for testing. The accuracy of these results must be further checked for confirmation. Another demerit of these tests is that it may show false-negative result that means patient is normal but the result will show positive due to recognition of other coronavirus causing common cold other than SARS-CoV-2 by the antibodies present inside the strip [17]. With the limited data now available, WHO does not currently recommend the use of antigen-detecting RDTs for patient care, although research into their performance and potential diagnostic utility is highly encouraged.

#### *3.3.4.2 Rapid diagnostic tests based on host antibody detection*

This is another type of RDT available for COVID-19 where antibodies in the blood of the patients infected with COVID-19 are detected. Antibodies are developed within 1 week of infection with the virus. The several factors like age, severity of infection, nutritional status, and certain infection such as HIV can affect the potency of antibodies response. Some patients infected with COVID-19, confirmed by RT-PCR, are reported to be weak, late, or absent antibodies responses [9]. Research on COVID-19 suggests that maximum positive cases develop antibodies response only in the second week just after appearance of symptoms. This signifies that antibody-based diagnosis of COVID-19 will only be possible in the phase of recovery of the patients when the transmission of the disease has already passed. Antibody-based COVID-19 detection may give false result as chances of cross-reactions with other pathogens, including other human coronaviruses.

## 3.4 Artificial intelligence–assisted rapid testing for COVID-19

The routinely used RT-PCR test for COVID-19 takes 2 days to complete; serial testing is required to avoid false negative result; currently, shortage of RT-PCR test kits leads to search the alternative methods for rapid and accurate diagnosis of patients with COVID-19 to meet urgent need. Chest CT is a useful technique of the diagnosis for COVID-19 but it is reported that some patients had normal radiological findings at early stage of the disease. Due to this drawback of CT technique, it alone is not sufficient to detect positive cases of COVID-19. In a reported study, the researchers had employed artificial

intelligence (AI) algorithms to integrate chest CT findings with clinical symptoms, exposure history, and laboratory testing to rapidly diagnose positive cases infected with COVID-19. They have also reported that out of a total 905 case, 419 cases were found to be positive for SARS-CoV-2 by RT-PCR assay, whereas out 279 patients in test, 257 patients were found positive for COVID-19 using AI-assisted system and showed equivalent result as that of a senior thoracic radiologist [18].

The AI system is also reported to be more accurate as compared to radiologists. In a typical test, 17 out of 25 were found to be positive by AI systems as well as by RT-PCR, whereas all 25 cases were reported negative by normal CT scans by radiologists. On availability of CT scan results along with the history of clinical patients, the proposed AI system can help to rapidly diagnose COVID-19 patients.

Limitation of this proposed AI-assisted study is the small sample size. Despite the promising results of using the AI model to screen patients with COVID-19, further data collection is required to test the generalizability of the AI model to other patient population. Collaborative effort in data collection may facilitate improving the AI model. The machine learning is also difficult in case of limited size of sample. Such type of reported model, the researchers implemented a pretrained tuberculosis model in order to select key parameters for representing a full 3D CT scan model. This attempt can minimize computational training of a 3D convolutional neural network (CNN), with a trade-off on missing information in the parameters that are not selected for model training and inference. The design of the CNN model offers a natural visualization to explain the prediction. The researchers aimed to explore different approaches in CNNs, including 3D deep learning models and improvement of interpretability of CNN models. The generalizability of the AI system evaluated at multiple centers will be necessary to validate the robustness of the models.

## 3.5 Lowest cost diagnostic kits for COVID-19

The Indian Institute of Technology (IIT) Delhi has invented a technique to detect COVID-19, which will reportedly be the lowest testing kit for COVID-19 and is quite affordable for large swathes of the population. It has also received green signal by the Indian Council of Medical Research (ICMR) [19].

### 3.5.1 How do the IIT Delhi test kits work?

In simplest terms, the test method is a “probe-free” method, as opposed to most current methods which are “probe-based” [20]. This will assist in reducing cost of testing without compromising on accuracy. The working principle of the test is to identify unique sequences of RNA associated with genome of SARS-CoV-2. RNA plays a crucial role in protein synthesis such as

transcription, decoding, regulation, and expression of genes [19]. Using comparative sequence analysis, the researchers have identified unique regions in COVID-19. These unique regions are not present in other human coronaviruses providing an opportunity to specifically detect COVID-19 as per Professor Vivekanandan Perumal, a lead member of the team [19].

## 3.6 Future projections

As the demand for COVID-19 tests increases as COVID-19 is showing little sign of decline, many diagnostic companies have increased their efforts to develop and launch tests that offer quick turnaround times and reliable results. In an attempt to meet requests for more tests, several diagnostic companies have reprioritized in-house developments opting to focus on creating in-lab/hospital, as well as at-home, testing options.

## 3.7 Conclusion

The currently available established technologies have empowered researchers to work perfectly in fabricating diagnostics for COVID-19. Although such technologies may take decades to be optimized, these technologies are now playing crucial role in detecting and managing spread of COVID-19. Lessons learnt from the outbreak of SARS in 2002 have been helpful for developing identification and detection methods for COVID-19 diagnosis.

## List of abbreviations

**cDNA** Complementary DNA
**CNN** Convolutional neural network
**COVID-19** Coronavirus disease 2019
**CRISPR** Clustered regularly interspaced short palindromic repeats
**CT** Computed tomography
**ELISA** Enzyme-linked immunosorbent assay
**LAMP** Loop-mediated isothermal amplification
**ORF** Open reading frame
**PCR** Polymerase chain reaction
**RCA** Rolling circle amplification
**RdRp** RNA-dependent RNA polymerase
**RPA** Recombinase polymerase amplification
**RT-PCR** Reverse transcription polymerase chain reaction
**SARS-CoV-2** Severe acute respiratory syndrome coronavirus 2

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