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Navigating Diagnostic Dilemmas in SARS-CoV-2 Testing: A Primer for Primary Health Care Teams, Public Health Practitioners and Policy Makers

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Abstract:

Primary care teams, public health professionals and policy makers are faced with numerous dilemmas related to patient care, outbreak response and community surveillance. Given the constant and rapid evolution of diagnostic testing, it is challenging for health care teams, public health practitioners and policymakers to keep track of emerging and existing technologies, understand their applicable scenarios in clinical or pandemic management and the pitfalls in interpreting the results. In this paper we provide an overview of advantages and disadvantages of the range of tests currently available and emerging for COVID19. We also use different case scenarios from our own practice to discuss the application of testing strategies. These case scenarios range from planning mass event openings to clinical decision-making to community surveillance. We discuss potential testing strategies, accuracy of tests, and ways to interpret results. We hope that the use-cases described in this paper will highlight the advantages while also underscoring the uncertainties in testing from clinical, public health and policy perspectives.

Introduction

Diagnostic testing for SARS-CoV-2 for clinical use, epidemiological surveillance and outbreak response is a constantly evolving field with multiple changing stakeholders and dynamics. Many players and groups globally and within India have been working hard to make a variety of tests available. The characteristics of these tests, uncertainties, interpretation of results, and role in clinical management and public health decision-making are rapidly evolving. Thus, frontline health workers (such as Primary health care teams including physicians, nurses, ASHA workers etc), policy makers (at governments and industries) and public health practitioners may find it challenging to respond to real life scenarios related to COVID19. These scenarios could include clinical decision making dilemmas, preventive measures for societies as well as policy dilemmas such as reopening of events, industries, economics and so on.

This paper, written by a collaborative group consisting of a PHC medical officer (in charge of a government fever clinic), practicing family medicine physicians, laboratory diagnosticians and public health experts. The objectives of this article are to:

a) Provide an overview of the range of tests available and emerging for COVID 19
b) Discuss, using case scenarios, the application of specific testing strategies, including determinants of test sensitivity, specificity and accuracy and pitfalls in interpretation.

Spectrum of presentation of COVID19

A recent paper (1) from ICMR shared a community surveillance protocol for estimating population prevalence of infection and data is still awaited. Of those infected, data from multiple countries is fairly clear that about 80% experience mild symptoms or are "asymptomatic", while 15% experience severe symptoms requiring hospital admission and oxygen supplementation and 5% experience SARI (Severe Acute Respiratory Illness) (2,3) Current death rates in India at the time of writing this article are close to 1-3%, depending on the region as per the Ministry of Health and Family Welfare (as on June 13 2020) (4,5). The figure below illustrates a spectrum of presentation of COVID19.
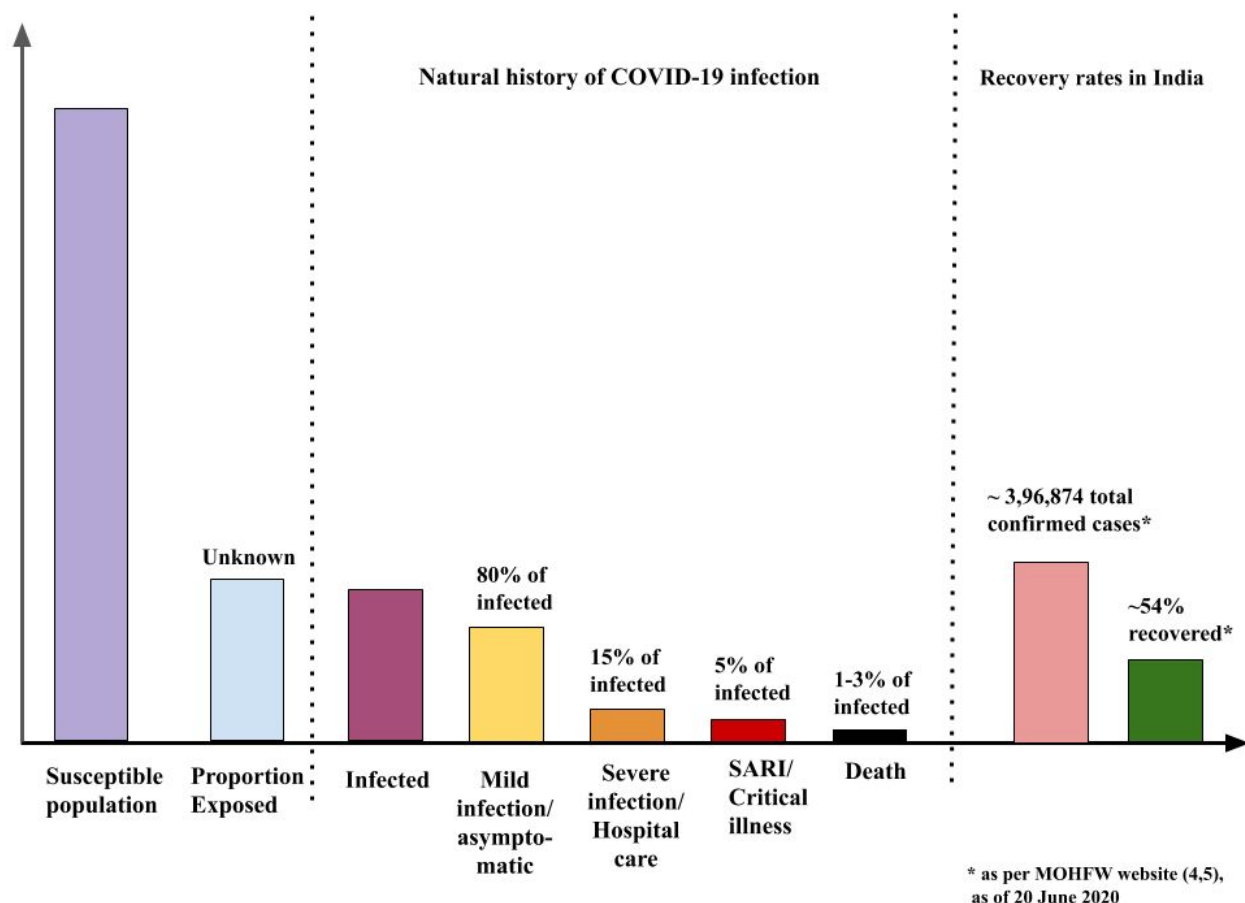

Fig 1: COVID19 Spectrum of Presentation

The role of diagnostic testing along the spectrum of presentation is as follows: a) Tests to identify mildly infected individuals who constitute almost 80% of the total infected b) accurate and early diagnostic tools to identify the ˜20% of cases severe enough to require hospital admission and critical care, c) tests to

detect viral shedding in infected individuals to identify their current status in disease progression or potentially infected quarantined individuals, d) tests to be able to discharge hospitalized COVID patients. Both c) and d) are important to identify those recovered or on their way to recovery. In addition to these clinical scenarios, testing is also required for epidemiological surveillance, to estimate prevalence in the population, and determine risk factors and geographical spread.

Diagnostic tools for testing SARS-CoV-2

The diagnostic tools either test directly for the virus itself (e.g. PCR) or indirectly for evidence of viral infection (e.g. antibodies). For direct testing of the virus, viral components such as nucleic acid (RNA, in the case of SARS-Cov2), or viral proteins (antigens) are examined. For indirect evidence of infection, multiple tests exist for the detection of antibodies (IgG and IgM) produced by the body against the virus. Other tools include radiological tests such as Chest X-ray and CT scans as well as those that test for pulmonary function, such as pulse oximetry; these tests while non-specific to SARS-CoV-2, are useful adjuncts to clinical decision-making in the management of COVID-19 (Fig 2).
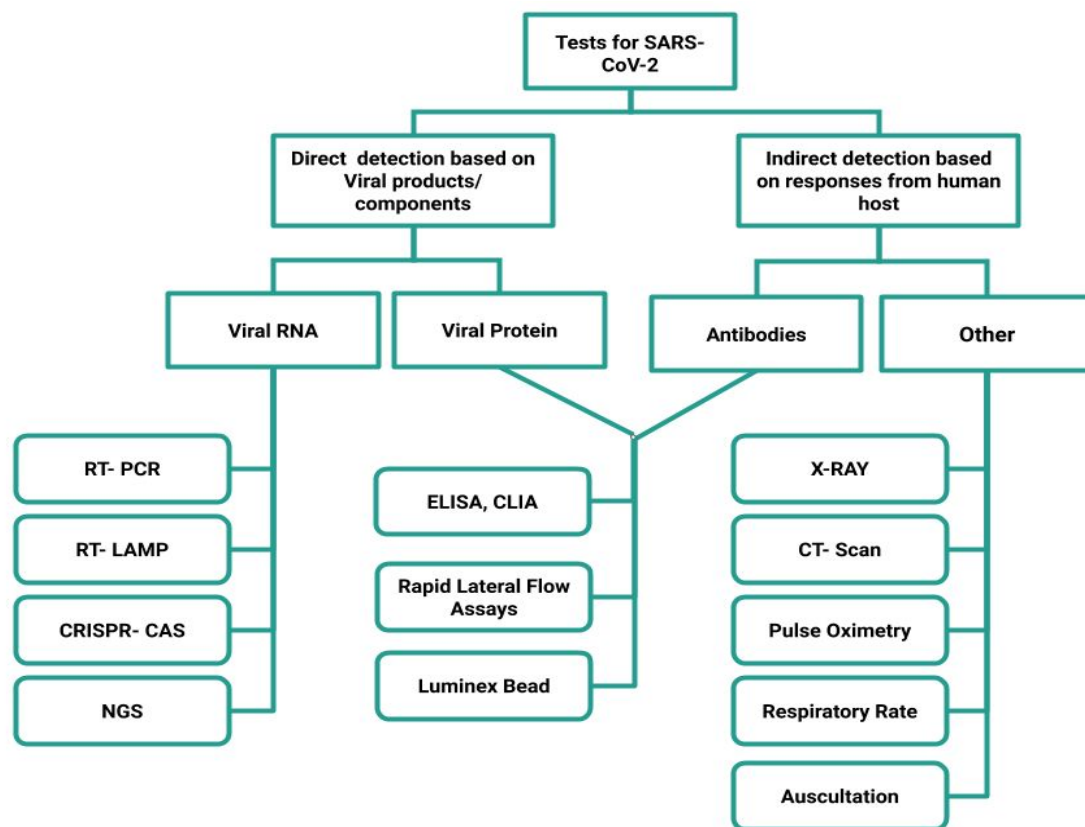

Figure 2: Type of tests for SARS CoV2
(RT-PCR- Real-Time Polymerase Chain Reaction; RT- LAMP: Reverse Transcription- Loop Mediated Isothermal Amplification; CRISPR :Clustered Regularly Interspaced Short Palindromic Repeats; NGS: Next Generation Sequencing; ELISA: Enzyme Linked Immuno-Sorbent Assay; CLIA: Chemiluminescence Immunoassay)

Tests for identifying viral components: Currently, nucleic acid testing to detect viral RNA using RT-PCR is considered the gold standard for SARS-CoV-2 testing and diagnosis in India and across the world (Table 1).

Detection of viral RNA: Detection of viral RNA can be done by techniques such as Real Time Polymerase Chain Reaction(RT-PCR), Reverse Transcription Loop-mediated Isothermal Amplification (RT-LAMP), CRISPR-CAS and Next Generation Sequencing (NGS).

RT- PCR and **RT-LAMP** both work on the principle of amplification of viral RNA to levels that are detectable. Both RT-PCR and RT-LAMP assays provide comparable results, although the extreme sensitivity of RT-LAMP is thought to produce false positives(6,7). (see Table 1). **CRISPR-CAS** based RNA tests are based on "molecular scissors" called CRISPR-CAS which cut out a specific target nucleic acid sequence (such as a segment of SARS-Cov-2 viral RNA). This cutting action releases a signal that can be detected. Several companies are looking to develop Crispr-CAS assays for SARS-Cov-2 but none are currently in the market yet (Table 2). **NGS** technologies are suitable for unbiased detection of COVID-19 and also enable processing of multiple samples. The advantage of NGS over RT-PCR, RT-LAMP and CRISPR is that prior knowledge of the virus genome is not necessary.

Detection of viral proteins or antigens: Various methods for detection of viral antigens from patients samples can be deployed such as Enzyme Linked Immunosorbent Assay (ELISA),Chemi Luminescent Immuno Assay (CLIA), Lateral Flow Assay (LFA) and Luminex Beads; these are all based on the same underlying principle but their method of detection of the antigen-antibody complexes varies. Recently ICMR has approved a rapid antigen test kit. However these are not yet widely available in the market (Table 2).

Detecting indirect evidence of viral infection: The immune responses to SARS-COV-2 are still being characterized but it is understood now that while at the start of the infection the body elicits a generalized immune response, in time infected individuals may develop virus specific antibodies that are either cross-reactive or neutralizing or both (8). For SARS-COV-2 so far it is clear that IgA, IgM and IgG antibodies (9) are produced. Laboratory based ELISA tests and rapid tests that use LFA techniques are currently available in the market. For COVID-19, National Institute of Virology, Pune has also developed an ELISA recent (10). A caveat of rapid antibody tests (LFA based) is their low sensitivity and specificity in real world settings. (Table 1)

Table 1 below shows the various tests available commercially in India and their key characteristics

Table 1: Commercially available SARS-CoV-2 testing methods

Test type	RT-PCR test	Rapid Antibody test (LFA)	ELISA/CLIA
Also called	Real Time-PCR, PCR test, NAAT	Rapid lateral flow assays, IgG/IgM test, rapid card test, Serology Test	IgG/ IgM ELISA/ CLIA
Detection	Nucleic Acid	Antibody (Protein)	Antibody (Protein)

Test type	Laboratory based	POC(Point of Care)	Laboratory based
Sample type	Nasal/Oro-pharyngeal swab preferred. Other samples include BAL* fluid, sputum, nasopharyngeal, tracheal asprate etc	Venous Blood or Capillary blood (varies by manufacturer)	Venous Blood
Test Performance	High (Sensitivity: 79-83.3% Specificity: 98.8-100%) (11)	Medium (Sensitivity: 93-100% Specificity: 65-85%) (12)	High (Sensitivity 92.37% ; Specificity 97.9%) (10)
When to Test? (optimally)	Anytime across the spectrum of illness (through pre symptomatic/ asymptomatic, through symptomatic and during recovery phases)	After 7-10 days following symptom onset	After 7-10 days following symptom onset
Current Status in India	ICMR approved, available commercially	Not approved by ICMR for clinical diagnosis/ management but approved for sero surveillance. Available commercially	ICMR approved, soon to become available commercially
Pros	1) High sensitivity and specificity 2) Extensively studied and utilized technology	1) 10-15 mins from addition of sample to result assuming no delays 2) Requires very little training to perform the test 3) Low cost	1) Can run multiple batches at same time 2) Higher accuracy compared to rapid card tests 3)Lower cost than PCR
Cons	1)High complexity test, often requires highly trained professionals and significant lab infrastructure** 2)High cost of operations 3) From sample collection to result can be many hours	1) The test is yet to be evaluated for accuracy, not recommended for clinical diagnosis at this time.. 2) Detects presence of antibody against COVID-19; does not provide information on whether it is a active infection or a past infection 3) More time consuming for large batch testing	1) Many hours from sample addition to result 2) Detects presence of antibody against COVID19; does not provide information on whether it is a active infection or a past infection 3) Not recommended for clinical diagnosis at this time. 4) Trained personnel and laboratory infrastructure to run (lower threshold than PCR but more complex than rapid testing)

* BAL - Broncho Alveolar Lavage

**POC NAT tests, such as TruNAT microchip technology, are an exception as they do not require highly trained staff and are not infrastructure heavy

Multiple novel tests are currently being developed to address the shortage of testing kits in India. Table 2 highlights some emerging technologies

Table 2: Emerging technologies for SARS-CoV-2 testing:

Test type	Rapid antigen test (LFA)	LAMP	CRISPR	NGS
Alternative names	Antigen test, Serology test	RT-LAMP	SHERLOCK, DETECTR, INSPECTR, SHINE, CRISPR CAS	Next generation sequencing
Detection	Protein	Nucleic Acid	Nucleic Acid	Nucleic Acid
Test type	POC/ Laboratory-based	Laboratory-based	Laboratory-based	Laboratory-based
Sample type	Nasal/Oro-pharyngeal swab preferred.	Naso/Oro-pharyngeal swab	Naso/Oro-pharyngeal swab	Naso/Oro-pharyngeal swab
Test Accuracy	Medium (Sensitivity ranged from 50.6% to 84% Specificity ranged from 99.3 to 100%) (13)	High (Sensitivity: 100% Specificity: 87%) (14)	High (Sensitivity: 90% Specificity:100%) (15)	Higher sensitivity and accuracy than those of qPCR kits currently in clinical use (16)
Test Timeline	Anytime across the spectrum of illness	Anytime across the spectrum of illness	Anytime across the spectrum of illness	Anytime across the spectrum of illness
Current Status	ICMR approved. Not commercially at this time.	Awaiting ICMR approval and Manufacturing Licence	Unavailable in Indian Market not approved by ICMR	Research only. Not approved by ICMR
Pros	1) 10-15 mins from addition of sample to result assuming no delays 2) Useful in early detection. 3) Requires very little training to perform the test.	1) 2-3 hours from sample collection to result assuming no delays 2) results can be read by naked eye	1) 1-2 hour from sample collection to result assuming no delays 2) Does not require complex instrumentation.	1) 2-3 hours from sample collection to result 2) Can detect presence of other infection simultaneously
Cons	1) The test is yet to be evaluated for accuracy 2) More time consuming for large batch testing	1) Newer technology compared to RT-PCR 2)Detects only current infection does not provide insights into past exposure to the virus 3) Depends heavily on the site of sample collection as virus distribution is not even.	1) Newer technology needs to be optimized for COVID-19 detection.	1) Newer technology needs to be optimized for COVID-19 detection 2) High complexity test, often requires highly trained professionals and significant lab infrastructure 3) Extensive downstream data analysis

When to use which test?: Case scenarios from real world practice

Below, we describe a few cases that primary care clinicians may typically encounter and the testing strategies/ options that can be considered throughout the spectrum of COVID19 presentation (Fig 1).

Testing dilemmas and uncertainties

a) **Non-specific symptoms that overlap with a number of common illnesses**: Covid19 symptoms are not distinctive. This complicates differential diagnosis. In addition, the clinical presentation of SARS- CoV-2 infection itself varies widely.

b) **Presence of a large number of infected but asymptomatic individuals:** Asymptomatic infected individuals may not know that they are truly infected. This challenge adversely impacts decision making around isolation and quarantine to reduce community transmission.

c) **Window period:** It takes about 5-7 days after infection for the viral RNA to reach detectable amounts that the RT-PCR can detect. Thus the window period for RT-PCR is 5-7 days. Similarly the window period for an antibody test (regardless of whether it is a rapid card test or an ELISA) is close to 12-14 days. Testing done within the window period has a high chance of leading to false negative results.

d) **Sampling technique influences accuracy:** The ideal sample for collection for SARS-CoV-2 RT-PCR is a nasopharyngeal (NP) or oropharyngeal (OP) swab. The right position to collect the sample is critical. Both NP and OP sampling is uncomfortable for the patient. The tentative or inexperienced technician can sample the incorrect site if not trained properly.

e) **Detection of viral RNA does not always mean that there is active infection:** Viral RNA shedding is known to go on for at least 5-6 weeks[17,18]. However, despite viral RNA being detected, some studies have shown that live viruses can no longer be isolated[19] from patients 8 days after symptom onset.

Box 1: Testing dilemmas and uncertainties

a) **Real world scenario 1: Asymptomatic infection and sports manager's dilemma**

Sanjay is an event organization CEO. With lockdown relaxation he wants to kick start large sporting events throughout the country. The athletes/players who would be part of this have been living either in a sports academy or their native towns during the lockdown. While he expects that the events would only be broadcast (no live tickets), he is concerned with how to ensure that the players, management staff and supporting staff can organise a good game without compromising anyone's safety throughout the duration of the tournaments (about 3-4 months).

Recommended test: RT-PCR

Rationale: In this scenario, testing is primarily being used for screening, monitoring, and follow-up contact tracing. If any individual is noted to be positive on PCR testing the clinical

action steps would be the same: isolation of the infected individual, quarantine of contacts and notification to local authorities.

b) **Real world scenario 2: Does Shanta really have COVID-19?**

Shanta had traveled to Switzerland and returned to India just before lockdown (on the 9th of March). She threw a party on that same day to celebrate her return. 4 days after this on the 13th she developed fever, sore throat and anosmia. She went to a private hospital where they took two nasal swabs at the same time, and sent them to two different labs. One returned first and was negative, but the other that came in a few hours later was positive. She was admitted to a recognized COVID hospital.

Recommended test: Repeat RT- PCR. Other tools include radiological tests such as Chest X-ray and CT scans as well as those that test for pulmonary function, such as pulse oximetry; these tests while non-specific to SARS-CoV-2, are useful adjuncts to clinical decision-making in the management of COVID-19

Rationale: Testing is required to determine- a) if a symptomatic individual has a current SARS-CoV-2 infection and b) clinical severity of illness. A drop in oxygen saturation or radiological findings supportive of COVID-19 may warrant admission to a COVID-19 ward/hospital or home isolation with close tele-monitoring. As of now, no specific therapies are proven against SARS-CoV-2.

c) **Real world Scenario 3: Can this employee return to work?**

Smitha returns from London post lockdown relaxations and begins self-imposed quarantine at home for 2 weeks. At the end of two weeks, she calls her company CEO to see if she can de-isolate and return to work. The company has re-opened post lockdown relaxations and most of the staff is back to work. Smitha is concerned if she will pose a threat of infection to the rest of the team if she re-joins

Recommended test: None

Rationale: Given that viral RNA can be detected in nasopharyngeal swabs even after 2 weeks of symptom onset in asymptomatic patients, studies have shown no live virus beyond 8 days after onset of symptom (19). Antibody tests currently are unable to determine immunity (20). As a result testing is best avoided. One can reassure the employee that she is safe to rejoin the work and poses no risk to anyone after 14 days of quarantine. While

d) **Real world Scenario 4: Discharge from hospital**

Gopal is a 60 year old who had been admitted to a COVID hospital after presenting with shortness of breath, fever and fatigue. Symptom onset was 4 days after he came in contact with his son in law, recently returned from Italy. In the hospital, Gopal tested positive by RT-PCR for the virus. He needed oxygen supplementation, although no ICU admission. After 3-4 days, his fever subsided, his oxygen saturation was at 95% and his other symptoms improved. His doctor at the hospital wants to discharge him 3 days after symptom resolution. Gopal asks the doctor if a test is required.

Recommended test: None.

Rationale: If Gopal has made a complete clinical recovery, without need for any medication (for fever etc), and has maintained oxygen saturation for 3 days and it has been at least 10 days since Gopal started showing symptoms, he can be discharged with no additional testing, as per the ICMR guidelines of May 9th 2020.

e) **Real world scenario 5: Is sewage testing the municipal commissioner's new weapon?**
With a sudden spike in positive cases in his city, Raja**,** a Municipal Commissioner, wants to know how to detect hotspots of COVID-19 in the city early so that preemptive measures can be taken to avoid an explosive outbreak.
Recommended Tests: Several approaches (established and novel) exist for surveillance and it is a combination of these methods that can help in early detection towards implementation of public health measures. These include: a) Sewage testing for viruses has been done earlier for community detection of polio (21), and has now been shown to be a valid testing option for COVID-19; b) Pooled RT-PCR (no more than 5 samples pooled together) in low prevalence areas has been recommended by ICMR; c) Antibody ELISA test for sentinel population surveillance (health care workers, outpatient attendees with non-ILI symptoms, pregnant women)(22) may also be done using a clear and rational protocol for sampling; d) Point of care molecular testing, such as TRU-NAT, could be installed in more primary care centers and mobile vans for random sampling with quicker results.

Conclusion:
There is no perfect test. Clarifying the purpose and the follow-up actions of testing are important steps before choosing the test. There are various testing options available and each of them come with their advantages and caveats to interpretation. Our article highlights the necessity of a nuanced approach to testing for COVID-19. We hope that use cases described in the paper, ranging from the management of individual cases to population surveillance, will underscore these advantages and caveats as seen from clinical, public health and policy perspectives.

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Glossary:

Antibody: A protein produced by the body's immune system in response to a foreign encounter in-order to counteract the threat. Antibodies combine chemically with substances which the body recognizes as alien, such as bacteria, viruses, and foreign substances in the blood.

Antigens: Toxins, viral proteins, bacterial proteins or other foreign substances which induces an immune response in the body, especially the production of antibodies.

ELISA: Enzyme Linked ImmunoSorbent Assay is a common laboratory technique that uses antibodies linked to enzymes that release color or other specific signals on reaction to detect and measure the amount of substances such as proteins, antigens and other antibodies in a sample.

LFA: Lateral Flow Assays often known as rapid tests are a simple form diagnostic test that do not need complex instruments for testing making these amenable for point of care testing. A common example is home pregnancy tests.

Naso/Oro pharyngeal swabs: A Nasopharyngeal or Oro-pharyngeal swab is a sample collected by using a sterile cotton sample collection swab(cotton bud) to collect samples of nasal secretions from the back of the nose and throat. This can be difficult to do correctly and safely to avoid COVID19 infection unless one is a trained technician and is mildly uncomfortable for the patient.

Next Generation Sequencing: It is a DNA sequencing technology. NGS includes different sequencing platforms based on different technologies which can sequence millions of fragments DNA copies in parallel.

Nucleic acid: These are large molecules in living cells or organisms where all genetic information is stored. There are 2 types of Nucleic acids in all living organisms, DNA or Deoxy-Ribo Nucleic acid and RNA or Ribo-Nucleic Acid. COVID-19 is a RNA virus.

RT-PCR: Polymerase chain reaction or PCR is a method widely used to rapidly make millions to billions of copies of a specific DNA or RNA sample, this amplification allows us to detect very small amounts of nucleic acid present in a sample.

RT LAMP: Reverse Transcription Loop-mediated Isothermal Amplification (RT-LAMP) is technology that works on a very similar principle as PCR defined above. The difference between them lies in the mechanism of amplification: Real time PCR amplifies viral RNA using thermocycling, where a tight sequence of increasing and decreasing temperatures allows amplification of viral RNA by an external enzyme (called polymerase). RT-LAMP, on the other hand, allows isothermal amplification of RNA. Both types of assays provide comparable results, although the extreme sensitivity of RT-LAMP is thought to produce false positives

Sensitivity: The ability of a test to correctly identify those with the disease -true positive rate

Specificity: The ability to correctly identify those without the disease- true negative rate

Serology tests: Tests that detect antibodies developed by the body in response to an infection

Viral load: Amount or count of virus in the sample collected