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SARS-CoV-2 Diagnostics

Leveraging Point-of-Care Testing in Next-Step Strategy

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COVID-19 Background

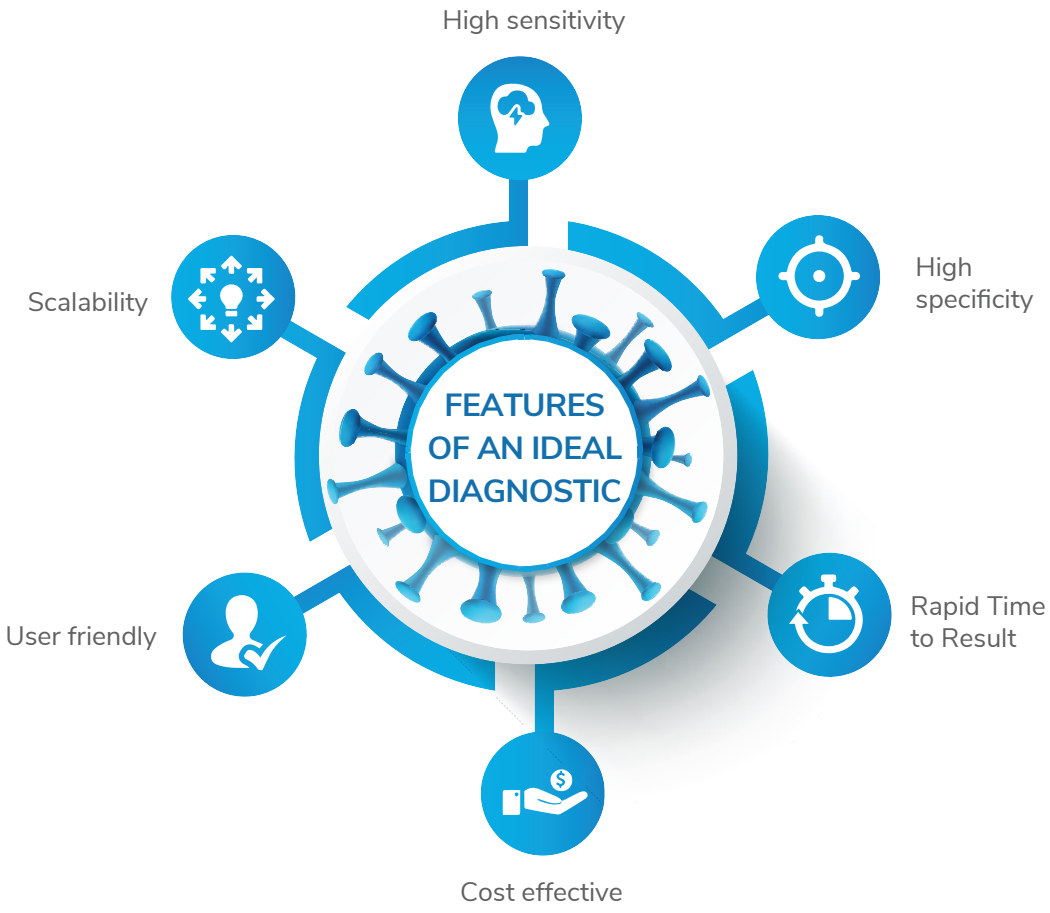
COVID-19 caused by the SARS-CoV-2 RNA virus emerged in 2019 and took only a few months to reach every country around the world. The World Health Organization (WHO) declared the deadly outbreak a global pandemic on March 11, 2020. More than 15 months later, it remains a far-reaching healthcare challenge. Multiple variants of the coronavirus are emerging. Currently, four variants of the virus—Alpha, Beta, Gamma and Delta—have been termed as Variants of Concern by WHO and are closely monitored.[1] Centers for Disease Control and Prevention (CDC) reports that the highly contagious delta variant is now the dominant strain in the US.[2] Four more variants—Eta, Iota, Kappa and Lambda—have been identified with high community transmission characteristics and have been labelled as Variants of Interest by WHO. The increasing number of cases infected with these variants indicates an emerging risk for global public health. This underscores the critical importance of accurate and rapid testing in the US, as well as in the global community.

In the uncharted territory before vaccines or antiviral therapeutic agents existed, limiting the virus's spread was the primary goal. Delays in diagnosis and treatment resulted in extended hospital stays (50% of Hospitalized patients developed dyspnea within a week of infection and the more severe cases progress to respiratory distress syndrome in the absence of timely treatment[3]) and needless quarantining of people who were ultimately found to not have the virus. Diagnostic tests quickly proved their value in the initial fight and in subsequent waves by enabling effective quarantine measures, contact tracing, and clinical management.

Even with COVID-19 vaccines now available, less than half of the US population (and only about 13% globally) is fully vaccinated.[4] Unknown factors, such as the duration of immunity and efficacy of vaccines on variants, mean that diagnostic tests will remain on the front line of the COVID-19 battlefield for some time. Equipping physicians' offices, clinics, and urgent care centers with the right diagnostic test is imperative.

A diagnostic test ideally features high sensitivity and specificity, ease of use, rapid turnaround time, and scalability, as Figure 1 shows. A fast and accurate result allows a clinician to promptly make the right treatment decisions. Tests that can be easily run at locations close to patients enable early detection of illness, resulting in faster care and lower overall cost of care. Higher-accuracy tests also help with reducing the additional costs and resources involved in repetitive and confirmatory testing, extended hospital stays due to delayed diagnosis, and needless quarantining of individuals.

Figure 1: Gold Standard Attributes of a Covid-19 Diagnostic



Diagnostic Tests for SARS-CoV-2

The US Centers for Disease Control and Prevention (CDC) currently recommends a diagnostic test for anyone with COVID-19 symptoms, a history of close contact with COVID-19-positive patients, or exposure to a high-risk environment. Nucleic acid amplification tests (NAATs) and enzyme immunoassays (EIAs) are the most common.

- **NAATs** detect the presence of RNA sequences (the genetic material of the SARS-CoV-2 virus) in a nasal or nasopharyngeal swab sample. The predominant reverse transcription polymerase chain reaction (RT-PCR) test involves RNA extraction and purification, and precise thermal cycles for amplification. Isothermal amplification is an alternative NAAT technology that uses constant temperature for the amplification process.
- **EIAs** are rapid tests that detect the presence of the viral antigen in a sample by using an enzyme-bound antibody to convert a substrate into a fluorescing or colored end product. Rapid antigen tests detect the presence of viral proteins in nasal or nasopharyngeal swab specimens. Rapid antibody tests, on the other hand, detect the host's response to the virus (IgG or IgM) but antibody tests are not used for diagnosis.

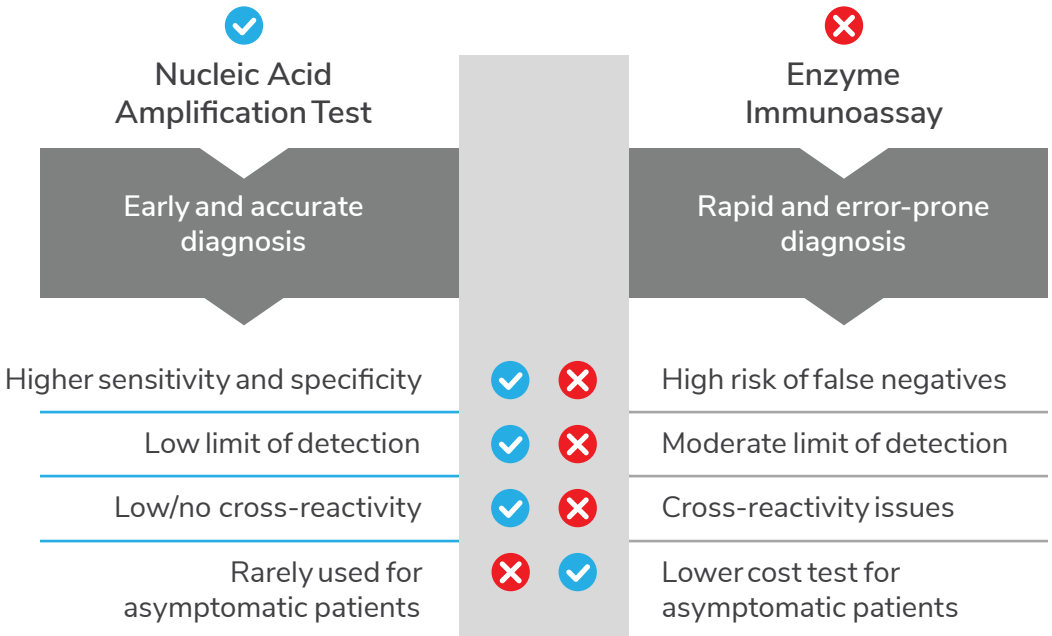
Choosing an Effective SARS-CoV-2 Diagnostic

Because of its speed and accuracy, NAATs are recommended to identify SARS-CoV-2 infection, and are considered confirmatory tests by the US CDC. The gold standard is the RT-PCR test, but its complexity historically meant that only highly trained technicians could run it at a lab certified under Clinical Laboratory Improvement Amendments of 1988 (CLIA) regulations to handle moderate- or high-complexity test systems. The centralization of testing resulted in turnaround times of multiple days, which delayed containment efforts and discouraged people from approaching test centers for fear of quarantine or simply the general anxiety of waiting for often delayed test results.

For these and other reasons, point of care (POC) diagnostics became the modality of choice. The benefits of rapid clinical decisions, effective contact tracing, and immediate quarantining of patients only when truly needed encouraged testing in the larger population.

Rapid antigen tests are portable and have a turnaround of just 15 to 30 minutes, but they are less accurate than NAATs, as shown in Figure 2. SARS-CoV-2 antigen may naturally clear from the body five to seven days after the onset of symptoms and present as a false negative. The high risk of false negatives is a major drawback of antigen testing. Because SARS-CoV-2 antibodies persist in the blood for a few months after infection, serology tests cannot detect current infection. In contrast, NAATs involve the amplification of the viral genetic material, and therefore can detect infection even when the viral copy number is low. This reduces false negatives and makes these tests suitable for early detection. The use of appropriately designed primers prevents cross-reactivity and amplification of other types of viral RNA. Redundancy of targets is built into the system, so sensitivity and specificity are very high.

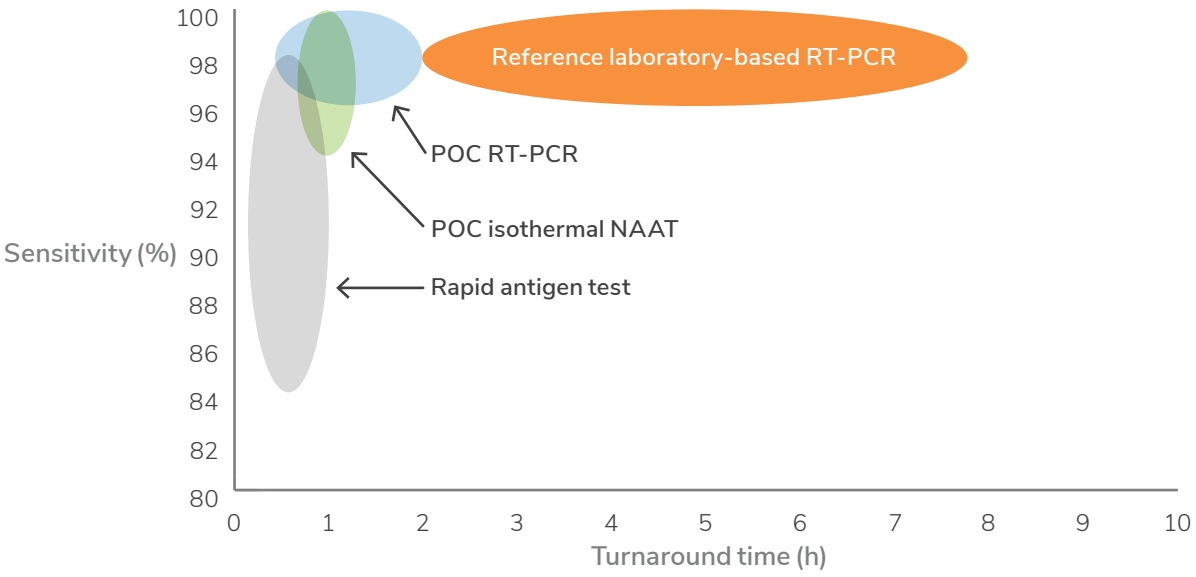
Figure 2: NAAT and Enzyme Immunoassay Comparison



Consequently, the CDC postulates a complicated algorithm to follow after an antigen test; in practice, it is often followed by a NAAT for confirmation.[5] Rapid antigen tests used for preliminary screening of a population at the point of care are around 100 times less sensitive than RT-PCR tests.[6] When the rapid antigen results contradict symptoms and exposure history, the patient is called back for a retest or confirmatory NAAT, adding to the burden on the patient, the physician, and the lab (in some cases reimbursement policies may not allow for payment of this full range of tests). Therefore, accuracy plays a major role in the usefulness of a POC test.

Sample-to-answer NAATs with inherent high accuracy, ease of use, and design for POC settings will be extremely valuable for the effective management of COVID-19 in the future. Figure 3 plots sensitivity against the turnaround time of the rapid antigen test, laboratory-based RT-PCR, POC RT-PCR, and POC isothermal amplification. Despite a slightly longer turnaround time when compared with rapid antigen tests, POC RT-PCR and POC isothermal NAAT technologies are more sensitive. Although isothermal NAAT technology involves less instrument complexity and has a rapid turnaround time of 20 to 30 minutes,[2] the World Health Organization declared RT-PCR to be the gold standard for SARS-CoV-2 detection because of its higher accuracy.[7] An infectious Diseases Society of America (IDSA) panel suggests that a rapid isothermal NAAT can be accepted when rapid RT-PCR and laboratory-based NAAT are unavailable but recommends confirmation with one of the others when a negative result contradicts clinical suspicion.[8]

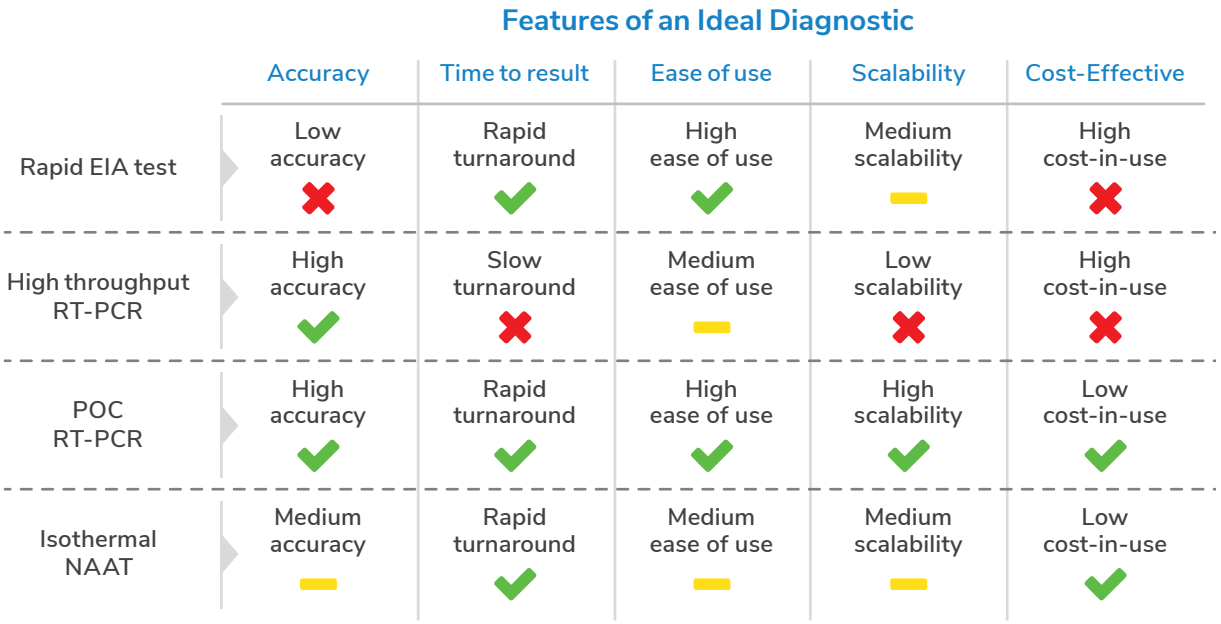
Figure 3: COVID-19 Diagnostic Test Sensitivity and Turnaround Time



As seen in Figure 4, POC RT-PCR surpasses high-throughput, reference laboratory-based RT-PCR in speed, scalability, ease of use, and overall cost, and outperforms rapid antigen tests and POC isothermal NAATs in accuracy. In spite of the low acquisition cost of rapid antigen tests, the need for retests and confirmatory NAAT at reference laboratories results in a higher overall cost or cost-in-use for COVID-19 diagnosis.[9] Enabling accurate diagnosis near the patient, POC RT-PCR tests eliminate the need for confirmatory testing at reference laboratories. Transporting

the sample to the reference laboratory is avoided, thus saving time; it is cost-effective as well. The quick turnaround compared to the laboratory-based RT-PCR tests can enable rapid clinical decisions, effective contact tracing, and timely quarantines.

Figure 4: Comparison of COVID-19 Diagnostic Test Features



POC Diagnosis for the Future

Public health experts expect COVID-19 to become endemic. As people return to work, school, and public gatherings, and as travel restrictions ease around the world, community POC RT-PCR testing sites could complement vaccine distribution as a way to keep the virus in check. Hospitals and clinics could routinely screen high-risk staff and patients, and long-term care (LTC) facilities would have another resource to ensure residents' safety.

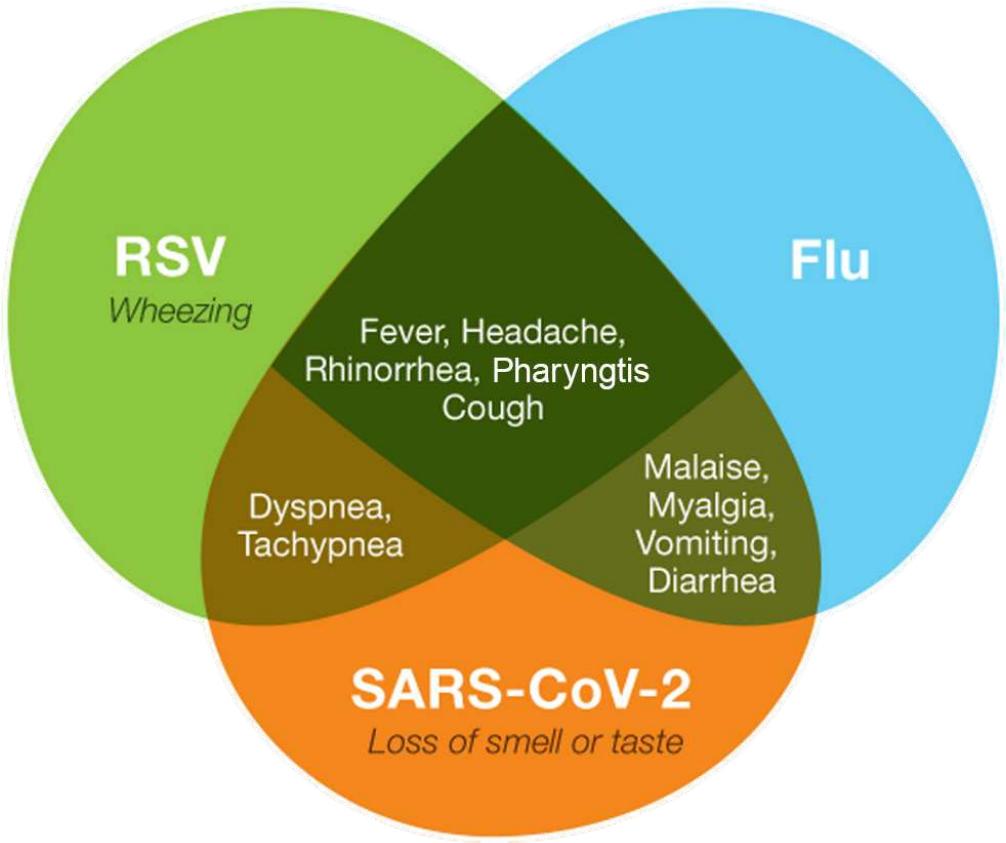
With the resumption of elective clinical procedures, rapid and accurate diagnosis of COVID-19 infection at hospitals will increase the operational efficiency. Better patient management will ensue in LTC centers when POC RT-PCR equipment is available on-site or at a nearby clinic. Furthermore, POC devices of scalable formats will be advantageous at the point of care when the number of tests vary every day in a vaccinated population.[10]

The lower accuracy with rapid antigen tests compared to NAATs will pose a larger problem in vaccinated communities, where the prevalence of COVID-19 symptomatic patients is low. The rate of false positives depends on the pretest probability and the test specificity. The low pretest probability in a vaccinated community and the low specificity of antigen test increases the probability of false positives. NAATs are again suggested as confirmatory tests when patients test positive with a rapid antigen test in a low-prevalence population.[11]

Furthermore, with the SARS-CoV-2 virus mutating over time, mutations in the viral genome can alter the viral proteins, which could render rapid antigen tests ineffective. In the past, the antigenic shift and drift during the 2007-2008 influenza season and 2009 H1N1 pandemic affected the sensitivity of rapid influenza antigen detection tests.[12] The US Food and Drug Administration suggests that viral gene mutations are less likely to affect molecular tests targeting multiple genes.[13] RT-PCR diagnostics targeting multiple gene sequences reduce the probability of false negatives.

Multiplexing RT-PCR diagnostic tests to include detection of other viral pathogens are a boon for physicians. With the SARS-CoV-2 virus COVID-19 presenting the same symptoms as those caused by respiratory syncytial virus and influenza A and B viruses (as shown in Figure 5), proper COVID-19 diagnosis can be a challenge, especially during the respiratory viral infection season. A multiplex RT-PCR assay, which detects and differentiates the respiratory illness–causing virus at the point of care, will enable appropriate patient management and rapid clinical decisions about the course of treatment.

Figure 5: SARS-CoV-2, Respiratory Syncytial Virus, and Influenza Virus Symptoms



Sources: https://www.cdc.gov/flu/symptoms/flu-vs-covid19.htm, https://www.cdc.gov/rsv/about/symptoms.html, *For use under US FDA Emergency Use Authorization*

Conclusion

Health experts agree that the world must remain vigilant as the COVID-19 vaccination rate slowly increases and vaccine hesitancy persists. Equipping laboratories, physicians' offices, and urgent care centers with highly accurate and rapid POC RT-PCR technology will be the way forward, allowing healthcare providers to reliably distinguish COVID-19 from other respiratory illnesses and take appropriate actions to quickly contain outbreaks. It will be a cost-effective routine screening tool for high-risk facilities and be scalable for deployment as a community's needs dictate.

The complexity and process inefficiencies in the clinical care setting from primary care to urgent care centers have grown significantly in the COVID-19 world. Performing the tests in "closer to patient" settings on an advanced technology platform like POC RT-PCR drastically reduces the complexity, time to results, and patient anxiety. It also makes the process more efficient for providers, leading to higher patient satisfaction and increased return on investment. This is also likely to gain higher acceptance from payors that view the reduction in "true cost of diagnostics" as a major benefit of POC RT-PCR. This aligns the interests of all segments of the ecosystem while helping achieve the larger goal of COVID-19 mitigation.

Scalable and multiplexed RT-PCR formats can facilitate sustainable testing by urgent care centers, physician offices, and other POC sites, while lowering the "true cost of diagnostics" to the patient, to clinical centers, and to society at large.

Endnotes

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