The Role of Diagnostic Testing in Combating COVID-19: Accuracy Matters

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Testing is crucial
SARS-CoV-2 remains poised for explosive spread until one of two outcomes is achieved: 1) development of an effective vaccine to impart immunity or resistance to infection or 2) the virus infects at least 60% to 70% of the population, sharply reducing the number of infected individuals encountering uninfected individuals. In the latter case, even though new infections continue, they would not grow exponentially. Nevertheless, without a vaccine, “herd immunity” will be realized only with much additional sickness and death.

As we move toward one or both of these outcomes, most experts agree that diagnostic testing to identify individuals infected with SARS-CoV-2 is essential for mitigating the rate of spread to avoid morbidity and mortality and overwhelming our healthcare system. Thus, testing is crucial to identify and isolate infected individuals. It also provides a starting point for contact tracing to identify individuals who may have had contact with infected patient(s) so the contacts can quarantine. As the United States attempts to restart the economy, the resumption of more normalized levels of social interaction makes testing ever more critical. Also, as some experts anticipate COVID-19 resurgence in the fall and winter, distinguishing COVID-19 from seasonal flu will be imperative to appropriately manage individual patients.

Two broad classes of COVID-19 tests are in use: viral tests and antibody tests. Viral tests are intended to directly measure SARS-CoV-2 infection by detecting the virus's genetic material in cell samples from an individual's respiratory passages. Antibody tests, by contrast, measure a body's reaction to infection. They quantify the number of antibodies, the complex protein molecules deployed by the immune system that attach to the virus and prevent it from entering cells. Basic research on the blood or plasma from those with antibodies may also accelerate development of an effective vaccine.

Incorrect results have serious consequences
How well either type of test—viral or antibody—performs is numerically expressed through two measures: sensitivity and specificity. Sensitivity measures how well a test minimizes chances for a false-negative result (i.e., when a test incorrectly labels as negative a person who is actually infected). The higher a test's sensitivity, the fewer false-negative results it yields. A test with 95% sensitivity yields about 5 negative results for every 100 samples from individuals who are truly infected. Conversely, specificity measures how well the test minimizes false positives, which occur when the test returns a positive result for an uninfected individual.

Virtually no diagnostic test is perfect. Typically, some tradeoff is made between minimizing false negatives at the expense of increasing false positives, or vice versa, depending on the test's purpose. In testing for viral presence, false negatives for SARS-CoV-2 infection are most alarming. Individuals with false-negative results may be tempted to relax social distancing practices. For healthcare providers, false-negative results can lead them to unknowingly infect patients. False-negative results in a patient suspected of COVID-19 infection can lead clinicians to doubt their clinical evaluation, thus negatively affecting diagnostic and treatment decisions for infected patients. In contrast, when testing for antibodies, false positives are the larger problem because such individuals falsely believe they are immune to infection. In either case, incorrect test results can be more dangerous than no test results at all when they inform behavior and decisions that incur unknown risks.

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Tests moved quickly from research to real-world use without full clinical validation data

Ideally, one would want a select number of high-performing, thoroughly validated tests to detect coronavirus infection, overseen by a centralized laboratory structure. This would ensure that, across the country, the same diagnostics were used with known performance characteristics (sensitivity and specificity) to facilitate direct comparison of infection rates across regions. To quickly make testing more widely available, private-sector laboratories were encouraged to fill the need for COVID-19 viral and antibody tests. Currently, more than 70 viral and antibody tests from different companies or academic laboratories are registered with FDA. Most of these tests have received Emergency Use Authorization (EUA), which employs less rigorous premarket evaluation than standard regulatory pathways. FDA provides guidance on the type of data and information developers should submit while seeking an EUA; however, test developers have considerable discretion. Most, but not all, organizations supplying these tests provided basic performance measures for their assays, such as analytic sensitivity and specificity.

Test performance in ideal conditions may differ markedly from real-world performance. A recent, unpublished study illustrates potential complications in making the jump from laboratory validation to real-world use. Researchers at New York University recently reported results from the rapid Abbott ID NOW COVID-19 test, which detects viral genetic material. This test purportedly yields results in 15 minutes. Researchers compared results of this test against those of another widely used viral test with longer turnaround times for results. Using the latter test as a reference, the Abbott test showed an alarmingly high false-negative rate: about one-third of samples testing positive with the comparator test were negative with the Abbott test when using nasopharyngeal swabs in viral transport medium (a solution typically used for storing and preserving collected samples). Performance was even worse—48% false negatives—when using dry nasal swabs. In contrast, reference test results showed good concordance with another widely used viral test, suggesting the Abbott test was the outlier. Accordingly, FDA has recently issued a warning about the danger of false-negative results with the Abbott test.

Whether results of this study stand up to further scrutiny is not yet known since its results have not been published in a peer-reviewed journal or replicated by other laboratories. However, the alarming discrepancy raises concerns about performance measures of tests that moved quickly from research to real-world use without full clinical validation data. FDA recognized this problem and responded by requiring data on real-world samples.

Guidance needed for uniform independent validation

For now, the method by which tests are deployed for COVID-19 detection is unlikely to change. The private sector quickly filled the gap for COVID-19 test development in light of inadequate test availability. Given the continuing need for testing, many tests from different commercial laboratories will remain available. A concerted effort is needed to study and report on the performance and reliability of available tests, particularly ones that use newer, less extensively tested methods. In this way, data collection and wide public dissemination of results could be possible to enable evidence-based decisions on which tests work best.

A May 20 report from the University of Minnesota Center for Infectious Disease Research and Policy recommended the federal government appoint a COVID-19 testing task force. ECRI agrees with this recommendation. Ideally, such a group would seek to include qualified experts from the public sector who are free of significant financial ties to diagnostic testing companies. Such a task force could oversee independent validation studies of test accuracy. Open discussion of independent validation studies would facilitate assessing tests’ strengths and weaknesses and could help elucidate key characteristics of test assays that contribute to the best diagnostic performance and reliability in real-world use.

Take-home messages

- Testing is critical to help mitigate spread of SARS-CoV-2.
- Without more rigorous clinical validation, available tests may produce incorrect results.
- Misleading test results may cause more infections and deaths than if testing is not conducted at all.
- Manufacturers typically submit only basic performance measures for their assays, such as analytic sensitivity and specificity.
- A COVID-19 testing task force of qualified experts in diagnostic testing should be created to provide independent oversight of testing efforts.

Policy Statement

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