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The Need for and Limits of More and Better Testing for COVID-19

Yukari C. Manabe[1], **Joshua S. Sharfstein**[2], **Katrina Armstrong**[3]

[1]Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD USA

[2]Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD USA

[3]Department of Medicine, Massachusetts General Hospital, Boston, MA, USA

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With continued community transmission of SARS-CoV-2 in the United States, there has been sustained focus on the role of testing to mitigate and suppress spread. After the first COVID-19 case was diagnosed in the U.S. in mid-January 2020, testing lagged behind due to challenges with test validation at the US Centers for Disease Control and Prevention (CDC). In late February, the US Food and Drug Administration (FDA) eased its restrictions on emergency use authorization that led to a rapid increase in the number of authorized tests. By May, the private sector was performing 99% of US COVID-19 testing. By August, the number of SARS-CoV-2 tests peaked and then plateaued at ~1 million tests per day. Multiple parallel efforts to bring diagnostic innovation to COVID-19 testing are underway and are likely to result in more tests, as well as new, innovative platforms. For instance, the Rapid Acceleration of Diagnostic (RADx) program is a $1.5 billion U.S. government program to the National Institutes of Health (NIH) to support development, production scale up, and deployment of rapid tests for a goal of 6 million tests available per day.[1]

Does the limit of detection matter?

On September 15th, the FDA published comparative performance data for a subset of the authorized tests against a standardized reference panel that revealed a more than 3 $\log_{10}$ span of test sensitivity.[2] For the clinical diagnosis of patients with symptoms of COVID-19, the use of testing strategies with high sensitivity is important because each 10-fold increase in the limit of detection will miss an additional one in eight infected patients.[3] Test sensitivity (limit of detection) as described by the FDA ranged between 180–600,000 (nucleic acid amplification test detectable units (NDU)/ml).

False negative molecular testing among hospitalized patients received substantial attention at the beginning of the pandemic, particularly for patients for whom the pre-test probability

Corresponding Author: Yukari C. Manabe, MD, 1830 East Monument Street, Rm 443, Baltimore, MD 21287, (410)955-8571 (office), (410614-8488 (fax).

was high based on clinical and radiographic appearance. Given that false negative tests occur even with the most sensitive tests due to timing during infection and sampling, diagnostic algorithms have been developed in many hospitals that include a range of clinical variables. Patients with a clinical presentation consistent with COVID-19 and an initial negative molecular test may warrant lower respiratory tract sampling and require continued isolation. Testing alone is not enough for clinical care.

A public health approach may utilize less sensitive, rapid, point-of-care tests in ways that are different from clinical care.

Testing in the public health setting brings different challenges. An important feature of SARS-CoV-2 is that it can be transmitted while a host is unaware of infection. Epidemiologic evidence has demonstrated that pre-symptomatic and asymptomatic transmission of virus has driven the current epidemic.[4] High rates of household transmission – where there is limited wearing of masks and social distancing – has been documented in a study that involved 382 SARS-CoV-2 exposed children, of whom 76% became infected.[5] To limit outbreaks, testing is needed to identify as many individuals who are transmitting infection as quickly as possible, so they can be isolated and their contacts identified and quarantined.

In this setting, the best test is not necessarily one that determines whether a person has any evidence of SARS-CoV-2, but one that quickly and accurately identifies individuals who are capable of transmitting the infection to others. However, data on the clinical and microbiologic characteristics of infectivity in both asymptomatic and symptomatic patients is limited, at least in part because upper respiratory samples must be cultured in biosafety level-3 containment laboratories. In animal models, virus culture corresponds with experimental transmission of SARS-CoV-2.[6] Other measures of active virus replication include tests to identify viral sub-genomic messenger RNA which is transcribed only in infected cells[7], and fluorescent *in situ* hybridization to visualize virus together with specific cellular changes; however, neither are available as approved *in vitro* diagnostic tests. Despite these limited laboratory data, most clinical studies suggest that the infectious period lasts from about 2 days after exposure to 12 days after symptom onset among those who develop symptomatic disease. This is also the period during which the viral load as measured by viral RNA copies/ml is likely to be highest.

Tests that can quickly identify many individuals with infectious virus (rather than simply viral RNA) including when individuals have no symptoms could limit the spread of infection and help prevent large outbreaks. Antigen tests have the potential to serve this role. These tests capture viral proteins in a rapid lateral flow format that can be easily performed by untrained personnel and give results in <15 minutes. Although less sensitive than RT-PCR tests, early data suggest that antigen tests can be used to diagnose individuals with infectious virus during symptomatic COVID-19.[8] Antigen tests may play a key role in rapidly identifying those at highest risk for transmitting disease. However, test performance for people without symptoms is poorly understood, and more research into the value of these tests is urgently needed.

Testing at scale also has to be accessible and acceptable.

Broad use of testing requires broad acceptance of testing procedures. Nasopharyngeal swab is not conducive to frequent retesting; most patients find clinician-collected NP swabs invasive and uncomfortable. The use of more easily obtained specimens like nasal swabs (self-collected as well as clinician-collected) and potentially salivary sample types will be important for a broad testing strategy to work in the clinical and community settings. Access to any test continues to be challenging, particularly for individuals without adequate insurance coverage for expenses related to testing and those without easy access to testing in their own communities.

In addition to understanding the performance of rapid antigen tests in the asymptomatic phase, more data are needed about how such tests could be effectively deployed in resource-limited settings. Furthermore, just as with the diagnostic setting, pre-test probability remains key in interpreting the results of any test that is less than 100% sensitive and specific. The low prevalence of SARV-CoV-2 infection in most settings where testing is broadly applied such as schools and university campuses will lead to false positive results and the need for secondary confirmation testing. As more tests are produced at scale, the optimized use case for each test must consider workflow (number of steps, ability to be performed by paraprofessionals at point-of-care, or even in the home setting), turnaround time, central reporting of testing results, especially positives, and accuracy. Tests with a lower limit of detection may allow for pooling of specimens to lower the cost of screening.

Testing must be part of a coordinated strategy.

Even as efforts continue to address these public health testing challenges, recent highly publicized outbreaks (such as university campuses and in the White House) are a stark reminder that testing alone is also not sufficient to prevent community transmission. It is more accurate to consider testing less a prevention strategy than a mitigation strategy. Testing in the absence of other proven prevention strategies is unable to prevent outbreaks.[9] Even as tests become faster with higher sensitivity and specificity, social distancing, mask wearing and avoidance of large indoor and outdoor gatherings must remain central to any public health strategy. While the evidence is growing that widespread access to rapid antigen testing may be a pragmatic tool to interrupt the community transmission of SARS-CoV-2, what will remain equally important to prevent spread of infection to others is what happens before and after test results are delivered. Even the perfect test cannot go it alone.

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