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Perspective

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Rethinking Covid-19 Test Sensitivity — A Strategy for Containment

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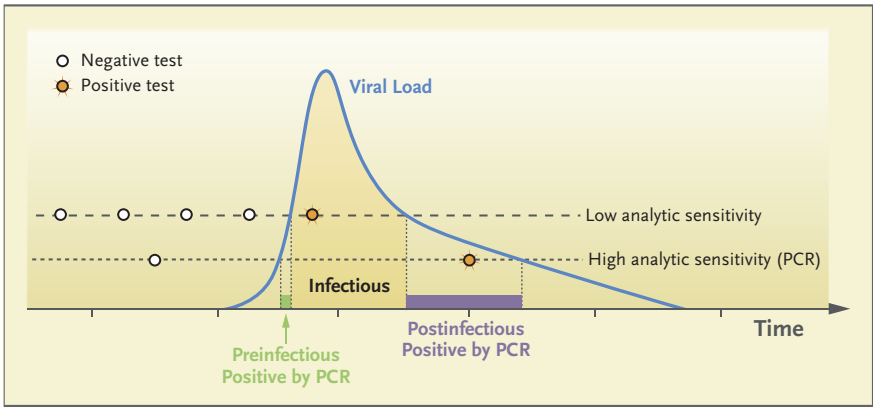
It's time to change how we think about the sensitivity of testing for Covid-19. The Food and Drug Administration (FDA) and the scientific community are currently almost exclusively focused on test sensitivity, a measure of how well an individual assay can detect viral protein or RNA molecules. Critically, this measure neglects the context of how the test is being used. Yet when it comes to the broad screening the United States so desperately needs, context is fundamental. The key question is not how well molecules can be detected in a single sample but how effectively infections can be detected in a population by the repeated use of a given test as part of an overall testing strategy — the sensitivity of the testing regimen.

A regimen of regular testing works as a sort of Covid-19 filter, by identifying, isolating, and thus filtering out currently infected persons, including those who are asymptomatic. Measuring the sensitivity of a testing regimen or filter requires us to consider a test in context: how often it's used, to whom it's applied, when in the course of an infection it works, and whether its results are returned in time to prevent spread.[1-3]

Thinking about impact in terms of repeated uses is a familiar concept to clinicians and regulatory agencies; it's invoked every time we measure the efficacy of a treatment regimen rather than a single dose. With Covid-19 cases accelerating or plateauing throughout much of the world, we urgently need to shift our attention from a narrow focus on the analytic sensitivity of a test (the lower limit of its ability to correctly detect small concentrations of molecules in a sample) to the more relevant measure of a testing regimen's sensitivity to detect infections (the probability that infected persons learn they're infected in time to be filtered out of the population and prevent spread to others). A point-of-care test that was inexpensive enough to use frequently would have a high sensitivity for detecting infections in time to act, without having to meet the benchmark analytic limit of detection (see diagram).

The tests we need are fundamentally different from the clinical tests currently being used, and they must be evaluated differently. Clinical tests are designed for use with symptomatic people, do not need to be low-cost, and require high analytic sensitivity to return a definitive clinical diagnosis given a single opportunity to test. In contrast, tests used in effective surveillance regimens intended to reduce the population prevalence of a respiratory virus



High-Frequency Testing with Low Analytic Sensitivity versus Low-Frequency Testing with High Analytic Sensitivity.

A person's infection trajectory (blue line) is shown in the context of two surveillance regimens (circles) with different analytic sensitivity. The low-analytic-sensitivity assay is administered frequently and the high-analytic-sensitivity assay infrequently. Both testing regimens detect the infection (orange circles), but only the high-frequency test detects it during the transmission window (shading), in spite of its lower analytic sensitivity, which makes it a more effective filter. The window during which polymerase chain reaction (PCR) detects infections before infectivity (green) is short, whereas the corresponding postinfectious but PCR-detectable window (purple) is long.

need to return results quickly to limit asymptomatic spread and should be sufficiently inexpensive and easy to execute to allow frequent testing — multiple times per week. Transmission of SARS-CoV-2 appears to occur days after exposure, when the viral load peaks.[4] This timing increases the importance of high test frequency, because the test must be used at the beginning of an infection to stop onward spread, and reduces the importance of achieving the very low molecular limits of detection of the standard tests.

By several criteria, the benchmark standard clinical polymerase-chain-reaction (PCR) test fails when used in a surveillance regimen. After collection, PCR samples typically require transport to a centralized lab staffed by experts, which drives up costs, drives down frequency, and can delay results by one or more days. The cost and effort required to get tested with a standard test mean that most people in the United States have never received one, and slow turnaround times mean that even when the current surveillance approach does identify infected people, they can still spread the infection for days before notification, which limits the impact of isolation and contact tracing.

The Centers for Disease Control and Prevention (CDC) estimated in June 2020 that there were 10 times as many Covid-19 cases in the United States as had been detected.[5] In other words, despite very high analytic sensitivity of the diagnostic tests deployed for surveillance, today's testing regimens have at best only 10% sensitivity to detect infections and are failing as Covid filters.

Moreover, the well-described long tail of RNA positivity after the transmissible stage means that many, if not most, people whose infections are detected during routine surveillance using high-analytic-sensitivity but low-frequency tests are no longer infectious at the time of detection (see diagram).[2] Indeed, a recent investigation by the *New York Times* found that in Massachusetts and New York, more than 50% of infections identified by PCR-based surveillance had PCR cycle threshold values in the mid-to-upper 30s, indicating low viral RNA counts. Although such low counts could imply either an early- or a late-stage infection, the long duration of the RNA-positive tail suggests that most infected people are being identified after the infectious period has passed. Crucially for the economy, it also means that thousands of people are being sent to 10-day quarantines after positive RNA tests despite having already passed the transmissible stage of infection.

For an effective Covid filter that will stop this pandemic, we need tests that can enable regimens that will capture most infections while they are still infectious. These tests exist today in the form of rapid lateral-flow antigen tests, and rapid lateral-flow tests based on CRISPR gene-editing technology are on the horizon. Such tests are cheap (<$5), can be produced in the tens of millions or more per week, and could be performed at home, opening the door to effective Covid filter regimens. Lateral-flow antigen tests do not have an amplification step, so their analytic limits of detection are 100 or 1000 times higher than that of the benchmark test, but that is largely inconsequential if the goal is to identify people who are currently transmitting virus. SARS-CoV-2 is a virus that grows quickly inside the body, so by the time a benchmark PCR test becomes positive, the virus is well into exponential growth. At that point, it is probably hours, not

days, before the virus grows by orders of magnitude, reaching the detection thresholds of currently available cheap and rapid point-of-care tests. It is after this point, when people would have positive results on both tests, that they would be expected to become infectious (see diagram).

We believe that surveillance testing regimens that can sever enough transmission chains to reduce community spread should complement, not replace, our current clinical diagnostic tests. Imaginative strategies can take advantage of both kinds of tests, using frequent, cheap, and rapid tests at scale to mitigate outbreaks,[1-3] with positive results confirmed using a second rapid test targeting a different protein, or using a benchmark PCR test. Public-awareness campaigns must also communicate that any one negative test does not necessarily imply a clean bill of health, in order to encourage continued social distancing and mask wearing.

The FDA's late August emergency use authorization (EUA) of Abbott BinaxNOW, the first rapid, instrument-free antigen test to receive an EUA, was a step in the right direction. The approval process emphasized the high sensitivity of the test to identify people when their infection is most likely to be transmissible, thus relaxing the required limit of detection by two orders of magnitude from the PCR benchmark. These rapid tests now need to be developed and approved for at-home use to enable true community-wide surveillance regimens for SARS-CoV-2.

Currently, there is no FDA pathway for tests to be evaluated and approved for use in a regimen rather than as a single test or for their public health potential to reduce community transmission. The regulatory lens remains focused exclusively on clinical diagnostic tests, but new metrics could be applied to assess tests in light of an epidemiologic framework if their stated purpose is to reduce community prevalence of the virus. In such an approval pathway, trade-offs among frequency, limits of detection, and turnaround time would be expected and evaluated appropriately.[1-3]

To defeat Covid-19, we believe that the FDA, the CDC, the National Institutes of Health, and others must encourage structured evaluations of tests in the context of planned testing regimens to identify those that will provide the best Covid filters. Frequent use of cheap, simple, rapid tests will accomplish that aim, even if their analytic sensitivities are vastly inferior to those of benchmark tests.[1] Such a regimen can help us stop Covid in its tracks.

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