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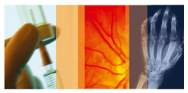

COVID-19 Testing: The Threat of False-Negative Results

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COVID-19 Testing: The Threat of False-Negative Results

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As healthcare systems around the world attempt to cope with the coronavirus disease 2019 (COVID-19) 'tsunami', concerns about ongoing spread of disease from individuals who are infected without symptoms have been raised.[1, 2] Efforts to develop and implement testing protocols are underway, and expanded testing for COVID-19 is a necessary immediate step toward understanding and resolving this crisis.[3] As tests become more available, observing principles of evidence-based clinical reasoning concerning the meaning of diagnostic test results is essential. For negative test results in particular, failure to do so has direct implications for the safety of the public and healthcare workers and for the success of efforts to curb the pandemic. Specifically, anticipation of a less visible second wave of infection from individuals with false-negative test results is needed.

The magnitude of this concern is difficult to determine because test performance characteristics (and the validity of the studies generating them) have not been reported clearly or consistently to date. Fundamental characteristics of clinical diagnostic tests for COVID-19 infection including sensitivity, specificity, and corresponding likelihood ratios are largely unknown. Sensitivity is particularly important in understanding the risk of false-negative testing.[4] The diagnostic sensitivity of reverse transcriptase–polymerase chain reaction (RT-PCR) testing for other viruses is highly variable, but early data from China suggested relatively poor sensitivity of initial RT-PCR tests.[5] Even with sensitivity values as high as 90% the magnitude of risk from false-negative test results will be substantial as testing becomes more widespread and the prevalence of COVID-19 infection rises.

Why is this relevant to stopping the spread of COVID-19? False-negative results are consequential. Individuals with these results may relax physical distancing and other personal measures designed to reduce the transmission of the virus to others. In the case of clinicians, they may be sent to the frontlines of care and inadvertently transmit the virus to patients and colleagues, further straining the already precarious ability of the healthcare system to respond to the pandemic.

To illustrate the potential magnitude of this problem in the general population, consider the following examples from Spain and the United States, assuming a test with 90% sensitivity. The president of the region of Madrid has predicted that 80% of Madrid's 6.5 million residents will become infected by COVID-19. If the entire population was tested, of the anticipated 5.2 million infected individuals, 520,000 people would be falsely classified as free of infection. Even with less widespread testing or targeted testing among random samples, the number of false-negative tests could be massive. Similarly, it has been estimated that the COVID-19 rate in California may exceed 50% by mid-May 2020. With a population of 40 million people, 2 million false-negative results would be expected with comprehensive testing. Even if only 1% of the population was tested, 20,000 false-negative results would be expected.

If the COVID-19 infection rate among the >4 million doctors, nurses, and other clinicians providing direct patient care in the United States was even 10% (far below most national prevalence predictions), more than 40,000 false-negative results would be expected if every clinician were to receive a test. If the sensitivity of the test was only 70%, as cited in early reports,[5] the number of false-negative results would triple to well over 100,000. Regardless of

the exact total, every one of these healthcare workers could spread disease despite the seeming reassurance of a negative COVID-19 test. At present, CDC guidelines for asymptomatic healthcare workers with negative COVID-19 testing are based on both the nature of clinical exposure to COVID-19 patients and personal symptoms, so that negative testing in an asymptomatic healthcare worker could lead to an immediate return to work for many engaged in routine clinical care.[6] Furthermore, restrictions on untested or test-negative asymptomatic healthcare workers with community exposures are limited or absent. To the extent that asymptomatic spread may contribute to disease transmission and serious illness, these policies could place colleagues and patients at ongoing risk.

At least four recommendations seem prudent given these concerns (Table). First, continued strict adherence to physical distancing, hand-washing, surface disinfection, and other preventive measures is required regardless of risk level, symptoms, or COVID-19 test result. In addition, adequate personal protective equipment (PPE) for healthcare workers may be necessary to protect these workers and their patients even when both have tested negative. This is problematic at present given PPE shortages, which will worsen as COVID-19 spreads unless production and distribution dramatically improve. Masks, eye shields, gowns, gloves, and other equipment must be available to prevent transfer of the virus to medical personnel so the risk of subsequent transmission is stopped before it can begin. Given concerns about the adequacy of cloth masks,[7] medical grade masks must be available for every healthcare worker, and consideration should be given to wearing masks in all clinical settings.[8]

Second, there is an urgent need for development of highly sensitive and specific tests or combinations of tests to minimize the risk of false-negative results and ongoing transmission based on a false sense of security. Improved RT-PCR tests and serological assays are needed. Diagnostic test characteristics must be ascertained in studies rigorously designed to minimize the risk of biased results,[4] and test performance characteristics should be clearly reported so the impact on disease likelihood can be determined.

Third, risk levels must be carefully assessed prior to testing. For example, individuals in endemic areas, including healthcare workers, may need to be considered at elevated risk of COVID-19 infection even without symptoms or known exposures. It is possible that individuals with false-negative test results may be less contagious, perhaps correlating with lower viral loads, but this is not yet known and cannot be assumed. Until such factors are better understood, negative test results should be viewed cautiously, especially for individuals in higher-risk groups.

Fourth, development and communication of clear risk-stratified protocols for management of negative COVID-19 test results is needed. These protocols must evolve as diagnostic test, transmission, and outcome statistics become more available. For truly low-risk individuals, negative test results may be sufficiently reassuring on their own. However, for higher-risk individuals, even those without symptoms, the risk of false-negative test results necessitates continued measures to protect against spread of disease. For members of the public, this may mean extended self-isolation or quarantine. For healthcare workers in endemic areas, return to work after negative testing may need to be delayed until more sensitive tests

can be administered and repeat testing is negative, even without symptoms. The adverse impact of such measures on a stressed healthcare system, especially in the hardest hit areas, further emphasizes the importance of prevention of transmission to healthcare workers to mitigate workforce limitations as COVID-19 diagnoses accumulate.

Practicing physicians and the entire healthcare workforce are facing a global crisis. The challenge of COVID-19 must be faced with our best science. As we rise to this occasion, we would do well to remember the principles of evidence-based diagnostic test interpretation lest we augment the very tide we are attempting to stem.

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Table. Recommendations to Mitigate Risk From False-Negative COVID-19 Test Results.

1.	Strictly adhere to infection control measures, including: Physical distancing Hand hygiene Environmental cleaning and disinfection Adequate personal protective equipment (PPE) for healthcare workers
2.	Develop and disseminate accurate diagnostic tests Improved reverse transcriptase–polymerase chain reaction (RT-PCR) tests Serological assays Report diagnostic test characteristics from methodologically rigorous studies
3.	Assess risk levels prior to testing For individuals and environments with higher pretest probability of COVID-19 infection, confidence in negative COVID-19 test results should be lower
4.	Establish risk-stratified protocols for management of negative COVID-19 test results For higher-risk individuals (including healthcare workers), delay return to work even in the absence of symptoms