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False Negatives Raise Doctors' Doubts About Coronavirus Tests

By Kristen V Brown
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(Bloomberg) -- False-negative results from coronavirus tests are becoming an increasing concern, say doctors trying to diagnose patients and get a grip on the outbreak, as a surprising number of people show up with obvious symptoms only to be told by the tests that they don't have the disease.

While still more research is necessary to determine the true prevalence of such false-negative results, experts agree that the problem is significant. False negatives not only impede the diagnosis of disease in individual patients and an accurate understanding of the extent of its proliferation, but also risk patients who think they aren't ill further spreading the virus.

Some doctors described situations in which patients show up with clear symptoms such as a cough and fever, test negative, and then test positive later on. It's a particular issue in New York, where the disease has likely infected far more than the 174,000 people confirmed through limited testing. At Jacobi Medical Center in the Bronx, doctor Jeremy Sperling says so-called false-negative tests are now a frequent occurrence in the emergency room.

“If a patient presents with classic Covid symptoms, but tests negative, they’ve still got Covid,” said Sperling, who is the chair of emergency medicine at the hospital. “There is just nothing else it could be in New York City in 2020.”

Concerns about false negatives arise from a mix of factors: quickly created tests from dozens of labs and manufacturers that haven't been extensively vetted by federal health regulators; a shortage of supplies and material for the tests that may impact results, long incubation times for the infection, and the challenge of getting an adequate sample from a patient.

Most tests rely on a nasal swab that penetrates deep into the pharynx, the mucous membrane behind the nose and mouth. Even for a trained health worker, it can be difficult: It’s an invasive procedure that often causes patients to squirm. With a shortage of staff to conduct such widespread testing, in many cases people not typically trained to do so are collecting samples.

Ryan Stanton, an emergency medicine physician in Lexington, Kentucky, said that most people likely aren't swabbing patients correctly. “They're not getting far enough back there to get a good sample,” he said.

The Food and Drug Administration has loosened rules for getting the tests out on the market. While a new test marketed by a major manufacturer would typically undergo a rigorous approval process with the FDA, including studies to confirm its accuracy, the agency is instead using a shorthand version of that process. Under what's known as an Emergency Use Authorization, or EUA, manufacturers can begin making and distributing tests for use in patients without the usual, more thorough process. The FDA has cleared more than 40 different Covid-19 tests through EUAs, according to the agency’s website, reflecting the need to get as many tests out into the field as possible.

“We have in this country a really robust system for pre-market approval,” said Erika Lietzan, a professor of law at the University of Missouri. “Emergency use authorization is not the same thing as approval. It is based on many fewer data.”

Similar measures have been taken around the world, as the U.S. and other health authorities race to build diagnostic capacity and get a handle on the outbreak. That haste, however, may have come at a cost. One study out of China published online prior to peer-review found that for the nasal-swab tests most commonly administered, as many as one in three tests may produce a false-negative result.

In some cases, lacking tests or not trusting the results, doctors have turned to chest X-rays or CT scans to diagnose patients by looking for signs of infection in the lungs.

"A clinical diagnosis is a lot more useful than the test in many cases," Sperling said. "Though it's nice to clinch the diagnosis.

The ramifications of false negatives are not just medical, but political.

"Especially as we talk about reopening the country prematurely, there is a serious risk of people who think they are negative contributing to a second round of the virus spreading," said Congressman Lloyd Doggett, a Texas Democrat and Chairman of the House Ways and Means Health Subcommittee, who on Thursday issued a call for more data on the accuracy of results.

Viral Genetics

The majority of tests rely on a technique known as PCR to process samples, which involves extracting ribonucleic acid, or RNA, from the virus samples taken from a patient. RNA, however, is especially unstable: Enzymes that break it down exist all over the place, including on our bodies. Amid a scarcity of supplies, hospitals have reported splitting the liquid that preserves samples in testing kits, or using supplies from flu and strep kits. Shortages of the right swabs have led some clinics to use alternatives; some are even attempting to validate Q-tips. Shortages of chemicals to process samples have also led to experimentation with substitutes. All of these situations could potentially lead to an inaccurate result.

Also unknown is the best time in a patient's illness to conduct a test. For the flu, for example, tests are effective when a person exhibits early symptoms because the virus has a short incubation period. Covid-19 appears to have a much longer incubation period, and there is a dearth of data about when in the course of the disease a test is most likely to be positive, said Catherine Klapperich, director of Boston University's Precision Diagnostics Center.

"Right now, we don't have enough data or knowledge of how this disease goes through a population to make those guidelines," she said. "We're making those guidelines on the fly."

This could account for why a patient suspected to have the virus might test negative several times before testing positive. One case study posted this week described a 34-year-old man who tested negative four times before finally testing positive five days

after being admitted to a hospital. Like the doctor in the Bronx, researchers suggested using chest X-rays for earlier diagnosis.

Under typical circumstances, said Jeffrey Gibbs, the director of Washington, D.C., law firm Hyman, Phelps & McNamara, the FDA would evaluate not just the test itself but how it performs in the real world.

“The FDA really can’t assess as they would in a normal scenario right now,” he said. “We don’t have time for a 100% perfect test that works every time.”

Good Enough

The Trump administration has appointed Brett Girior, a senior official in the Department of Health and Human Services, to oversee U.S. testing efforts, which are crucial to attempts to reopen the economy, track cases and stop new infections.

False negatives are always a concern,” Giroir said in an interview with Bloomberg News. “The tests that we have we think are really pretty good.” Giroir said that a 90% accuracy rate or better, including false positives and false negatives, is the goal. “With any test, there's always false positives and false negatives, that's just the reality of testing.”

Giroir said that doctors and nurses should continue using their judgment, especially when patients show up with clear Covid-19 symptoms in an area with lots of cases. “If a person comes in today in New York with interstitial pneumonia, coughing, with fever, you don't even need a test to tell you that's likely Covid,” Giroir said.

With the combination of long waits for results, tests being given only to the sickest patients, and the concern over false negatives, some jurisdictions are changing how they characterize their outbreaks. At Reid Health in Indiana, the health-care network now includes the number of “patients in containment areas” rather than simply positive and negative results. The small town on the Ohio border where Reid is headquartered has about 36,000 residents. At least 6,900 cases have been confirmed in the state.

“This data will no longer include the number of negative tests results as studies are showing a relatively high ‘false negative’ outcome of testing,” the health system said on its website.

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"Our infectious disease experts think that about 30% of patients we believe have Covid are testing negative," said Thomas Huth, the health network's vice president of medical affairs. "We have tested some again, but they remain negative."

In mid-March in Berkeley, California, Christine Miksza's toddler went to the emergency room with Covid-19 symptoms, only to test negative. A week and a half later, Miksza, 33, came down with symptoms and tested negative herself. In the meantime, they had gone to the grocery store several times and on one occasion her husband had been to work.

"We would have been much stricter about not leaving the house," she said, had they had a positive result. It was only after another week of worsening illness and a chest X-ray that her doctors decided there was nothing else she could possibly have. "We could have been spreading germs, but we just didn't know. This test is just taken as 100% fact."

She's still waiting for her second test's results.

Source: https://www.msn.com/en-us/health/medical/false-negatives-raise-doctors-doubts-about-coronavirus-tests/ar-BB12uwHS