Medical News & Perspectives

COVID-19 Testing Moves Out of the Clinic and Into the Home

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During the COVID-19 pandemic, people have become used to watching movies at home instead of in a theater, ordering takeout or delivery instead of eating in a restaurant, and meeting with coworkers via Zoom at the kitchen table instead of face-to-face in the office.

And, apparently, many individuals have opted to test for COVID-19, or at least collect specimens for testing, from the comfort of their own home instead of at a clinic or physician's office.

Over-the-counter COVID-19 tests and specimen collection kits became the top selling product group at CVS Pharmacy in mid-July, spokesman Matthew Blanchette told *JAMA* in an email. CVS Pharmacy in mid-April began selling the Ellume and Abbot BinaxNOW COVID-19 rapid antigen tests that provide results in 15 minutes. The retailer also offers the Pixel by Labcorp home collection kit, which requires that specimens be sent to a laboratory for processing.

By mid-September, the US Food and Drug Administration (FDA) had authorized emergency, over-the-counter use of 7 at-home rapid antigen tests by both symptomatic and asymptomatic individuals.

The home tests, most of which are also sold on Amazon and at other pharmacies and supermarkets—reached the top of the CVS bestseller list just as the B.1.617.2 (Delta) variant took off in the US. Weeks earlier, many health departments had shut down or reduced testing because cases had been declining, and they shifted resources to vaccinating people.

"Health departments definitely scaled back testing because there was less demand," Marcus Plescia, MD, MPH, chief medical officer for the Association of State and Territorial Health Officials, said in an interview. "They were running these [testing] sites and no one was coming."

Vaccination alone, when a sizeable segment of the US population remains unvaccinated in the face of the highly transmissible Delta variant, isn't enough to contain the spread of SARS-CoV-2. "Testing for SARS-CoV-2 is central to COVID-19 management," a group of US and UK scientists wrote in a commentary this past spring.

"The speed of the results is so much more important for infection control," coauthor Michael Mina, MD, PhD, noted in an interview. Mina, assistant professor of epidemiology, immunology, and pathology at Harvard, has long advocated for frequent, rapid antigen testing as a public health strategy to help control the pandemic.

Vaccinated individuals still need to be tested because they can become infected and transmit SARS-CoV-2 to others, the US Centers for Disease Control and Prevention (CDC) advises. They should get tested if they have COVID-19 symptoms or 3 to 5 days after exposure to someone with suspected or confirmed disease, and, if positive, isolate, the CDC recommends.

Speed vs Sensitivity

Len Lichtenfeld, MD, sought to buy the BinaxNOW test after going to a late-July conference in southern Georgia, an area with high COVID-19 incidence near the Florida border. About 150 oncologists, all vaccinated but not all masked, had attended the meeting. Three days after returning home to Atlanta, Lichtenfeld, former deputy chief medical officer of the American Cancer Society, learned via email that 2 attendees had tested positive for COVID-19.

After consulting with a friend who's an infectious disease specialist, Lichtenfeld opted for the BinaxNOW test. "Home tests are not as accurate" as the gold standard polymerase chain reaction (PCR) tests, he acknowledged in an interview. "I'm fully aware of the issues around sensitivity and specificity." However, he valued the speed with which the tests provide results. Rapid antigen tests, which detect proteins on the virus surface, are cheaper and provide answers within minutes instead of a day or 2 (or 5 or 6) like PCR tests, which detect genetic material from SARS-CoV-2.

PCR tests' high sensitivity isn't always a good thing. They can return positive results weeks after someone has recovered from COVID-19 and is no longer infectious. In infected people who become symptomatic, the highest risk of transmission appears to occur 2 days before symptom onset through 5 days after, while asymptomatic people seem to clear the virus even more quickly, according to a systematic review and meta-analysis published in January.

But now that 7 over-the-counter rapid antigen tests have received Emergency Use Authorization (EUA) from the FDA, research is beginning to suggest that they aren't as sensitive in the real world as they appeared to be in clinical trials. That's not always the fault of the tests themselves but is sometimes due to user error, such as testing too soon or too long after a possible SARS-CoV-2 exposure or not correctly swabbing the nose.

"Tests have different uses," Lao-Tzu Allan-Blitz, MD, a resident physician in internal medicine and pediatrics at Brigham and Women's and Boston Children's hospitals and coauthor of a recent study comparing BinaxNOW with PCR, told *JAMA* in an interview. "What we're trying to understand is what is the best use for this type of test."

Comparing Antigen, PCR Tests

Using specimens from the same person, research found that antigen test results are more likely to agree with positive PCR tests when viral load is high, as determined by the PCR test's cycle threshold value.

Cycle threshold is the number of cycles viral RNA must be amplified to be detected with PCR, which is why cycle threshold values are inversely proportional to the amount of target nucleic acid in the specimen. Lower cycle threshold values are associated with higher viral loads and more severe COVID-19. Typically, though, physicians who order PCR tests are given only positive or negative results, not cycle threshold values.

Allan-Blitz and Jeffrey Klausner, MD, MPH, a public health infectious disease specialist at the University of Southern California's Keck School of Medicine, analyzed data from 18 457 individuals who had been tested in October and November 2020 with both BinaxNOW and PCR at 4 Florida sites.

Of that total, 17.1% had a positive PCR test result. However, only about half of those who tested positive with PCR, whether symptomatic or asymptomatic (a recent systematic review concluded that at least a third of infected people never develop symptoms), also tested positive with BinaxNOW.

But the likelihood that an antigen test would agree with a positive PCR test increased along with the specimens' viral load. When a positive PCR test's cycle threshold value was less than 30, suggesting a higher viral load, BinaxNOW was positive 75% of the time, Allan-Blitz and Klausner found.

The authors noted that they saw a lower frequency of SARS-CoV-2 antigen detection in people with positive PCR tests than Abbott's clinical trials did. For example, in a clinical trial of 52 people who tested themselves or their child with BinaxNOW and also were tested with PCR, 91.7% of those positive with PCR were also positive with BinaxNOW. Unlike the people in Allan-Blitz and Klausner's study, though, all the Abbott trial participants were symptomatic and tested within 7 days of becoming sick—before their viral loads fell too low for the antigen test to detect—which could help explain why the level of agreement with PCR was so high.

Even with in-person guided instruction, BinaxNOW's sensitivity was lower when people swabbed their own nose or their child's nose than when a trained staff person collected the specimen, found another recent study comparing the antigen test with PCR in symptomatic individuals.

When staff swabbed 297 people's noses, BinaxNOW detected 74% of the infections that PCR identified. But when 44 people collected their own specimen or their child's, BinaxNOW's agreement with PCR tests dropped to 57%. Like the Allan-Blitz and Klausner study, this one also found that BinaxNOW was more likely to agree with positive PCR tests that had lower cycle threshold values.

Probably the biggest variable with at-home tests is how adept people are at swabbing their noses to collect specimens for testing, coauthor Greg Martin, MD, said in an interview. "They don't have a great sense of how much to collect, how deep to push."

BinaxNOW and other over-the-counter rapid antigen tests offer how-to videos, and "the instructions themselves are actually quite good," noted Martin, professor of pulmonary, allergy, critical care, and sleep medicine at Emory University.

Timing of testing could also play a role in whether antigen tests detect an infection, he said. "Viral load changes over the course of the disease," Martin explained. "If your exposure was yesterday, testing the next day does not make sense."

On the other hand, testing too long after symptom onset or possible SARS-CoV-2 exposure could result in a false negative because of a diminished viral load. The BinaxNOW fact sheet for health care professionals indicates that specimens collected from SARS-CoV-2–infected patients who've had symptoms for more than 5 days may be more likely to have a negative antigen test result than a negative PCR test result. "Negative results should be treated as presumptive and confirmed with a molecular [PCR] assay, if necessary, for patient management," according to the fact sheet.

Martin and his coauthors also conducted laboratory assessments of BinaxNOW to see how effective it was in detecting SARS-CoV-2 variants of concern and how it compared with other rapid antigen tests. Using remnant clinical samples of the variants of concern, they found that BinaxNOW detected the Delta variant in samples with a PCR cycle threshold value of less than 22, which was the lowest cycle threshold value of all variants tested. BinaxNOW's sensitivity in detecting SARS-CoV-2 was comparable with the 2 other rapid antigen tests they evaluated in the laboratory, both of which cost more, the authors noted.

"The Delta variant, along with all other variants of concern, are primarily defined by mutations in the spike protein," Abbott pointed out in an August 10 statement. Rapid antigen tests "do not rely on the spike proteins to detect the virus, which means that these new variants do not affect test performance."

Not Positive About Negatives

In areas with high SARS-CoV-2 transmission, which at present is virtually the entire US, research suggests that people can be pretty sure they're infected if their rapid antigen test result is positive because the tests are highly specific.

"A positive result really means a positive result," Allan-Blitz said. On the other hand, the antigen tests' lower sensitivity translates into a higher rate of false negatives than with PCR testing, especially when SARS-CoV-2 is circulating widely.

The BinaxNOW consumer fact sheet notes that "you could possibly still have COVID-19 even though the test is negative." People who continue to have COVID-19–like symptoms after testing negative should consult their physician to see if they need follow-up testing, the fact sheet states, using wording similar to that of other rapid antigen home tests. Symptomatic individuals who test negative should confirm that result with a PCR test, although 2 negative antigen tests likely means symptoms are not due to SARS-CoV-2 infection, Plescia said.

Antigen tests' sensitivity is even lower in people who don't have symptoms, suggests a study published in January. Health professionals at 2 community-based testing sites in Pima County, Arizona, collected 2 specimens each, 1 for testing with BinaxNOW and 1 for PCR, from 3419 individuals, about three-quarters of whom were asymptomatic. Compared with PCR testing, BinaxNOW's sensitivity was 64.2% for specimens from symptomatic individuals but only 35.8% for specimens from asymptomatic people.

However, Mina, who wasn't involved in the study, argues that compared with

symptomatic people, asymptomatic individuals have often been infected longer before getting tested, so their viral load could be too low to detect with antigen tests, or, for that matter, spread to others.

That's not always the case, though. Epidemiologist Michael Osterholm, PhD, MPH, pointed out in an interview that "These false negatives are a problem in that they're giving people the assurance that they're okay when they're not."

Who's Keeping Track?

As more people use home tests, an unintended consequence is that COVID-19 case reporting has "fundamentally changed" from earlier in the pandemic, Osterholm, founder and director of the Center for Infectious Disease Research and Policy at the University of Minnesota, noted.

"We're seeing very, very little reporting despite brisk sales" of the tests, he said. "That's a real challenge."

Testing sites are required to report all results to the CDC. But with most over-the-counter home tests, "we have no idea whether somebody who takes that test is positive or negative," Plescia said. "I was hoping that there would be some bold writing somewhere [on the test packages]: Please report your test results."

Ellume home test users must download an app that, according to the company's website, complies with CDC reporting requirements via an encrypted cloud connection that complies with the Health Insurance Portability and Accountability Act. The app automatically reports results, following the guidelines of "appropriate public health authorities," according to Ellume.

Other tests depend on the honor system. Abbott announced September 1 that BinaxNOW users can now choose to report their results via the company's Navica platform. Instructions for health care professionals about Quidel's QuickVue over-the-counter rapid antigen test simply state that "individuals should provide all results obtained with this product to their healthcare provider for public health reporting."

While over-the-counter self-tests can improve COVID-19 surveillance, that depends on people reporting positive results, and the likelihood of that happening varies from person to person, Martin said.

In recommendations updated August 2, the CDC advises that people whose self-test is positive should tell a health care professional. People who don't have a health care professional should report their positive result to their local or state health authorities, according to the CDC.

However, Lichtenfeld noted that, "we should not make the assumption that everyone is able to participate in the health care system."

Testing, 1, 2, 3, Repeat

When a test is about as good as a coin toss, it's not useful as a one-off, such as testing people before allowing them to enter a theater or a restaurant, Allan-Blitz said.

But although rapid antigen tests aren't as sensitive as PCR, their speed and lower cost make it easier to conduct serial testing, which improves the chance of detecting infection as viral loads increase. Using the tests in "closed environments" where people are tested regularly, such as in schools, would likely be a better application, Allan-Blitz said.

"They're not as accurate as the lab-based PCRs, but if you do serial testing, they're pretty accurate," Plescia said. "You will eventually catch [positive] people."

A recent research letter in *JAMA Network Open* highlighted the potential benefit of rapid antigen home tests for the workplace. The letter described a study comparing an investigational rapid antigen test developed by E25Bio, headquartered in Cambridge, Massachusetts, with PCR testing of 257 people affiliated with 3 coworking laboratories in Cambridge and Boston.

Twice a week for 6 months, study participants self-collected a pair of nasal swabs: 1 used for rapid antigen testing and the other sent to a laboratory for PCR testing. Fifteen developed COVID-19, and the twice weekly antigen tests detected infections in all of them, before most recognized that they had disease symptoms. The antigen test's sensitivity within 0 to 12 days of symptom onset was 78.9%. "Frequent at-home testing with [direct antigen rapid tests] allows infected individuals to be identified and quarantined immediately," concluded the authors, some of whom worked for E25Bio. "Such surveillance can prevent viral transmission in in-person work environments or other social settings. "

The UK and Greece distribute free rapid antigen self-tests, although the latter, in an effort to increase vaccination rates, began requiring in mid-September that unvaccinated individuals pay for the tests, which are required once or twice a week, depending on their profession. In the US, though, "we have yet to embrace [rapid antigen] tests as a public health tool," Mina said. "It's just dumbfounding that we are so short-sighted here."

People in the UK can order a free pack of 7 rapid antigen tests from the National Health Service (NHS) as often as every day or pick them up at pharmacies or community centers. The tests, which are to be used twice a week, are for asymptomatic people aged 11 years or older who can't get them at work or school, according to the NHS.

In the US, rapid antigen tests with EUA are too expensive for serial testing, Mina noted. BinaxNOW is the cheapest, but it's still $24 at CVS and $20 on Amazon for a package of 2, which are supposed to be used by the same person twice over 3 days with at least 36 hours between them. A package with 1 Ellume home test costs $38.99 at CVS. (If they can even be found. In mid-September, both Ellume and BinaxNOW were listed as "currently unavailable" on Amazon.)

Lichtenfeld said he and his wife ended up not using any of the 5 packages of BinaxNOW that he bought after the conference. They felt fine and instead decided to limit their contact with other people for 10 days. Not that the tests were a waste of money, said Lichtenfeld, who has a second home in north Georgia. "I travel with a couple of these tests just in case we do run into a problem up there because it's pretty rural," with few testing sites, he explained.

"To me, the message is there is a value to home testing," said Martin, president of the Society of Critical Care Medicine.

Martin is also co–principal investigator at the Atlanta Center for Microsystems Engineered Point-of-Care Technologies, 1 of 5 such National Institutes of Health (NIH)–funded centers in the US. The Atlanta center has evaluated 40 to 60 potential COVID-19 tests for the NIH's Rapid Acceleration of Diagnostics initiative, Martin said.

"People should be able to rely on these," he said of rapid self-tests. "As long as they perform well with variants, I think they're an invaluable resource." ■

Note: Source references are available through embedded hyperlinks in the article text online.

Disclosures: Dr Mina reports receiving an honorarium in February 2020 to speak on an Abbott-sponsored expert panel about coronavirus epidemiology and serving as a medical advisor for Detect, a startup company planning to make molecular diagnostic tools.