Researchers race to develop in-home testing for COVID-19, a potential game changer

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For most people, COVID-19 test entails a swab up the nose in a doctor's office or at a drive-in site. The sample then goes out to a lab. Results come back within a few days to a week—a waiting period that's simply too long to stop the spread of the virus on a wide scale.

That default approach to testing may soon change. On July 29, the US Food and Drug Administration (FDA) released new recommendations encouraging companies to pursue diagnostic tests that could be used outside the lab.

Such tests could be game changing. A widely available, quick, and accurate home test could dramatically reduce community transmission of the virus and help identify emerging hotspots. Some companies already have tests ready for the FDA to assess for Emergency Use Authorization (EUA)—a special designation for urgently needed but unapproved medical products. In August, the agency issued an EUA for a 15-minute rapid test similar to a pregnancy test, which could be administered by healthcare providers at point-of-care locations such as clinics and schools. It was a potentially important step.

But rapid at-home tests could be an even greater public health advance. "The potential is huge, to say it bluntly," says epidemiologist Michael Mina at the Harvard T.H. Chan School of Public Health and a medical director of molecular virology at Brigham and Women's Hospital in Boston, MA. Imagine a pack of testing strips, he says, similar in size and shape to a pack of gum. Now imagine if such a product were available at drugstores and cheap enough for millions of people to use daily. These sorts of tests would arm the public with real-time knowledge of their infection status. Newly infected people could isolate at home, severing transmission chains and stopping the spread of the virus.

To contain the COVID-19 pandemic, we need more frequent testing with faster turnaround times. Recent testing advances, and a move by the FDA, could help bring rapid in-home tests to market. Image credit: Shutterstock/ Pordee_Aomboon.

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Even low-sensitivity tests, which only catch people at the early and most-contagious stage of infection, could still be useful, says Daniel Larremore, an infectious disease modeler at the University of Colorado, Boulder. Larremore recently coauthored a modeling study with Mina and others, now available in a preprint (1), showing that daily rapid testing, even with low-sensitivity tests, could be a useful screening strategy to discreetly identify asymptomatic COVID-19 patients. "What we need is something cheap and fast," Larremore says, "that can be rolled out to orders of magnitude more people with regular frequency." To do so would require overcoming a number of challenges—regulatory, logistical, and behavioral. Any viable test would need to be reliable enough to secure an EUA but affordable enough to be manufactured and distributed to millions of people—and user-friendly enough to keep people self-testing day after day. Such a test could have a huge impact on reopening plans in the United States and elsewhere.

Primary Care

Two broad categories of tests exist for active SARS-CoV-2 infections: nucleic acid and antigen. Nucleic acid tests, considered the gold standard for accuracy, are typically done by polymerase chain reaction (PCR). These tests work by identifying even tiny concentrations of viral RNA, down to tens of copies per microliter, in nasal swabs and saliva. Although PCR tests are sensitive, they require expensive laboratory equipment and robotics to amplify viral RNA. "So it's not exactly a test you could have at home," says Gavin Knott, a postdoctoral biochemist at University of California, Berkeley. There have been advances in the speed of PCR tests recently, in particular the SalivaDirect test. Awarded an EUA in August, SalivaDirect processes saliva samples without a time-consuming, costly RNA extraction step before the PCR itself (2). Although SalivaDirect is still a lab-based test, it is one to three hours faster than other PCR protocols, says co-developer Nathan Grubaugh, a virologist and epidemiologist at the Yale School of Public Health in New Haven, CT.

Although PCR can reliably confirm an infection once a patient suspects they have COVID-19, the approach is too labor intensive for widespread screening of the larger asymptomatic population. A few other tests also detect nucleic acids, without PCR. These include Loop Mediated Isothermal Amplification (LAMP) tests as well as CRISPR-based tests, both of which can amplify a target viral DNA or RNA sequence at room temperature. LAMP and CRISPR are very accurate although somewhat less sensitive than PCR. They don't need as much equipment as PCR, making them promising candidates for home testing, says Janice Chen, cofounder and chief technology officer of San Francisco, CA-based Mammoth Biosciences. That possibility has been stymied thus far by a variety of factors, says Chen, including pricing pressures and the prospect of an uncontrolled testing environment with unskilled users. Mina says the FDA has set a high bar for testing sensitivity, and these tests just aren't there yet.

New protocols for LAMP testing could help hasten the development of cheap, fast-turnaround tests. One such protocol, published September 8, can detect amplification of viral RNA via color change after about 30 minutes, according to the study—although as of now, it would be a lab-based test requiring a technician (3).

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Antigen tests, run via a paper strip, are a faster and less costly alternative to nucleic acid tests. Dip the strip into a patient's saliva or mucus, and the fluid of the sample climbs the strip by capillary action. As it does, antibodies preloaded onto the strip hunt for viral proteins in the sample. A simple visual cue, such as the appearance of a line or color, indicates a positive result, similar to a home pregnancy test.

Although fast and user-friendly, antigen tests are less sensitive than nucleic acid tests, particularly when a patient has a low-level infection. In those cases, the tests often fail to detect very dilute viral proteins in the sample. Hence, a negative result from an antigen test doesn't necessarily mean that a patient is free of infection. One August study, for example, found that the Coris BioConcept COVID-19 Ag Respi-Strip antigen test, now approved in Belgium, only detected 32 of 106 positive samples, a sensitivity of just over 30% (4).

However, antigen tests do reliably catch people at the peak of their infection, when the viral load is highest and most contagious, Mina notes. In that sense, an antigen positive means a person is likely shedding the virus; whereas a PCR test, which stays positive for weeks longer, could be picking up an older infection that's no longer contagious. Quarantining at that point is too late.

Indeed, Larremore's recent preprint study suggests both gold-standard PCR and less-sensitive antigen or LAMP tests could be useful to stop COVID-19 (1). Rapid and frequent testing is paramount, according to the study, not the sensitivity of individual tests. Larremore and coauthors modeled a variety of different testing strategies in hypothetical human populations, administering PCR, LAMP, or antigen tests at different frequencies and with different result turnaround times. The models assumed that everyone in the population was tested, that symptomatic patients self-quarantined, and that asymptomatic patients only quarantined after testing positive. Based on existing tests, the models also assumed that LAMP is 100 times less sensitive than PCR, whereas antigen is 1,000 times less sensitive than PCR, Larremore says.

Ultimately, the study found that twice-weekly PCR, LAMP, or antigen testing could all contain the epidemic. Thresholds for containment were every six days for PCR, every five days for LAMP, and every 4.5 days for antigen testing, Larremore notes. But crucially, any testing regimen had to give patients same-day or next-

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day results. Hence, frequent testing and rapid turnaround were much more important than the accuracy of individual tests in the models, Larremore says, because infected patients who test twice weekly will eventually get a positive test, even if they get a false negative first. The finding opens the door to more widespread antigen-based screening, he adds. Rapid, affordable, and easy to use, antigen strips could facilitate in-home testing. Today, there are several antigen tests for COVID-19 on the market that already have EUAs. But none is authorized for home use yet (and none has the more general FDA approval required for medical products in nonemergency situations).

Bringing Testing Home

When the FDA released its late-July recommendations for companies developing at-home diagnostic tests, Commissioner Stephen M. Hahn said in a press release that rapid at-home tests "will be a game changer in our fight against COVID-19" (5).

The FDA outlined the information companies should include in their EUA applications: technical data on the safety and efficacy of the test; how it was validated, including clinical performance data; and basic science, such as the viral proteins an antigen test would target. The FDA also asked for information about how the products will be sold, whether by prescription or over the counter, as well as where the test will be manufactured and its timeframe for production and distribution (6).

Companies, though, are by no means starting from scratch. Among those aiming to seek FDA authorization is E25Bio, a biotech startup based in Cambridge, MA. E25Bio makes rapid, paper-based antigen strip tests that target spikey proteins studding the outside of the novel coronavirus. The company has already developed a lab-based test that's handheld and gives results in 15 minutes. It could easily be adapted to home testing, says E25Bio cofounder Bobby Brooke Herrera. The only difference between the lab test and an at-home test is that the lab test concentrates a person's sample using a centrifuge.

E25Bio developed and validated its lab-based test at the start of the pandemic, in April. But the test languished on company benchtops because it wouldn't have met the FDA's very high bar for sensitivity to win an EUA, according to Herrera. Since the start of the pandemic, the FDA has heavily favored highly sensitive tests, typically PCR that can detect even low-level infections, according to Mina. Companies, he says, have been racing to develop the most sensitive test at all costs. Sensitive lab-based tests can reliably diagnose patients. But at the peak of their infection their viral load would've been high enough that even a less-sensitive antigen or LAMP test could have picked it up.

Even six weeks ago, "the FDA didn't take that into consideration at all," Mina says, although he adds that the agency now seems more willing, based on new language on their website, to exchange some amount of sensitivity for frequent and expedient tests (7). Herrera says that his company has been "screaming out loud" for five months, trying to get the attention of the FDA, Department of Health and Human Services, as well as government officials. He's been eager to see the FDA grant EUAs for the kind of rapid but less-sensitive tests that could give faster turnaround results to patients in home. Now that the FDA has opened the door, Herrera hopes that E25Bio's lab-based rapid test will be authorized "within weeks," followed by a product launch in early September and a home test available soon after, he says. The company claims it could produce millions of low-cost tests within a few weeks of authorization.

Antigen strip tests aren't the only home tests in development. Mammoth Biosciences is now working on a CRISPR-based test that would come in a disposable handheld cartridge and cost about as much as a home pregnancy test, says Chen. Users would insert their swab sample into one end, and see a simple color result on the other in less than 20 minutes. A CRISPR-CAS enzyme preloaded into the cartridge would recognize a target sequence of the viral genome to produce a positive readout. Mammoth's CRISPR technology now has an EUA, but only for use by trained medical lab professionals, not yet for the general, at-home public. The company will need to apply for a second EUA for a home test later this year, Chen says.

But Chen doesn't expect to see any in-home tests hit the market until 2021. And whatever technology those tests ultimately use, whether CRISPR or something else, they will have to be both user-friendly and accurate. "The key problem," Chen explains, "is dealing with an environment that's less controlled." At home, there are no trained technicians to help users ensure that the testing is consistent and careful. From collecting the sample to reading the test, a home device needs to be foolproof for untrained users. Both regulatory and scientific limitations have hampered the rollout of home testing, says Chen. Regulators, she says, have to balance the urgent need for testing with the risk of launching an unreliable test that erodes public trust. Unreliable tests would also undermine these regulators' ability to track patterns of infection across the country.

Larremore points to the FDA's new recommendations as a signpost of things to come. The FDA and the general public, he says, initially thought of testing as a tool for symptomatic patients. Attitudes are changing. "Only now have people started to shift their thinking," he says, approaching testing as a screening strategy for the whole population rather than just for the sick. "FDA's changes reflect shifts in thinking about how testing can be used," he says, "and this is really exciting."

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