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How SARS-CoV-2 Tests Work and What's Next in COVID-19 Diagnostics

Current methods to detect infections of the novel coronavirus rely on identifying particular genetic sequences, but new assays are being developed to meet the growing demand for rapid answers.

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The quick sequencing of the SARS-CoV-2 genome and distribution of the data early on in the COVID-19 outbreak has enabled the development of a variety of assays to diagnose patients based on snippets of the virus's genetic code. But as the number of potential cases increases, and concerns rise about the possibility of a global pandemic, the pressure is on to enable even faster, more-accessible testing.

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Current testing methods are considered accurate, but governments have restricted testing to central health agencies or a few accredited laboratories, limiting the ability to rapidly diagnose new cases, says epidemiologist and immunologist Michael Mina, the director of the pathology laboratory and molecular diagnostics at Brigham and Women's Hospital in Boston. These circumstances are driving a commercial race to develop new COVID-19 tests that can be deployed within hospitals and clinics to provide diagnostic answers in short order.

Globally, nearly 89,000 cases have now been reported—more than 80,000 of these in China—along with more than 3,000 deaths. The virus has been found in 64 countries, six of those in just the past day.

How the current SARS-CoV-2 assays work

The full genome of the novel coronavirus was published on January 10 of this year, just weeks after the disease was first identified in Wuhan, China. A week later, a group of researchers led by German scientists released the first diagnostic protocol for COVID-19 using swabbed samples from a patient's nose and throat; this PCR-based protocol has since been selected by the World Health Organization (WHO).

The assay was initially developed from genetic similarities between SARS-CoV-2 and its close relative SARS, and later refined using the SARS-CoV-2 genome data to target viral genes unique to the newly discovered virus. In particular, the test detects the presence of SARS-CoV-2's *E* gene, which codes for the envelope that surrounds the viral shell, and the gene for the enzyme RNA-dependent RNA polymerase.

Not all countries have adopted the WHO's recommended diagnostic, including the US.

Yvonne Doyle, the medical director and the director of health protection for Public Health England, tells *The Scientist* in an email that once a sample is received by a laboratory, it takes 24–48 hours to get a result. Commenting on the test's accuracy, she says all the positive results to date in the United Kingdom, a total of 36 so far, have been confirmed with whole genome sequencing of the virus isolated from patient samples, and "the analytical sensitivity of the tests in use is very high."

This approach also underpins COVID-19 laboratory testing in Australia, where 27 cases have so far been diagnosed, says medical virologist Dominic Dwyer, the director of public health pathology for NSW Health Pathology at Westmead Hospital in Sydney. "We decided in the end to have a screening approach using the WHO primers that target the so-called *E* gene of the coronavirus," he says. "If a screening test is positive, we then do some confirmatory testing which selects other targets of the virus genome."

The laboratory at Westmead Hospital also does a complete sequencing of every virus sample to look for possible new strains of SARS-CoV-2 and has shared some of those sequences in the international Global Initiative on Sharing All Influenza Data (GISAID) database for other researchers to study. The staff also cultures the virus and images it using electron microscopy. "That's not really a diagnostic test, but gives you some confirmation of what you're seeing in the laboratory," Dwyer says.

He adds that, so far, there's no suggestion of false positive findings, because every positive test has been confirmed with whole genome sequencing, viral culture, or electron microscopy. As for false negatives, he adds, it would be hard to know if any infected patients were mistakenly given the all-clear.

Not all countries have adopted the WHO's recommended diagnostic. The US Centers for Disease Control and Prevention (CDC), for instance, has developed its own assay that looks for three sequences in the *N* gene, which codes for the nucleocapsid phosphoprotein found in the virus's shell, also known as the capsid. The assay also contains primers for the *RNA-dependent RNA polymerase* gene. Dwyer says that the principles of testing are the same; it's just the genetic targets that vary.

Mina says it's not clear why the CDC chose to develop a different assay to that selected by the WHO and taken up by other countries. "Was this actually based on superior knowledge that the CDC had, or was this more of an effort to just go our own route and have our own thing and feel good about developing our own test in the US versus the rest of the world?" says Mina, who is also assistant professor of epidemiology at the Harvard School of Public Health. The CDC declined to respond to questions from *The Scientist*.

Who does the testing

In the UK, testing for COVID-19 is being done by a range of accredited laboratories across the country. In the US, all laboratory testing for COVID-19 has until recently been done exclusively by the CDC. The turnaround time for a result has been 24–72 hours. Mina argues that enabling hospitals to conduct their own on-site diagnostics could speed up the process. For instance, hospitals can generate flu results within an hour, Mina says, most commonly using assays that detect viral antigens. "We spend a lot of money getting rapid turnaround tests in the hospital for flu, for example, because we have to know how to triage people."

The day or two or three that it takes to get COVID-19 results has had logistical ramifications for hospitals, Mina says. "If we have a patient who we only suspect is positive, even if they are not positive, just the suspicion alone will lead us to have to find an isolation bed for them," he says.

There has been a move by the CDC to send out RT-PCR test kits to state health laboratories, says Molly Fleece, an infectious diseases physician at the University of Alabama at Birmingham. "Hopefully, more laboratories around the country will be able to have access to these testing kits and be able to test specimens instead of having to send all the specimens to the CDC for testing," she says.

However, that plan hit a snag recently when one of the CDC kits' reagents was found to be faulty. The agency has announced that the reagent is now being remanufactured.

SARS-CoV-2 tests in development

There are now numerous companies working on commercial test kits in response to the rising diagnostic demands of the epidemic. Most are applying the same real-time PCR methods already in use, but others are taking a different approach. For instance, Mina and colleagues are trialling a diagnostic in partnership with Sherlock Biosciences, based in Cambridge, Massachusetts. The researchers are using CRISPR technology to tag the target SARS-CoV-2 sequences with a fluorescent probe.

"In many ways it's similar to real-time PCR but it's just more sensitive and much more rapid," Mina says. Another CRISPR-based diagnostic protocol developed by researchers at the McGovern Institute at MIT uses paper strips to detect the presence of a target virus, and claims to take around one hour to deliver the result. It has not yet been tested on COVID-19 patient samples, and the institute has stressed the test still needs to be developed and validated for clinical use, for COVID-19 or any other viral disease. Meanwhile, Anglo-French biotech company Novacyte has announced the release of its real-time PCR diagnostic kit for COVID-19, which it says will deliver results in two hours.

We're not at that stage yet of rolling out the serology or antibody tests.

—Dominic Dwyer, **NSW Health Pathology at Westmead Hospital**

A different diagnostics approach would be to devise blood tests for antibodies against the SARS-CoV-2 virus, a development that Mina says will be an important next step for monitoring the spread of the virus. "Could we just start taking blood samples from people around the world and see how many people who had no symptoms or very minimal symptoms may have actually been exposed to this?" Mina asks.

Dwyer says such approaches could help detect any false negatives that slip through the PCR-based protocols, but "we're not at that stage yet of rolling out the serology or antibody tests." Numerous groups are trying to isolate antibodies, some with more success than others. Researchers at Duke-NUS Medical School in Singapore have used antibody testing to demonstrate a link between two separate clusters of infections, and in patients who had cleared their symptoms at the time they were given the antibody test. Meanwhile, researchers in Taiwan are also working to identify a SARS-CoV-2 antibody that could be used for diagnostic testing, and they say such a test could deliver a result in a matter of minutes rather than hours.

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