

## Medical News &amp; Perspectives

## The Promise and Peril of Antibody Testing for COVID-19

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**A**s coronavirus disease 2019 (COVID-19) raged around the globe in late March, hundreds of San Miguel County, Colorado, residents turned out for a blood test. Standing 6 feet apart outside a Telluride school gym, they waited for the blood draw that would tell them whether they had mounted an immune response to the disease-causing virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—a sign that they'd been infected.

In the first such community-wide campaign in the US, the San Miguel County Department of Health offered the voluntary screening to most of the area's 8000 residents over 2 weeks. Just 8 of the 986 individuals tested on March 26 and 27 were positive for SARS-CoV-2 antibodies. Another 23 were borderline, suggesting that they'd recently been exposed to the virus and were just starting to make antibodies against it. But those were early days. The screenings, paid for by test manufacturer United Biomedical Inc and the county, eventually would be repeated to see how much things had changed.

Unlike polymerase chain reaction (PCR) tests—also referred to as molecular or nucleic acid-based tests—antibody tests aren't intended to identify active SARS-CoV-2 infections. Instead of detecting viral genetic material in throat or nasal swabs, antibody tests reveal markers of immune response—the IgM and IgG antibodies that for most people show up in blood more than a week after they start to feel sick, when symptoms may already be waning.

Serologic antibody tests not only can confirm suspected cases after the fact, they can also reveal who was infected and didn't know it. Up to a quarter of people with SARS-CoV-2 infection may unwittingly spread the virus because they have mild or no symptoms.

Implications for the health care workforce could be substantial, microbiologist Florian Krammer, PhD, of Mount Sinai's Icahn



School of Medicine, said in an interview. "If we find serologically that you are immune, it's very unlikely that you can get reinfected, which means you can't pass the virus on to your colleagues or to other patients. And I think it also gives a peace of mind if you have to work with COVID-19 patients to know that you're probably immune to the infection," he explained.

Antibody tests are ramping up quickly, with a growing list of commercial kits and test protocols from academic researchers including Krammer's team and a Dutch team coming online in recent days and weeks. Scientists said the tests will be critical in the weeks and months ahead, when they may be used for disease surveillance, therapeutics, return-to-work screenings, and more. But the tests must be deployed appropriately, they added, and with an acknowledgment of unanswered questions.

### Turning Antibodies Into Therapies

In their first therapeutic application, serology tests are being used to screen donor blood for antibodies to SARS-CoV-2. Plasma containing the antibodies from recovered patients is then transfused to gravely ill patients in an experimental treatment known as convalescent plasma. Early

results from a small number of Chinese patients, published in *JAMA* in late March, were promising.

The US Food and Drug Administration (FDA) is coordinating a national effort to develop blood-based, antibody-rich COVID-19 therapies. They include convalescent plasma and the hyperimmune globulin derived from it, which ideally will provide passive immunity to people who have been exposed to the virus.

In an interview, Carlos Cordon-Cardo, MD, PhD, who chairs the Mount Sinai Health System pathology department in New York City, said physicians there have begun to transfuse convalescent plasma to critically ill patients as part of an FDA expanded access program. Krammer's research team developed the test that's being used to screen donor blood.

They recently described their new assay in a preprint article (which has not been peer-reviewed). The test detected antibodies in plasma from blood drawn as early as 3 days after patients first developed symptoms. Crucially, it did not react with human coronaviruses already circulating in the population, demonstrating that it's specific to SARS-CoV-2. "What we've found with our test is that basically everybody's naive,"

Krammer said. "There's no preexisting immunity. And that makes it very easy to distinguish between people who have been infected and who haven't been infected."

Antibody testing could also help to address a potential unintended consequence of receiving convalescent plasma or hyper-immune globulin. It's possible that some COVID-19 survivors who undergo these treatments won't develop their own immunity, putting them at risk for reinfection, Lee Wetzler, MD, a professor of medicine and microbiology at the Boston University School of Medicine, said in an interview. Serologic testing could be used to check their antibody status after they've recovered; those with low or no immunity would be prime candidates for a vaccine when one becomes available.

Mount Sinai and United Biomedical's tests are both enzyme-linked immunosorbent assays (ELISAs), a common laboratory platform that can measure antibody titers. Being able to quantify antibodies will be important for identifying convalescent plasma donors with abundant titers and studying how the immune system responds to the virus. "The titers that we measure in ELISA seem to correlate with neutralizing antibodies," Krammer said. "So basically the idea is the higher these titers, the better you are protected."

Krammer has shared his test's reagents and tool kits with about 150 different US clinical labs. These types of quantitative tests will help scientists to understand if there's a certain antibody type or threshold a person needs to be protected, according to Wetzler, who is also an infectious disease physician at the Boston Medical Center.

However, a substantial number of the new commercial COVID-19 antibody tests aren't ELISA-based. They're lateral flow assays, which provide a simple positive or negative result, with no quantitative information. These kits are cheap and easy to use and, depending on how they're employed, may be helpful for disease surveillance, Elitza Theel, PhD, director of the Mayo Clinic Infectious Diseases Serology Laboratory in Rochester, Minnesota, said in an interview.

Palo Alto-based Nirmidas Biotech is one of many companies offering a rapid, point-of-care [lateral flow assay](#). According to Meijie Tang, PhD, the firm's CEO and president, a state Centers for Disease Control and Prevention (CDC) laboratory and other partners are evaluating the test's per-

formance. "We plan to collaborate with hospitals, clinics, health care and medical institutions to validate the test and make [it] widely available," she said in an email.

Diazyme Laboratories in Poway, California, has developed [chemiluminescence immunoassays](#), which are closer in concept to ELISAs than lateral flow assays. The tests generate a light signal proportional to SARS-CoV-2 IgM antibodies. In an email, cofounder and Managing Director Chong Yuan, PhD, said the company would ship about 2 million tests to clinical labs over the over the next month.

### The Right Test at the Right Time

On April 1, the FDA [granted](#) Emergency Use Authorization (EUA) to a rapid SARS-CoV-2 IgG and IgM lateral flow assay from Cellex Inc in Research Triangle Park, North Carolina. Mount Sinai's test received EUA 2 weeks later.

The agency by early April had also [allowed](#) more than 70 companies to sell COVID-19 antibody tests without this authorization, albeit with some stipulations. Among other [requirements](#), manufacturers operating without EUA must state that they've clinically validated their tests using specimens from patients with PCR-confirmed infections. The test reports must note that the FDA has not reviewed the assays and that they should not be used as the sole basis to diagnose or exclude SARS-CoV-2 infection or to inform patients of infection status.

Yet, according to Theel, several companies are marketing lateral flow assays as rapid point-of-care tests to identify active COVID-19, something the FDA [announced](#) it will take action against. "We do not really know how well these assays work at this point," Theel said in a follow-up email.

Although commercial manufacturers claim their tests have high sensitivity and specificity, they haven't published their data yet. This lack of transparency is worrisome, Theel said: "The question is, when following symptom onset were these samples collected to show that sensitivity and specificity?"

Her laboratory has found that most people with SARS-CoV-2 don't start producing antibodies—or seroconvert—until at least 11 to 12 days after symptom onset. "So, if we were using these rapid lateral flow assays at the point of care to test recently symptomatic patients,...they are more likely than not going to be negative," she said.

Greater FDA oversight for antibody tests could be coming, according to [news reports](#). In addition, the World Health Organization (WHO) is working with partners and its own global laboratory network to evaluate available assays for diagnostic and research purposes, a spokesperson said in an email. One partner in the effort is the Foundation for Innovating Diagnostics (FIND), a Geneva, Switzerland-headquartered nonprofit that's evaluating both PCR and serology tests. As of mid-April, the group had selected 27 antibody tests, mostly from China, for its first round of evaluation. The tests' performance results will be posted on the [FIND website](#) as they become available.

According to [news reports](#), newly available rapid, point-of-care PCR tests, like a recently announced 5-minute assay from Abbott Laboratories, won't substantially increase diagnostic testing capacity in the short-term. Faced with a PCR test shortfall amid incredible demand, health systems may consider subbing in serology tests. But experts strongly underscored that antibody testing generally should not be used to diagnose active cases.

Krammer said that resorting to antibody testing to diagnose active infections is a "complete misuse." Not only are antibody tests likely to report false-negatives early on, they'll also miss infections among people who are immunocompromised and don't produce antibodies.

"Molecular testing is still going to be the go-to preferred method for diagnosis of COVID-19 in symptomatic patients," Theel said. In her view, the only appropriate use of antibody testing for active infection may be for people who have had symptoms for over a week but are PCR negative. But the precise timing of that still hasn't been defined.

"I think that it is very important that we understand the limitations of serologic testing, recognizing that it takes time to mount a detectable immune response, and to use them for the right reasons," Theel said. "A false-negative serologic result in an acutely symptomatic patient with replicating and shedding virus has serious public health consequences."

### Back to Work

San Miguel County's public health department has said it will use its test results to detect and contain COVID-19 in the community and provide a clearer picture of the

disease's prevalence there. Other areas may soon follow suit: United Biomedical co-founder and Telluride resident Mei Mei Hu said in an email that screenings in additional communities are being planned.

Government officials and health systems need accurate infection counts to understand COVID-19's spread, conduct contact tracing, craft public health recommendations, and prepare for health care surges. When the dust has settled, epidemiologists will use widespread serosurveillance data to more accurately estimate just how many people who contracted the virus became seriously ill or died.

To that end, a National Institutes of Health-funded [antibody survey](#) is enrolling 10 000 volunteers from around the country and, according to [news reports](#), nationally representative, CDC-funded serosurveys are slated to begin later this year. Meanwhile, the WHO is providing countries with an [early protocol](#) and technical support for seroepidemiological studies and is launching a multicountry antibody testing study called [SOLIDARITY II](#).

Crucially, many believe that antibody testing can also be used to return people with immunity to the workforce or keep them there, starting with health care professionals and emergency first responders. Krammer suggested that staffing nursing homes with immune workers could bring down their high case-fatality rates, for example.

"[S]erosurveillance is going to play a major role in...a framework for getting back to normal," Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases and a White House Coronavirus Task Force advisor, said in an April 8 [JAMA livestream](#). Two prominent COVID-19 roadmaps—[one](#) from former FDA Director

Scott Gottlieb, MD, and [the other](#) from the University of Pennsylvania's Ezekiel Emanuel, MD—include widespread antibody testing as a critical step toward reopening society.

"I think it makes total sense that if immunity is increasing and we have, let's say, 50% of people immune against this, then we have a much less chance that the virus will spread," said Melanie Ott, MD, PhD, a senior investigator at the Gladstone Institute of Virology and Immunology in San Francisco. "At a certain point, we will be able to minimize that risk with potentially minimal additional measures that have to be taken."

Along those lines, media outlets have reported that researchers in [Germany](#) and [Italy](#) will conduct and study large-scale antibody testing, with Germany planning to issue "immunity certificates" to transition its citizens out of lockdown. Public Health England, which provides evidence-based support to the National Health Service, recently [discussed](#) plans for nationwide antibody screening that would begin once a rapid, at-home finger-prick test under consideration was assessed for accuracy. At press time, the White House hadn't announced similar plans.

Allowing people to reenter society based on their antibody status assumes that past infection guards against reinfection, something that researchers said was likely but not yet well defined. "How broad and how long and how effective this immune response is is still not clear," Ott said.

Scientists around the world will be working to understand what sort of protection infection bestows, both in the laboratory and by following up recovered patients to see if reinfections occur. So far, the novel coronavirus doesn't appear to mutate quickly. This, coupled with experience with

other viral infections, suggests that people with SARS-CoV-2 antibodies may be protected at least for some time, Wetzler said.

There's another potential snag, however. Individuals can be PCR positive even after antibodies develop. "The question is, is that live virus that we're detecting? Is it replicating? And is it transmissible? And I think that's still an unknown at this point," Theel said. Coupling a positive antibody test with a negative PCR result could reduce the chance that people who are still contagious reenter society.

Ultimately, a positive antibody test could be a sort of get-out-of-isolation card. "In the long run, I think it would be nice to provide this for the whole population because everybody who is immune could basically go back to normal life because they can't infect anybody else," Krammer said.

For now, he cautioned that novel coronavirus infections are probably not yet widespread among the general population in the US, which is just in the "beginning of a large epidemic." But as more people become infected and immune, they could help jumpstart the economy by going back to work. They could also provide practical support for those who are vulnerable to serious infection, potentially until a vaccine arrives.

In early April, Cordon-Cardo said Mount Sinai would likely expand its assay's use beyond experimental therapeutics to testing health care workers. And at the Mayo Clinic, clinical antibody testing began in mid-April. If these applications are followed by a roll-out of widespread antibody testing for the general public, they could lead to a gradual reopening of society to a world changed by COVID-19. ■

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