Vendors Search for New Applications After SARS-CoV-2 Serology Fails to Fulfill Early Hype

Sep 17, 2020 | Adam Bonislawski

NEW YORK — In the early days of the SARS-CoV-2 pandemic, many observers saw substantial commercial and clinical potential for serology tests for the virus.

Yet, despite this initial enthusiasm, these assays have struggled to carve out a significant market, hampered by concerns about test performance and the lack of a clear role in clinical decision-making.

Data from revenue cycle management and lab informatics firm Xifin shows serology testing volumes peaking in May and then dwindling. As of September 13, 2020, serology SARS-CoV-2 testing accounted for less than 3 percent of all lab volume, compared to around 40 percent for molecular SARS-CoV-2 testing. In a July research note, Xifin observed that "antibody testing volumes have been significantly lower than anticipated."

During Siemens Healthineers Q3 2020 earnings call in August, company CFO Jochen Schmitz similarly noted that "the contribution of serology testing volume" to the firm's revenues "is still very low," and added that this was "not a function of the ramp-up" of testing.

This is in large part due to the lack of clear clinical uses for serology testing, Schmitz said, noting that "as long as the clinical use of these tests remains unclear, we expect demand to remain muted and to stay far below our projected capacity potential for these kinds of tests."

Xifin CEO Lale White likewise said that a lack of obvious medical necessity has hampered uptake of serology testing.

Much of the original excitement around serology testing was driven by the notion that people who had recovered from infection would have developed immunity against it, and that this immunity could be determined by antibody testing. Serology tests, according to this line of thinking, would be key to identifying people who could, for instance, safely return to work following infection and, as such, essential tools for reopening society.

This vision has not come to fruition, due in part to the fact that the relationship between patient antibody levels and immunity to SARS-CoV-2 infection has still not been firmly established. Additionally, some have raised ethical and legal concerns around the idea of so-called "immunity passports" that would allow antibody positive individuals to move about freely.

The performance of antibody tests has also caused concern. The reputation of SARS-CoV-2 serology testing took a hit when low quality tests flooded the US market following the loosening of US Food and Drug Administration regulations. However, even high quality tests can deliver large numbers of false positives when used in populations with low prevalence of the disease.

Alan Wu, professor of laboratory medicine at University of California, San Francisco, and clinical chemistry laboratory chief at Zuckerberg San Francisco General Hospital, said that his center has been steadily using

serology testing throughout the pandemic, primarily for evaluating patients who test negative for SARS-CoV-2 infection using PCR but who have symptoms that suggest the likely have the disease.

"The [molecular] test could be negative because we are sampling at the wrong time or the sampling wasn't good," he said.

In some cases, imaging may indicate that a PCR-negative patient has COVID-19, in which case serology can provide useful information, Wu added. He noted that, for instance, if a serology test is positive in a patient with several days of symptoms, the patient is most likely positive for the virus even if a PCR test is negative.

Wu said that he and his colleagues have found quantitative tests that distinguish between levels of IgM and IgG antibodies to be most useful clinically. IgM antibodies are generally produced earlier in an infection while IgG antibodies persist longer and are the major players in long-term immunity. Tests that measure levels of IgM and IgG separately therefore provide information that can be useful in understanding the timing of the infection and what stage a patient might be in.

For instance, a patient with symptoms and higher levels of IgM antibodies than IgG is likely suffering from an active infection, Wu said. "On the other hand, if the IgM is negative and the IgG is strongly positive but the PCR is negative, maybe it's not COVID, or maybe it was COVID from months before."

Serology data "is thrown into the larger milieu when you're trying to figure out what is going on with a particular patient," he said.

From a commercial perspective, the problem is that there aren't that many cases where physicians suspect a patient with a negative molecular test actually has the virus.

"If you're looking at 80 percent to 90 percent sensitivity for PCR, it’s a small percentage of people who we need to do [serology] on," Wu said. "That's not to say we won't do it on some people who are positive as well, but it's not automatic. If they have the positive PCR and the story fits with regard to the onset of symptoms, we don't do antibody testing."

In terms of use in PCR positive patients, Wu said that one area he saw serology being used was to track antibody levels in patients during long-term hospital stays.

In those cases "antibody testing can be very useful," he said. "If antibodies are going up after three weeks, that is something very different that if they are going down."

Again, though, this is a relatively small group of patient compared to the larger SARS-CoV-2 testing market.

Wu said his lab has been using serology tests from Palo Alto, California-based ET Healthcare, whose test, he said, provides good quantitation of IgM and IgG antibodies. Many other quantitative tests provide only total antibody levels, which he said he felt was not as clinically useful as getting the IgM and IgG levels separately.

He said that at this point he considered qualitative serology tests "fairly useless."

Unsurprisingly, serology test makers are looking to drive uptake of their assays, seeking out areas where they could be used for clinical decision-making in individual patients and for guiding public health.

Fernando Chaves, global head of medical and scientific affairs at Ortho Clinical Diagnostics, suggested that serology could be used to detect positive patients missed by molecular testing in not only the symptomatic population but the asymptomatic population, as well.

In a recent webinar hosted by Ortho Clinical, Karen Roush, vice chair of pathology at Dallas, Texas-based Methodist Health System offered an example of such an application, detailing the system's use of serology as part of its SARS-CoV-2 management.

Like Wu and Zuckerberg San Francisco General, Methodist uses serology to evaluate symptomatic patients who test negative with PCR. The healthcare system has also begun using serology combined with PCR testing for asymptomatic patients, both for patients in the hospital to test them prior to procedures and for outpatients coming to the hospital for procedures.

Roush said that the hospital system plans in the new term to start testing all admitted patients for SARS-CoV-2 using both PCR and serology.

Deepak Nath, president of laboratory diagnostics at Siemens Healthineers, also suggested that serology could be used to follow up negative PCR tests, much as Wu and his team have been using them.

Nath also suggested that serology testing could see increased use if and when vaccines for COVID-19 come to market.

"Post the introduction of vaccines, there is a very clear use case to determine whether there is a sufficient level of antibody [generated] to provide immunity," he said.

Wu likewise said that he expected the launch of vaccines to increase uptake of serology testing.

"Certainly the response to vaccines will put a renewed interest on antibody testing," he said. "I'm pretty sure that we are going to need to do baseline and the vaccine and post-vaccine testing, and then possibly if there are booster shots you will want to monitor vaccine efficacy over time."

Nath noted, though, that work will need to be done to more firmly establish the link between antibody presence and levels and immunity to SARS-CoV-2.

"We can't say right now that the presence of antibody confers immunity, and we have not established a threshold for what levels of antibodies confer immunity," he said.

Siemens this week announced a collaboration with the US Centers for Disease Control and the Joint Research Centre of the European Commission to develop a standardization process for SARS-CoV-2 serology assays that could help address these kinds of questions.

Under the collaboration, the partners will standardize assays by defining the concentration of antibodies to specific SARS-CoV-2 proteins and against the level of antibody required to block the virus from entering cells in virus neutralization assays.

The company hopes that this kind of standardization will improve uptake by making it easier to compare the performance of tests from different manufacturers and will also strengthen the link between serology results and immunity, paving the way for more use of serology in determining immunity provided both by infection with the virus and by vaccines.

Wu said that he has been calling for vendors to move in this direction for some time.

"I've been arguing with these various companies that they should try to get their FDA authorization of antibody tests to have a claim against virus neutralization," he said. "I think that would give consumers, meaning doctors and the general public, a little bit more confidence that a positive test on a particular device... would mean they are immune, or at least immune for a period of time."

Filed Under

Filed Under

Infectious Disease | Immunoassays | Clinical Lab Management

North America | coronavirus | Ortho Clinical Diagnostics | Siemens