Testing is crucial to combating the coronavirus disease 2019 (COVID-19) pandemic. Along with identifying the infection in individuals seeking treatment, testing sheds light on the virus in the population and how to mitigate transmission.

The MJH Life Sciences™ COVID-19 Coalition discussed the current state of COVID-19 testing and emerging testing strategies during “Innovative Testing Strategies for COVID-19 Containment,” the sixth in a series of webinars. The coalition is a partnership with top health care thought leaders across a variety of medical disciplines.

The event was moderated by Paul E. Sax, MD, clinical director of the Division of Infectious Diseases at Brigham and Women’s Hospital, professor of medicine at Harvard Medical School, and editor-in-chief of Open Forum Infectious Diseases.
Speakers were:

Carlos del Rio, MD, executive associate dean of the Emory School of Medicine & Grady Health System in Atlanta, Georgia, and distinguished professor in the Department of Medicine, Division of Infectious Diseases, at Emory University School of Medicine, and

Esther Babady, PhD, D (ABMM), FIDSA, director of Clinical Microbiology Service and the CPEP Clinical Microbiology Fellowship Program at Memorial Sloan Kettering Cancer Center;

Michael Mina, MD, PhD, assistant professor in the Center for Communicable Disease Dynamics, Department of Epidemiology, at Harvard T.H. Chan School of Public Health;

Omar Abudayyeh, PhD, fellow at the Mc Govern Institute at Massachusetts Institute of Technology; and

Jonathan Gootenberg, PhD, fellow at the McGovern Institute at Massachusetts Institute of Technology.

“There is a lot to consider when testing for COVID-19, such as when to do the test, how to test, which test to use, as well as how to interpret the results,” Sax said. “So we rely on testing to give us an accurate picture of the disease both in an individual patient and for a population. Our testing has come a long way since early 2020. But what if there’s a better strategy than the current approach?”

What follows are 7 key takeaways from the webinar.

1. Three types of tests that have been used for the SARS-CoV-2 virus include viral culture, molecular testing for viral RNA, and antigen testing.

Determining which test to use requires understanding how the disease progresses and when the various markers are most likely to be detectable.

“Once someone gets exposed to COVID-19 there is a period of time where none of these markers would be detectable, not the virus itself, not the antigen, not the RNA,” Babady said. It takes a few days from the time of exposure for the virus to replicate within the host to levels that are detectable by any of the tests.

As the disease progresses, the markers that are identified in testing wane at different times.1 The duration of time when they are detectable varies by host, depending on factors such as whether the host is immunocompetent or immunocompromised.

“Understanding at what point the markers appear, at what point they are likely to be detected, is really important in terms of trying to determine which test to use to diagnose this patient,” Babady said.

Viral culture testing detects the cytopathic effect (CPE) of the virus on the host cells.2

“You can see actual variant of SARS-CoV-2,” Babady said. “But, as you can see, this takes a few days. For most of us who have been doing this for a long time, viral culture has really lost appeal because of how long it took for this virus to be detected.”

Nucleic acid amplification tests (NAAT), such as polymerase chain reaction (PCR) tests, work by amplifying viral RNA to a detectable level, with a turnaround time of 20 to 90 minutes.
Most antigen tests are developed as lateral flow assays, with the sample applied to a strip coated with an antibody linked to a detector molecule to determine whether the combination of viral antigen and antibody occurs.

2. Declaring a public health emergency allowed testing to advance.

Health and Human Services Secretary Alex Azar declared a public health emergency for the United States on January 31, opening the door for a public response to the novel coronavirus.

Babady said the first commercial test for SARS-CoV-2 was approved in March, with limited public health testing available before that. As of November 30, more than 195 tests had received emergency use authorization from the US Food and Drug Administration.

“For many clinical labs, the declaration of a public health emergency really had a significant impact on our ability to react to the pandemic,” Babady said.

The first commercial test for the virus was Roche Diagnostics’ cobas SARS-CoV-2 test, which was awarded emergency use authorization (EUA) in mid-March. The first commercial antigen test, Sofia SARS Antigen FIA, was approved on July 17.

Despite the abundance of tests that have been developed and received EUA, supply shortages have crippled the ability of labs to respond to the pandemic, Babady said.

3. Innovative solutions were developed to respond to obstacles such as shortages of swabs, viral transport media, and extraction kits.

One of the first obstacles labs had to overcome was a shortage of swabs to collect samples. Labs responded by developing alternative sample types such as oral rinses and saliva samples, which had sensitivity of 96%.³

“In addition to running out of swabs and just deciding to use a different type of sample, others looked at alternative swabs,” Babady said. “So this is when we started talking about 3D printing of nasopharyngeal swabs.”

These alternative collection devices also performed well in studies.⁴

Without available viral transport media (VTM), labs evaluated potential alternatives, including saline, phosphate-buffered saline, and minimum essential medium.⁵

“You could use viral transport media or just saline and your result would be the same when you look at the Ct values,” Babady said. “This was using two different assays, which was encouraging. So, labs could forget about using VTM.”
Extraction kits also were in short supply and investigators began evaluating whether extraction-free PCR testing was feasible, with promising results.\textsuperscript{6} Another innovative strategy to address shortages of test kits was sample pooling, which could stretch a test kit by pooling multiple samples into one test, with a study in Spain showing sensitivity of 97%.\textsuperscript{7}

4. There are different testing strategies, including medical diagnostic testing, surveillance testing, and screening.

“Clinical labs have always been doing diagnostic testing,” Babady said. “We’ve never really been in the business of surveillance testing. It’s been an interesting push now to screening masses and masses of people for this virus.”

While medical diagnostic testing is done for patients who are sick or have been exposed, surveillance testing may include people who have no symptoms as part of a public health effort to combat the pandemic and guide resource allocation, contact tracing, and other measures.

Screening strategies include entrance screening, which involves testing people before they enter a location such as a nursing home, hospital, or school.

“This is a type of screening that can be very powerful to decrease the odds, not to stop necessarily, but to greatly reduce odds that an outbreak is going to happen,” Mina said, calling it a “powerful tool” that helped ward off an outbreak at the White House between March and October despite the absence of other public health measures there.

Another screening strategy is public health screening, which is widespread testing aimed at creating a herd effect by stopping enough people from transmitting the virus that the outbreak gets controlled.

“We have done a terrible job so far with this pandemic of trying to define why it is we’re testing,” Mina said. “We’re just flagrantly testing and diluting out the tests that we do have available by not having any strategy associated with them.”

He said tests have been treated as medical diagnostic tests, involving prescriptions from physicians, which drives up costs.

5. Test characteristics, including sensitivity, cost, and speed of results, come with trade-offs.

The primary performance metrics of tests include sensitivity, or the ability to detect the virus, and the specificity, or the ability detect that specific virus.

“Sensitivity became the sort of end-all, be-all of testing early on in this pandemic,” Mina said. “There was a lot of discussion back in February, March, April about this issue and it really caught on and it led the FDA to require sensitivity metrics as one of their major goals to achieve near-PCR-level sensitivity for all of the tests. Frequency of testing and cost of tests and the speed to get results took a huge back seat. In fact, they’re not part of an FDA authorization program.”

He said that approach makes sense for a medical diagnostic use but may not be as effective in a public health response.

“Should sensitivity be priority No. 1, or what about having a very fast test that gives results in minutes that is not expen-
sive and can be made in the tens of millions per day but is 100 or 1000 times less sensitive?” Mina said. “That goes against everything we want to do in microbiology, molecular virology. We usually want the sensitive test for medical uses. But is this OK if the trade-off is that you get very fast results and you get many, many more tests that maybe can be done in the households?”

While PCR tests have greater sensitivity than antigen tests, which range in sensitivity from about 30% to 95%, Mina explained that PCR tests continue to detect the virus later into the disease progression, after it is no longer transmissible.

“In those people, you would not be expected to have a positive antigen test,” he said. He said the sensitivity of antigen tests is probably around 95% for people who are infectious.

He also questioned whether too much attention has been placed on Ct values.

“Do we need such sensitive tests, and do we need to be squabbling over Ct values of 30 to 40 when really we need to be capturing people at Ct values of, say, 10 to 25?” he asked.

To answer these questions, Mina and a team of investigators ran mathematical simulations comparing high- and low-sensitivity tests by total infections and infectiousness removed by testing/isolation.

6. Population-scale testing to control the spread of the virus requires a different approach from medical diagnostic testing.

“What we found essentially is that it is the frequency of testing that matters much, much more than the sensitivity of the test,” Mina said. “The analytical sensitivity becomes truly secondary relative to the frequency of the test. If you have a high-frequency test, whether it’s the high-sensitivity or the low-sensitivity test, if you’re doing it daily or every three days, they’re both going to be incredibly powerful tools to stop outbreaks. But the moment you start testing people every two weeks, regardless of whether you’re using PCR or an antigen test, you really lose your ability to catch infections before they transmit.”
Another important factor is how quickly test results are returned. Fast results enable public health efforts to isolate infectious people more quickly and reduce the spread of the disease.

“If you have daily or every-3-day testing but the result is not getting back for 5 days, you’re not going to do any better than weekly testing or 14-day testing. Essentially, those tests are garbage,” Mina said. “Even [with] a 2-day return time, you start to really lose the public health benefits of removing people from the population because this virus transmits so quickly.

“So, even when given at the same frequency, a lower sensitivity test that gives results immediately is essentially always better than a PCR test that gives results even 24 hours later,” Mina said.

Mathematical models also showed that a testing program with low-sensitivity tests with a fast turnaround distributed communitywide during an outbreak with 4% incidence in the community could get the outbreak under control with an R value of less than 1 within a couple of weeks, even if 50% of the population refused to take the tests and 10% of the tests failed.

“So, from a public health perspective, sensitivity should really take a major back seat,” Mina said. “We should really be pushing for these tests to get out to the public, especially as a bridge to vaccines, but even after vaccines are rolled out.”

Mina also said contact tracing should be prioritized based on Ct values and suggested that patients with Ct values above 35 probably don’t need to be contact-traced or isolated because they were likely identified through asymptomatic surveillance screening and are mostly likely past the period when they would be infectious.

He estimated that the current US surveillance testing strategy, using PCR tests with slow turnaround and low frequency, has about a 5% sensitivity to detect cases in time to act.

**7. New rapid tests are emerging.**

Emerging testing platforms include at-home molecular tests that are available with a prescription and high throughput antigen tests. Abudayyeh and Gootenberg are part of a team working to develop at-home and portable tests using CRISPR technology. The method uses a CRISPR molecule to detect the nucleic acid signature of the SARS-CoV-2 virus.

Dubbed the Specific High-sensitivity Enzymatic Reporter Unlocking (SHERLOCK), the detection technology operates at a single temperature and can be adapted for use with lateral flow strips.

“We’ve been working on this technology for several years and so when we saw this emerging pandemic in China in January, the two of us along with our former mentor thought, ‘How can we actually determine how we can develop this test and use it for detection of SARS-CoV-2?’” Gootenberg said. “So, in mid-January and early February we actually started adapting our SHERLOCK-based test for detection and we came out with a protocol on Valentine’s Day for detecting the SARS-CoV-2 genome using this technology.”

Abudayyeh said they have continued to work to further develop the test for a streamlined assay called STOPCovid, which involves a rapid sample extraction placed in
an extraction buffer and heated in a single incubation step before results are read on a lateral flow strip.

References:


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