Current Testing Strategies for SARS-CoV-2 in the United States

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Q&A

Current Testing Strategies for SARS-CoV-2 in the United States

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Introduction

Since the discovery and recognition of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the official declaration of the coronavirus disease-2019 (COVID-19) pandemic at the beginning of 2020, various different test methodologies have been developed at record speeds and made available for the diagnosis, screening, surveillance, and management of SARS-CoV-2 infection and COVID-19 illness. The rapid scientific developments in the quest to learn and define the mechanisms of SARS-CoV-2 transmission, illness, and recovery, in combination with the public health challenges of a rapidly spreading virus, have forced the healthcare community to adapt continuously to the unfolding pandemic.

Official testing guidelines and proposed algorithms continue to evolve, as we learn more about the variety of symptoms early in infection, changing public health needs, and the need to return to pre-pandemic activities that include in-person school attendance, travel, sports, and other economic and social activities. Initial testing guidelines focused on detection of the SARS-CoV-2 virus using molecular techniques, but as the pandemic has progressed other technologies such as SARS-CoV-2 antigen tests have emerged and are attaining wider acceptability and availability.

Coincident with the evolution of different testing methodologies, changes in sampling techniques from naspharyngeal swabs, to nasal swabs, and potentially to patient self-collected swabs further complicate the development of testing strategies and guidelines.

While high complexity molecular methods for viral RNA are the gold standard for diagnosis, a bottleneck in testing capacity and speed has become apparent. This bottleneck has led to a recognition that rapid point-of-care or laboratory SARS-CoV-2 antigen testing may play an important role in screening and surveillance for COVID-19 illness.

To help answer some of the questions about how testing is being used and how the in vitro diagnostic industry can help meet diagnostic testing needs, a panel of experts was convened with the objective of gaining critical insights regarding different testing strategies for SARS-CoV-2 in a variety of healthcare, community, congregate, and public health settings

We have invited back a select group of experts who participated in the Scientific Advisory Board to share their perspectives and to provide an update on the current state of testing strategies for SARS-CoV-2 from their respective points of view.

Briefly describe the current testing strategies for SARS-CoV-2 employed at your institution. How has this changed since the beginning of the pandemic?

Bart Buxton: McLaren Health Care is an integrated health system based in Michigan, with companies in Indiana and Ohio. Our system has developed a large reference lab to support all of our hospitals and to drive value for our insurance subscribers and patients.

We are actively testing using polymerase chain reaction (PCR) on 3 different platforms (rapid response, small platform, and large

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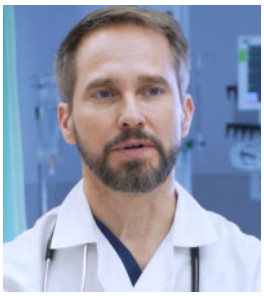
throughput). We also have serology testing available both for patients and for employees in direct or indirect contact with COVID patients, with insightful guidelines for physicians and patients regarding their testing results.

We are testing patients of all age ranges with our PCR testing platform. Most patients who are being tested are over the age of 10. Most of our PCR testing has been done on symptomatic patients in the hospitals and clinics. Hundreds of patients have been tested several times for various reasons, including test was negative on rapid response platform, physician re-ordered on RT (reverse transcriptase)-PCR platform, physicians trying to get a positive PCR patient to test negative for placement in nursing home, and patients with multiple exposures and mild symptoms over a span of a couple of weeks. The population includes all age ranges and all demographics. Michigan is trying to test the entire population prior to letting people go back to work, so we have recently experienced a rush of testing on an asymptomatic population, and additionally all patients prior to surgery, both elective and emergent, regardless of symptoms.



Sean Neath: I am an Emergency physician in San Diego, California. My clinical work is divided between Emergency Department (ED) and Urgent Care settings. We work in a rapidly evolving world of testing for this disease. I think we are at a point where we consider every patient with upper respiratory infection symptoms as potentially having COVID-19. Testing is critical to establish the diagnosis, not only to help limit the spread of the disease, but to monitor patients closely for progression. The development and refinement of COVID testing is important as we become entrenched in a protracted battle, with an enduring need to really risk stratify patients. This will become increasingly important as we navigate the influenza season.

Patients without active symptoms, but with risks such as exposures, are given an appointment for a tent PCR swab (available 7 days a week). If the phone triage nurses get a sense that the patient is symptomatic, the patient is referred either to the urgent care facility or ED, depending on the perceived severity of those symptoms. No patients who mention COVID-19 type symptoms are seen in the primary care clinics. If they present for an appointment with their primary care physician and the door screener notes symptoms, they are then referred to urgent care.

We are testing pretty much everyone from the worried well, to exposures, to the symptomatic. All age ranges, shapes and sizes, employees, pre-op and pre-procedure patients are tested. As early as the past summer, we started to see patients with more than 1 COVID test result done at different points in time over the last few months.

Jennifer Zreloff: I am a primary care physician, as well as medical director of the Emory Healthcare Network. In response to COVID, we opened an acute respiratory clinic to provide access to care for ambulatory patients who were either known COVID-positive or had the potential to have COVID. We have now reopened our regular operations and we are trying to navigate best practices for infection prevention and alleviate stress for the staff and providers worried about exposure.

Initially, we were testing symptomatic adults only. We have now expanded to patients with potential exposures, those for pre-op testing, and asymptomatic testing prior to travel and/or upon request.

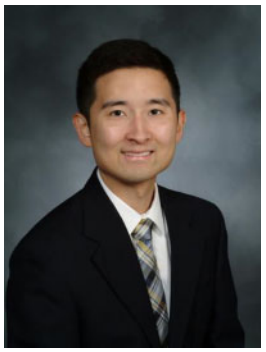
Omai Garner: My health system has 2 tertiary care hospitals and around 200 outpatient clinics. Early in the outbreak, COVID PCR testing was critical to determine which patients with influenza-like-illness (ILI) had the disease (including inpatient, ED, and outpatient). This allowed for appropriate patient treatment and management. The next most important group to test was our symptomatic healthcare workers. We began in-house PCR testing on March 10th in Los Angeles and found a substantial number of positives right away in these 2 groups. It took us a month of active symptomatic testing to get the outbreak under control. At that time, we were also focused on testing symptomatic outpatients with known comorbidities.

Once social distancing began to bring down the overall symptomatic patient number and we came out of the first surge (early May), we began an aggressive plan of asymptomatic screening for all inpatients coming to our hospitals and all pre-op and pre-procedure

patients. This was critical to bringing our patients back to UCLA for all non-COVID related health care, determining appropriate personal protective equipment (PPE) usage for procedures and surgeries, and helping our house staff feel safe when performing their jobs.

The patient population encompassed in our PCR testing strategy includes all age ranges and:

- Symptomatic: inpatients, ED patients, health care workers identified through daily symptom screening, and outpatients with known co-morbidities that make them high risk.
- Asymptomatic: all admitted patients, all pre-op and pre-procedure (within 48 h)



Justin Choi: I am a hospitalist at Weill Cornell Medicine, which saw a large volume of cases during this pandemic. I am also a lead investigator on a COVID registry database that includes over 4500 hospitalized patients at 3 affiliated hospitals in New York City. COVID-19 testing was critically important as the pandemic evolved. Early on, we encountered a shortage of testing kits and swabs, and also had delayed turnaround times due to limited in-hospital testing. Now we are able to turn around test results in just a few hours and we are screening all hospitalized patients. Testing is repeated for any hospitalized patient who tested negative but remains at high clinical suspicion. All patients being discharged to skilled nursing facilities must have repeat testing that is negative prior to discharge.

What role would either a rapid point-of-care (POC) or laboratory-based antigen test play in making admission and discharge decisions? What role do antigen tests play in the re-opening and surveillance of schools, colleges, and long-term care facilities?

Justin Choi: It depends on the availability of PCR testing, which would be preferred over antigen testing, given the greater sensitivity and specificity, as well as the pre-test probability of disease. If PCR testing is not available or the turnaround time is large, antigen testing may be useful for early triage decisions. However, given the decreased sensitivity and potential for false negatives with antigen testing, it has limited utility in cases where the index of suspicion for COVID-19 is moderate or high (i.e., a negative test does not effectively rule out disease, and a positive test only confirms how you were likely going to manage the patient in the absence of testing). Antigen testing has a potential role for screening in lower prevalence settings such as schools, colleges, and even long-term care facilities (in comparison to symptomatic patients in the hospital), and so a negative antigen test may be useful to quickly rule out those who do not have COVID-19.

Jennifer Zreloff: In terms of POC antigen testing, if the false negative rate is quite low in the asymptomatic patient, I think this could be a great option. What I understood was that to improve the specificity a confirmatory test was required, so I would do that. For a negative result, it could be fantastic for removing patients from isolation or going forward with procedures, concerts, and sports.

When it comes to lab-based antigen testing, the only benefit would be if it were more sensitive and specific than current molecular assays or, if similar, if it were cheaper, faster, or the sample was less invasive.

In my mind, if the sample is already being sent to the lab, there is no reason to use an inferior test. I must saythat I was initially thinking about patients in a clinical setting such as clinic or hospital. Thinking more broadly, I could see the value of a laboratory-based antigen test for massive screening. It would be worth the sacrifice of sensitivity if the patients could self-test, particularly if the specimen could withstand transport by mail. I can see this being useful for return to campus, pre-op, and other scenarios (isolate after test obtained until procedure/campus/sporting event type scenario). I could also see the benefit if an institution was doing daily/frequent tests or surveillance for a population. I would think in these situations, lower sensitivity than PCR could work.

Omai Garner: Antigen testing can be used for asymptomatic surveillance when PCR testing is not available. Testing should be performed as often as possible (ideally daily) to mitigate outbreaks. Some positive patients will be missed (false negatives) because of the reduced sensitivity of antigen testing. In addition, the POC antigen tests also can give false positive results. I would suggest following up any POC antigen positive test with a PCR confirmation test.

Sean Neath: When it comes to POC antigen testing, I envision 2 scenarios where this may be useful, both related to mass screening where medical personnel are not available to perform even CLIA-waived type antigen tests: 1. Schools and universities, and 2. Employers.

Massive batch testing is being contemplated on the more expensive nucleic acid amplification testing (NAAT) platforms. You certainly get more "bang for your buck" by doing an automated lab-based (high-sensitivity) antigen testing with reflex to NAAT for

positives. For institutions that may be doing a lot of serial screening, saving $10 per student or employee by using an antigen test adds up really quickly.

My view on lab-based antigen testing is that it has limited utility unless performance characteristics are similar, in which case the cost savings may make this a winner for certain settings, not just in the United States (US) but globally.

In my opinion, a sensitive antigen test has value even if there are no issues with supply chains. PCR tests are expensive and we cannot be doing them in all settings indefinitely with financial impunity. Healthcare system budgets are totally busted in the US. The cost of confirmatory testing for a lower percentage of positives will likely make this a favored cost-justified model in many settings.

Bart Buxton: I don't see a role for POC antigen testing or lab-based antigen testing and think it could be problematic. I would prefer the molecular PCR in a lab-based test and if we used an antigen test, I would prefer that in an outpatient or screening methodology.

What are the advantages of multiplex testing for other respiratory viruses in addition to SARS-CoV-2?

Jennifer Zreloff: I am seeing patients with symptoms who would like to start Tamiflu for their symptoms prior to getting their COVID tests back just in case it is flu. To manage use of medications, I can see the utility of influenza testing at the same time. Also, with common practice being to repeat negative testing in patients with high suspicion, I wonder if a respiratory panel with a different virus being detected would decrease the rate of repeat testing for negative PCR.

Omai Garner: I would prefer a multiplex Flu A/B, COVID 19 test. This will be critical for the current respiratory season where symptoms of disease will be similar. I would also like to include respiratory syncytial virus (RSV) as a target, in a perfect world. We would use this in all symptomatic populations during respiratory seasons.

Justin Choi: One of the main advantages is the ability to also test for other pathogens that have overlapping clinical features with COVID-19, particularly for influenza, which remains important for epidemiologic tracking as well as management of the patient. There may also be an impact on antibiotic use—increased detection of viral pathogens may decrease antibiotic use in patients with a clinical syndrome for pneumonia or respiratory tract infection.

Bart Buxton: This would be ideal.

Sean Neath: Absolutely. Particularly with POC and small facilities with only a few devices. If and/or when influenza enters back in circulation, it will be essential. It is hard to think of this in a univariate manner even if the focus in this discussion is on COVID testing specifically. I think the clinical reality of several different upper respiratory viruses circulating muddles the waters of a one-size-fits-all approach. If we get really good data on what is currently circulating, perhaps targeted ordering may be possible. Absent that, in a world where flu, RSV, metapneumovirus, adenovirus, rhinovirus, SARS-CoV-2, and the "garden variety" coronaviruses are all circulating at once, my testing strategy in my high acuity patients, who are frequently immune-suppressed, may change to multiplexing with a panel that includes SARS-CoV-2 among myriad others.

What additional information is needed to determine the clinical utility of antibody testing? Are there separate criteria needed for qualitative and quantitative antibody tests?

Justin Choi: There is no role for serology in the acute care setting; however, serology is helpful for identifying either prior infection or patients with prolonged symptoms that could be attributable to COVID-19. It is also possible that the detection of antibodies confers some degree of immunity; however, we need more data on the correlation between quantitative levels of SARS-CoV-2 antibodies and immunity, the risk of infection and transmission, and clinical outcomes. As we learn more, especially in light of the new COVID-19 vaccines and whether we can determine at which antibody titers they are effective, there is potential clinical utility for both qualitative and quantitative antibody testing.

Omai Garner: Antibody testing doesn't have a role in symptomatic testing, unless there are no acute disease diagnostics (antigen or molecular). In that setting, perhaps antibody positivity can help with a differential diagnosis. If a quantitative assay can be shown to be correlated with immunity, then it would be useful. It may provide additional specificity over a qualitative test and allow for a much higher positive predictive value (PPV) in a lower prevalence setting. Finally, a quantitative assay may be required to be coupled with a successful vaccine to prove effectiveness.

Until we understand the correlation between antibody in the blood and immunity, there will continue to underutilization of antibody testing. Antibody testing will be most useful for vaccine efficiency testing.

Jennifer Zreloff: For symptomatic individuals, I am not sure of the role unless the symptoms were persistent for a while. I have been seeing patients with COVID-like

symptoms that have lasted more than 3 weeks but were not tested for COVID (or they assumed they have COVID and now have pleuritic chest pain, fatigue, tachycardia, which are common symptoms in later stages). I can see that it might be helpful in this scenario.

At this point, I would be unsure how to interpret the quantitative test. If it helps to predict future immunity, then it would be valuable.

The results are not actionable (at this time) compared to molecular tests. We don't know how to apply the knowledge of a positive antibody test in most cases.

Bart Buxton: I believe that there is a role for antibody testing (laboratory-based, not POC) as we need to be able to identify patients with antibodies for multiple reasons, including but not limited to, convalescent plasma collection, longevity determination, and determination of neutralizing effects of antibodies, to name a few. Just because patients had symptoms, doesn't mean that we completely understand the totality of the impact of antibodies and the immunizing effects. We need to collect as much data as possible, especially early on so that we can be better prepared for future resurgence. Understanding who has antibodies, regardless of symptoms, will give us better insight and potentially improve decision making during future outbreaks. It may be that people with antibodies can become re-infected, but with a different strain or mutation. At this point, our knowledge base is too limited to rule out or limit antibody testing, even for empirical observations.

I think that antibody testing is extremely important to better understand whether healthcare workers or other members of the population can be exposed, not exhibit symptoms, or have mild symptoms and still create antibodies. To me, this is the basis of answering the "herd immunity" question and becomes a key to understanding the future status during a resurgence. Further, it becomes important to understand who, other than post symptomatic patients, has convalescent plasma, how long these antibodies last in the system and if they are neutralizing against future outbreaks.

Sean Neath: Earlier in the pandemic I saw no role for serology in a symptomatic patient. My view on this has changed. Now that we are months deep into this, there are patients presenting a subsequent viral-like illness. While we do not yet have solid consensus about this, the presence of SARS-CoV-2 antibodies reduces my pretest probability that the current presentation is due to COVID, and therefore increases my suspicion and testing for *other* viruses. Assuming exposure confers immunity, antibody testing affords a certain degree of reassurance. Our current test is more likely to show antibodies in patients with prior documented infections.

How can self-collected samples (nasal, nasopharyngeal, or oral fluid) be incorporated into symptomatic and asymptomatic testing algorithms?

Jennifer Zreloff: I have to believe that samples collected by healthcare workers would be at least slightly superior. However, self-collected samples have a much farther reach and a higher success rate at serial testing. I see this method primarily in the surveillance of an asymptomatic population. For those with symptoms, I find the risk of a false negative not worth it unless a healthcare worker collected specimen was not available.

Justin Choi: If we can demonstrate through scientific study and perhaps clinical trials that self-collected samples are effective for surveillance or testing of symptomatic individuals, this would be a potentially useful strategy for increasing the availability of testing, those who get tested, and limiting exposure to healthcare workers.

Sean Neath: We have had good success with other self-collected sample matrices. It broadens testing capabilities. For COVID, I believe it can reduce risk of aerosolization and contact for healthcare providers. The critical element is that the test is well-validated with a relatively fool-proof technique. Saliva is great example, pretty much everyone beyond the age of 3 knows how to spit. For a well-vetted test, this carries great value in both symptomatic and asymptomatic populations.

Omai Garner: Self-collected samples are probably the best way to move forward with large scale asymptomatic testing. It's the only way to efficiently handle the pre-analytic process.

Bart Buxton: Self-collected swabbing can be a standard part of any collection and testing algorithms for nasal and oral fluids, but is not recommended for nasopharyngeal collections. The nasopharyngeal collection process requires a sense of anatomy as well as a delicate touch. Based on the current tests available on the market, I would support self-collection for nasal and oral testing protocols.

As compared to previous Advisory Boards on which you've served, what aspects of the virtual format did you find to be limiting? Do you feel that these limitations impacted the quality of the opinions that were shared via the virtual/remote session?

Justin Choi: I do not think the quality of opinions was influenced by the virtual format. The virtual format allows for the interaction between individuals who might not otherwise have had a chance to participate

either due to geographic and travel considerations or time. There are some benefits with asynchronous communication given everyone's busy schedules. However, the virtual format is challenging for the kind of brainstorming and back-and-forth exchanges and feedback that are possible when meeting and discussing in person.

Omai Garner: The virtual format lacked the back-and-forth conversation from typical advisory boards. That said, I think the opinions that were shared were valuable.

Jennifer Zreloff: I do prefer the in-person Advisory Boards due to my desire to have a more rapid back and forth in sharing of ideas. When in the same room, there is more understanding of other's viewpoints. That being said, the virtual sessions were well done and valuable. I just feel I have been a better contributor in the face-to-face sessions.

Bart Buxton: I didn't find the virtual format limiting at all, even though it was my first one. I thought that having the ability to answer questions in the written fashion, made the process more focused and the fact that I could do it at my own pace was helpful. I also like the ability to see everyone else's responses and be able to add comments and also to ask questions.

Sean Neath: I found the virtual Advisory Board to be richer in terms of depth of information shared. Opinions appear to be more considered and better contemplated since a typed response usually has bit more reflection going into it. Each advisor speaks their piece, the clock isn't running, so much more is captured. Everyone has the chance to speak, and yet no one is interrupted. This format allows the more reticent or polite advisor to register key points that might be missed. The loudest opinion is not necessarily the more correct one! As to limitation, while discussions can actually build in this format, this requires that the advisor read and reply to other posts ("tagging" them). Since some advisors reply later than others, it's impractical to continually reread the same post for updates after you've already been there once or twice. Therefore, robust exchange appears to be more limited than it would be in face-to-face or a video advisory board. However, I believe the overall *volume* of advice gained in this format goes a long way to counterbalance the decrease in jousting dialogue that can often be seen in face-to-face meetings.

Nonstandard Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; COVID-19, coronavirus disease-2019; PCR, polymerase chain reaction; RT, reverse transcriptase; ED, Emergency Department; ILI, influenza-like-illness; PPE, personal protective equipment; POC, point-of-care; NAAT, nucleic acid amplification testing; RSV, respiratory syncytial virus; PPV, positive predictive value.

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