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SCALING UP

1,300 TESTS/DAY

Peak of SARS-CoV-2 testing at NYU Langone Medical Center

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Laboratories Are Rising to the COVID-19 Challenge

Labs' expertise, flexibility, and dedication help patients and hospitals through the crisis

BY DEBORAH LEVENSON

The SARS-CoV-2 virus spread across the globe with unprecedented speed, resulting in surges of COVID-19 cases that exceeded hospitals' capacities in hotspots in China, then Italy, Iran, Spain, France, the U.S., and the U.K. Unheard of until December, the virus had affected most of the U.S. by mid-March. Hospital laboratories responded quickly. While the technical processes for developing the initial SARS-CoV-2 diagnostic tests differed little from steps taken to launch other high-complexity, polymerase chain reaction (PCR)-based viral tests, "no one expected the volume we had to do," said Amy Fox, MD, MS, director of virology labs and director of research and pathology at Montefiore Medical Center and Albert Einstein College of Medicine in hard-hit New York City.

Fox and other lab directors heading pandemic-related testing efforts reported making test choices quickly, speeding test development and setup, and experiencing major changes in workflow as they educated clinicians about new tests and contended with shortages of staff, reagents, and other necessary supplies. In facing the pandemic, clinical laboratorians also said a renewed sense of teamwork inside their labs, and outside with clinicians and manufacturers, continues to drive their spirited response to the crisis.

Launching Tests and Stretching Capacity

Early on, labs had no tests except those from the Centers for Disease Control and Prevention (CDC) and state public health labs. They weren't enough, said Gary Procop, MD, medical director of the molecular microbiology, mycology, parasitology, and virology labs at Cleveland Clinic in Cleveland, Ohio. Larger labs had to make decisions about whether to develop tests themselves or wait for commercial ones.

During the last week of February, New York state worked with labs to start making high-complexity PCR diagnostic tests available. The Food and Drug Administration (FDA) issued its first emergency use authorization (EUA) on February 29. The next day, the Wadsworth Center, the lab for the New York State Department of Health, called Fox about setting up a PCR test. She and her associate director, Yitz Goldstein, MD, decided to use World Health Organization primers and then delved into clarifying EUA requirements. They also reached out to their vendor for additional guidance.

Facing a backlog of reagents, Fox decided to add platforms and reached out to various companies. With three she worked on securing additional EUA-approved reagents. "It was important to work with industry partners early on. Using multiple platforms was the only way to keep up," Fox noted. With support from Montefiore leadership, engineering staff renovated another lab to

handle COVID testing in just 4 days and Fox purchased new equipment for this location.

More than 2,000 miles away, ARUP Laboratories selected an assay based on its having been through the EUA process and the vendor's assurance of a reliable reagent supply chain. The chosen platform could also test for seasonal influenza and SARS-CoV-2 from the same extracted specimen, allowing more streamlined testing of symptomatic patients, said David Hillyard, MD, ARUP's medical director for molecular infectious diseases.

NYU Langone Health in New York City also relied on its relationships with manufacturers. Maria E. Aguero-Rosenfeld, MD, director of clinical labs, knew the CDC's manual PCR test would not provide enough volume. "Large companies with reliable PCR tests were our go-to early on," she said. In the second week of March, she received her first PCR test kits, had staff validate them over a weekend, and began running them the following Monday. She also used an alternate company's test when reagents became available.

On the serology testing front, Elitza Theel, PhD, director of the Infectious Diseases Serology Laboratory at Mayo Clinic in Rochester, Minnesota, has been vetting COVID-19 antibody tests carefully. With over 180 commercially available serologic tests to choose from, her laboratory selected assays from multiple manufacturers and performed nearly full-scale verifications for 10 kits. They did not perform equally well. "Do not sacrifice a quality verification process for speedy test implementation," she advised.

Workflow Changes

The surge in COVID-19 testing brought swift changes to processes, workflow, workspaces, and staffing.

The University of Washington (UW) in Seattle created a new lab dedicated solely to running diagnostic tests, doubling the available space for testing, said Keith R. Jerome, MD, PhD, head of UW's Virology Division in the Department of Laboratory Medicine. The lab increased automation, instituted special receipt procedures to keep staff safe, and began a 24-hour schedule, with a "huge" night shift performing SARS-CoV-2 assays, he said. For the first 2 weeks of COVID-19 testing, Jerome's lab also postponed tests for rare non-COVID viruses.

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CHRISTOPHER DOERN, PHD

At Mayo, Theel faced a shortage of space for lab technologists working 6 feet apart. In response, the lab, which previously had two shifts, became a three-shift, 24-hour operation. Theel also worked around a shortage of space for samples and kits. Because of higher test volume and worries about technologists' safety, the lab is working to buy additional tube cappers and decappers, she said. The Mayo lab also tweaked serology test processes, an exercise that she said will serve the lab well in the future.

Back in Salt Lake City, ARUP Laboratories saw some of its usual molecular infectious disease test volume fall off and was able to reassign 40 infectious diseases staff to perform high volume COVID-19 testing, Hillyard noted.

NYU Langone Medical Center sometimes ran close to 1,300 SARS-CoV-2 PCR tests a day. To meet demand, Aguero-Rosenfeld purchased new equipment and trained reassigned anatomic pathology technologists and residents to do COVID-19 testing.

Christopher Doern, PhD, director of clinical microbiology at VCU Health in Richmond, Virginia, said surge planning that accounts for staff illness and lack of childcare was a tremendous challenge amid a pre-existing shortage of microbiology lab technologists. He hired and retrained former staff members and is considering taking up offers from researchers who want to help. All staff had to train on working with personal protective equipment (PPE) and maintaining extra space between themselves.

Getting Creative to Tackle Shortages

Most labs have been hit by shortages of reagents or other necessary supplies. At Montefiore, Fox responded early on to a reagent shortage by sending out tests for less acute cases to its reference lab. Her staff has been following hospital guidelines for using N-95 masks. And a swab shortage forced her lab to quickly validate alternatives. "We've done the best we could with what we had," she said. "I am extremely proud of the work we have done."

At NYU Langone, Aguero-Rosenfeld offset shortages of swabs and transport media with media that NYU Grossman School of Medicine researchers made in-house. Following a published procedure, the school produced "tens of thousands" of tubes containing transport media used to make kits, she said.

Jerome's UW Virology lab has had enough reagents but not enough plastic tips for extraction instruments. He put out a plea on Twitter, and local labs responded with boxes of supplies that kept the UW lab testing until the scheduled delivery from its supplier arrived. Shortages of swabs and transport materials continue.

Because the pandemic hit Virginia relatively late, Doern had time to stock up on PPE. Reagents have remained "a huge problem," however. In response, he was exploring using more than 10 test methods. He was also considering 3D printing to supplement his dwindling swab supply.

How to Talk About COVID-19 Tests

Clinicians want to know COVID-19 tests' clinical sensitivity and specificity. Even in normal situations, those figures vary by population, severity of disease, and collection method, Doern pointed out. But with COVID-19 tests, it's impossible to give a solid figure for clinical sensitivity.

Many clinicians had sick patients with negative results, and didn't understand why, Aguero-Rosenfeld recalled. They did not realize that like many other viruses, SARS-CoV-2 is detected easily in the early stages of disease, but becomes less detectable as illness progresses, viral load decreases, and severe complications appear. So a patient could have lung failure but a negative diagnostic test. "I could only tell them that we only knew the analytical sensitivity, the lowest limit of detection of the viral RNA in the sample, as determined by the manufacturer," she said.

Some clinicians also needed an explanation of test performance characteristics, said Cleveland Clinic's Procop. He explained to them differences in tests' sensitivity, the need for use of higher sensitivity tests in inpatients, and that lower sensitivity tests might be acceptable for outpatients with appropriate guidance.

"Clinical providers have varied levels of knowledge," Doern said. "Not being able to give those clinical sensitivity numbers has been a big challenge. Instead, I discuss limit of detection to help explain sensitivity."

Theel recalled telling clinicians that antibody-positive healthcare workers still had to use appropriate PPE. She explained that while serology tests indicate whether someone has been exposed to the virus, these tests cannot give information about the level or duration of protective immunity, or whether an individual is still infectious. ARUP's Hillyard related giving similar explanations.

Back at UW, Jerome said that compared to the "exuberant regulation" for diagnostic tests, little regulation was initially aimed at serology tests. Additionally, many clinicians have been put off by poorly performing ones, which flooded the U.S. market. FDA on May 4 updated its EUA policies for COVID-19 antibody tests, requiring developers to submit their EUA requests, along with their validation data, within 10 business days. FDA also set performance characteristics for approved tests, including 90% sensitivity and 95% specificity. Good tests are now available, and labs must make sure providers trust them, Jerome added.

At Mayo, Theel refers clinicians to guidance from various organizations including the American Society of Microbiology, the Infectious Diseases Society of America, and other published expert opinions, which all generally agree on both the utility and limitations associated with serology tests.

A Call for Communication and Lab Stewardship

Having good relationships with colleagues and representation with hospital leadership is critical, Procop emphasized. He serves on Cleveland Clinic's Incident Command Committee, where he explains differences among COVID-19 tests to clinical leaders. Lab leaders "must speak up to institutional leaders and demand representation on committees that make decisions about care related to the pandemic," he said.

Montefiore created a command center that made key testing decisions. Run by the department of pathology and staffed with lab personnel and MD and PhD student volunteers, the center received clinician test requests through a dedicated email address, and along with Fox's lab decided which patients to test and which platforms to use.

At VCU, clinicians are free to choose among COVID-19 tests, but still need education about the consequences of misuse, Doern said. For example, he may dissuade a clinician from using a rapid test on an outpatient by explaining the choice means a test might not be available for an acutely ill inpatient who really needs it.

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GARY PROCOP, MD

Lessons Learned So Far

Lab directors identified several lessons from the pandemic based on their early experiences, including the need to prepare for widespread infectious disease outbreaks going forward.

"The story of COVID-19 has been about preparation or lack thereof," Hillyard said. "Reach out and plan early if you see something on the horizon." He suggested specific steps. Look at all required testing components and consider how to get reagents and maintain the supply chain, and maintain good relationships with supply and test manufacturers, even if a lab designs its own assay. Think creatively about repurposing and revalidating available sample collection materials and ensure a lab can reposition and retrain enough skilled personnel. "Reach out to FDA early, and make sure your lab has accurately quantified control material to validate a diagnostic test," he added. Meanwhile, lab directors should communicate with trusted and experienced colleagues for advice and collaboration, Hillyard noted.

"Everyone needs to be more aware of local epidemics throughout the world. Prepare before someone else decides you should do something," Jerome advised. "Labs need to be flexible in their operations, be able to shift personnel and make sure they are well-trained, with good management."

At Montefiore, the pandemic has had a silver lining, Fox said. COVID-19 spurred more collaborative relationships between laboratorians and basic scientists focused on developing new tests. And they now have COVID-19 samples for future research.

The pandemic has also underscored the value of laboratory medicine to the general public as media reports highlighted shortages, discussed different tests, and explained laboratorians' important role in patient care. "Laboratorians are being interviewed on TV. I hope this will be a success story for our profession," Doern said.

Fox and Aguero-Rosenfeld emphasized how their staffs and hospitals rose to challenges with dedication and unity. Fox called herself "a lucky leader of an extraordinary team of people" who worked 15-20 hour shifts to help establish a lab and new platforms, and flipped between them while contending with shortages.

"It's been very draining to face the crisis, especially because so many employees became ill with New York City at the epicenter. It's been a great challenge for all of us," Aguero-Rosenfeld said. "But against this adversity, we worked together."

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Thank you!

We're grateful to laboratory professionals on the front lines working tirelessly in the fight against COVID-19.

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