

INNER WORKINGS

Molecular biologists offer “wartime service” in the effort to test for COVID-19

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As the novel coronavirus spreads, communities across the United States are struggling to offer public testing. The need is urgent. Testing got off to a delayed start in the United States as a result of technical missteps and a slow response from government officials. Now cities across the country are playing catch-up (1).

Many researchers with the appropriate skills are eager to help. And in principle, they're well placed to do so. The relatively simple assay to diagnose the novel coronavirus entails RNA extraction and the polymerase chain reaction, or PCR. The two methods are so straightforward that many researchers are

questioning why their labs can't just pivot into guerilla testing centers.

The limitations have more to do with regulations than with scientific technique—handling samples that will ultimately deliver medical results to patients involves legal oversight that's far more complex than the assay itself. Although most molecular biologists won't be able to offer their assistance in short order, some states have made it easier for them to contribute. And in some cases, researchers can help out with essential tasks associated with the tests, even if they can't actually perform the tests themselves.



Molecular biologists have the skills to run COVID-19 tests, but not the legal approvals. Some states are now relaxing restrictions to enable more researchers to run tests. Image credit: University of California, Berkeley/Max & Jules Photography.

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Researchers are offering equipment and reagents as well as lab skills. Here, a UC Berkeley professor loads a liquid handler, which should help increase COVID-19 testing throughput. Made available via an emergency loan, the device is headed to the University of California, San Francisco, where hospitalized patients are being tested. Image credit: Julia Schaletzky (University of California, Berkeley, CA).

Getting Certified

In order to legally perform diagnostic work on human samples in the United States, a lab needs certification from the Centers for Medicare & Medicaid Services, through its Clinical Laboratory Improvement Amendments (CLIA) program (2). To handle testing, the lab also needs to employ medical laboratory scientists—medical professionals with typically two to five years of academic training—to collect human samples, analyze them, and interpret the results. Eleven states, including California, New York, and Louisiana, require a license to practice the medical laboratory science profession (3). Biochemists, microbiologists, and ecologists with general molecular training may have the technical skills to run COVID-19 assays, but they don't have the appropriate certifications.

Even so, the urgency of the pandemic has spurred some states to relax legal restrictions on who can perform COVID-19 testing. On March 12, for example, California Governor Gavin Newsom issued an executive order suspending certification and licensure requirements for any researcher with relevant skills who meets CLIA requirements to run the COVID-19 test; such a person may now temporarily run the assays under the supervision of a medical laboratory scientist in a CLIA-certified lab (4). On March 19, Louisiana Governor John Bel Edwards issued a proclamation to temporarily suspend some certification and licensure requirements for running COVID-19 assays. Now,

laboratory personnel “who demonstrate molecular biology polymerase chain reaction (PCR) experience” can legally run COVID-19 tests if they are supervised by a licensed physician or PhD with related lab experience, according to the proclamation (5). Hence, an ecologist trained in PCR might now be a candidate to run COVID-19 assays, if properly supervised, says Vincent Culotta, executive director of the Louisiana State Board of Medical Examiners in New Orleans.

Lending a Hand

Even without special legal allowances, molecular biologists are finding ways to pick up pipettes to aid coronavirus testing. At the University of Washington School of Medicine's clinical Molecular Virology Laboratory in Seattle, for example, graduate students, retired faculty, and other university volunteers with backgrounds in molecular science are performing some of the simpler processing steps to prep COVID-19 assays. Although the RNA extraction and PCR steps are reserved for certified medical laboratory scientists, the volunteers tackle simpler steps such as pipetting samples into vials before testing.

To biochemist Julia Schaletzky, executive director of the Center for Emerging & Neglected Diseases at the University of California, Berkeley (UC Berkeley), the many barriers to processing human samples don't make sense right now, especially considering that the scientific technique is so straightforward. “Most of us scientists are like, ‘Wow we can easily do this PCR no problem,’” she says. “We're realizing these rules are there for good reason but not useful in an emergency.”

As a technical matter, running the novel coronavirus assays is indeed relatively straightforward. Because the pathogen, labeled novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a single-stranded RNA virus, testers first isolate viral RNA from a nasal swab sample using an RNA extraction kit (6). Then they apply a solution of selected nucleotides and the enzyme reverse transcriptase to create complementary DNA to the RNA. Finally, the DNA is amplified into many copies using a polymerase chain reaction in a quantitative PCR (qPCR) machine. A fluorescent dye in the PCR reaction specifically binds and illuminates SARS-CoV-2 gene sequences. So if the qPCR detects a strong fluorescent signal, the sample is positive for the coronavirus.

However, “there is honestly a lot more to this than the assay itself,” says Keith Jerome, director of the University of Washington School of Medicine's Molecular Virology Laboratory. From the moment a human sample is collected, a series of formalized steps ensure its controlled transfer to the clinical lab, appropriate testing, and the eventual communication of results to the ordering physician. “Things like that are foreign to people who've worked exclusively in research labs,” Jerome says.

Institutions with medical centers, such as the University of Washington, have the advantage of large clinical labs and some certified medical laboratory scientists onsite, meaning they can, in fact, legally and

appropriately pivot into COVID-19 testing centers. The Broad Institute, a biomedical research center in Cambridge, MA, had an established clinical lab with qualified laboratory scientists onsite during the emergency. "Broad scientists have been working round-the-clock to adapt our existing, highly automated clinical testing facility to accurately perform the existing CDC RT-qPCR COVID-19 test at high scale," says Stacey Gabriel, senior director of the Genomics Platform at the Broad Institute of Massachusetts Institute of Technology and Harvard University in Cambridge. Across the country in hard-hit California, five medical centers in the University of California system—on the Los Angeles, San Francisco, San Diego, Davis, and Irvine campuses—will offer COVID-19 testing, confirms Omai Garner, section chief of the Clinical Microbiology Laboratory at UCLA Health.

But some schools without big medical centers, associated hospitals, or large clinical labs can also offer testing, although it's logistically challenging (7). UC Berkeley's only CLIA-certified lab, for example, is in their student health center, Schaletzky notes. It

San Francisco Bay Area. They chose molecular biologists, all of whom were previously working with human cells, many in the context of basic research related to genetic engineering and CRISPR. "I made the decision 'I'm only going to hire people whose middle name is qPCR, and whose first name is RNA extraction,'" Urnov says. Ecologists, microbiologists, and other researchers with molecular training did apply as well, Urnov says, and could legally qualify to volunteer to run the testing in California.

Ready for Service

Researchers who don't have legal approval to help fight this virus may still lend their skills to clinical centers for some of the simpler work, as in the University of Washington School of Medicine's Molecular Virology Laboratory. Anticipating that clinical centers will need help, postdoctoral neuroscientist Michael F. Wells of the Broad Institute and Harvard University is independently collecting contact information for a database of US molecular researchers. In the project's

How to Help Out.

Here are a few ways that molecular biologists and other researchers may be able to help with COVID-19 testing efforts:

- 1) Harvard University and Broad Institute postdoctoral neuroscientist Michael F. Wells is collecting contact information for a database of US molecular researchers who might be able to offer their expertise. Thus far, Wells has distributed the list to the Federal Emergency Management Agency (FEMA) and medical centers, who will be in touch with researcher signees. See the site for more information: <https://docs.google.com/forms/d/e/1FAIpQLScXC56q2tPgZ0WbPrhP7WareiclfxfKQFI0ZbXg4FkKan5iQ/viewform>.
- 2) For those researchers with personal protective equipment in their laboratories that they are authorized to donate, visit <https://getusppe.org/>, a site set up by workers on the front lines of the pandemic. Organizers are attempting to coordinate donation efforts around the country.
- 3) See <https://crowdfightcovid19.org/> to explore an international initiative aimed at connecting active COVID-19 researchers with scientists around the world who may be able to help with data analysis and other tasks.

didn't have the appropriate setup to handle testing for the virus. But there are potential workarounds. To get around its limitations, UC Berkeley is temporarily extending the clinical lab's CLIA certificate into the larger Innovative Genomics Institute on campus, and will staff it with volunteer researchers who have the relevant skills to run the assay, supervised by a licensed medical laboratory scientist. Governor Newsom's executive order, as well as revised emergency guidelines from the US Food and Drug Administration (FDA), made the temporary extension possible, as Berkeley's CLIA-certified lab in the health center can extend its certification to another location on campus. The several medical laboratory scientists already working there will oversee at least 15 Berkeley postdoctoral molecular biologist volunteers, who will run the COVID-19 assays.

Fyodor Urnov, the Innovative Genomics Institute's scientific director of technology and translation, says he and his team selected about 20 candidate volunteers from a pool of 862 applicants from UC Berkeley and other research institutions and universities in the

first 42 hours it attracted more than 2,900 molecular researchers, and it now has more than 8,100 volunteers. Each volunteer filled out a form including their email address, phone number, job title, and experience with qPCR, RNA extraction, biosafety authorization to work with viruses such as SARS-CoV-2, and other skillsets, although whether they can legally volunteer their skills will vary by state.

As of March 31, Wells had shared the list with the Federal Emergency Management Agency, and with universities, medical centers, and several state- and county-run health departments that anticipate needing backup staff for COVID-19 testing or other tasks. They will contact people on the list directly. Wells' volunteer form also asks whether signatories have reagents or equipment that they can donate, specifically RNA extraction kits. For those interested, Wells suggests reaching out to decision makers at local universities and hospitals at state and county levels to let them know about the researcher volunteer database. He also suggests organizing like-minded researchers in your local community.

Unfortunately, even as facilities race to ramp-up capacity, supply shortages, not just personnel and lab space shortages, have waylaid some testing efforts (8, 9). First, in February, the CDC's faulty test kits delayed efforts by three weeks (7). Some testing centers made their own COVID-19 assays, choosing their preferred brand of RNA extraction kits, primers, PCR machines, and swabs, Schaletzky explains. Bespoke testing protocols must be granted emergency authorization by the FDA and cross-validated by an independent CLIA-certified lab. The problem is that once a testing protocol is approved, none of the reagents or equipment can be changed, not even by brand if the original supplier runs out. "If you run out of swabs, there's no way to suddenly accept a different kind of swab in your protocol according to the guidelines," Schaletzky explains. "That's what leads to the shortages we have, because it's not flexible."

New point-of-care rapid tests, such as one from the Abbott Park, Illinois-based medical device company Abbott, could relieve some pressure on clinical labs, by reducing physicians' need for send-away testing. The new test runs on a toaster-sized, portable,

molecular device that detects the viral genetic material in a patient sample. Abbott says the device offers results in minutes and can be used in a doctor's office or urgent care clinic. After the FDA granted emergency-use authorization for the test in late March, Abbott estimated that it could deliver 50,000 COVID-19 tests per day (10).

Molecular research volunteers are still useful and needed, despite advances in point-of-care testing, Wells notes. It's unlikely that every health department and physician will switch to the new test immediately, whether for financial, logistical, or scientific reasons, he says. And although the test can detect whether a patient is currently infected, it won't be useful, notes Wells, when testers "start trying to identify previously infected individuals (and, by extension, those who are now presumably immune to COVID-19) using antibody-based tests." Still, with any luck, point-of-care testing, new pop-up COVID-19 clinical testing centers, and an army of researchers willing to aid in the fight will make tracking and slowing the virus easier in the coming weeks.

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