Cutting cultures: the move to all molecular in virology

Kevin B. O'Reilly

March 2016—For laboratories performing virology testing, taking advantage of molecular testing's superiority to traditional testing methods is a no-brainer. But leaders in the University of Michigan's clinical microbiology laboratory have found that the push to go all molecular for virology testing must be tempered by attentiveness to clinician preferences and a collaborative approach that's likelier to make the journey a success.

So says Duane Newton, PhD, clinical microbiology director at the University of Michigan Health System in Ann Arbor. Compared with a high of nearly 6,000 viral cultures performed in-house during the 2009–2010 fiscal year, the Michigan clinical microbiology laboratory performed fewer than 1,000 viral cultures during 2014–2015, and that figure appears to be dropping to "essentially zero" in this fiscal year.

It is unclear how many laboratories performing virology testing have gone this far in their transition to molecular, Dr. Newton tells CAP TODAY.

"We're at least in the middle part of a journey where it's becoming more commonplace," he says. "What is clear is there's some contention and debate about approaches, and differences of opinion about how to approach this [move to molecular].... There's lots of communication that has to happen within your institution. What might be right for mine might not be right for your institution."

At Michigan, one of the few examples in which molecular is not the go-to method is for nonblood specimens tested for cytomegalovirus. In retrospect, Dr. Newton said during a session at the Association for Molecular Pathology's annual meeting last November, this was a case where he and his laboratory colleagues moved too far too fast.

"One of the mistakes that we made was assuming too much," said Dr. Newton, who is also associate director of the Division of Clinical Pathology and an associate professor of pathology at Michigan. "In our quest to eliminate cultures, CMV culturing was one of our targets. We started evaluating quality assays for testing of nonblood specimens, primarily respiratory tract specimens. We went through the process of validating specimen types and demonstrating that we could consistently and accurately detect CMV with those specimens and as a result felt comfortable discontinuing CMV cultures.

"That's when we decided to talk to clinicians and say, 'This is what we're going to do,'" Dr. Newton added. "And our infectious disease doctors and lung transplant pulmonologists said, 'Wait a minute. PCR is going to be way too sensitive. We already over respond to the positive cultures. And now you're going to give us 30 to 50 percent positives, and people are going to over respond to this as well.'"

Duane Newton, PhD

In response, Dr. Newton and his laboratory colleagues decided to cancel plans to perform CMV testing by PCR and developed a process to send out any requests for culture so they could eliminate the culturing in-house. Nonetheless, it was a lesson learned.

"It's one of those things where we should have talked about this before we went down this road," he said. "It

reinforces to us that need to engage the users as early in the process as possible."

Another example, more recently, where Dr. Newton has opted to defer to clinicians is in neonatal herpes simplex virus testing. Some pediatricians and infectious disease physicians at his institution objected to using PCR for HSV in neonatal patients, noting that the American Academy of Pediatrics' Red Book embraces culturing as the gold standard method in these cases.

These clinicians "were not supportive of using molecular in this scenario because they felt it was too sensitive and would pick up colonization that you can have exposure to during birth. They felt that it was not necessarily infection—that it's superficial contamination and that culturing would be definitive because it's more specific for infection," Dr. Newton tells CAP TODAY.

How is neonatal HSV testing handled now?

"We send it out for culture," Dr. Newton says, noting there is about one request a month for HSV culturing. "The volume is too low to have it in-house but it's available on request, when that clinical situation arises, and that's something communicated by the clinical teams [to] the lab so that we can facilitate that. And that was one of the parts of the decision. Since we weren't going to perform conventional methods anymore, including culturing, we needed to figure out how our level of service needed to change to accommodate that."

Pathology residents help manage all viral culture test requests by consulting a protocol for when send-out of such test requests is warranted, Dr. Newton said at the AMP meeting.

The pathology residents will "look at the order, look at the patient's chart, and communicate with the physician as necessary," he said. "We want to see that this is a clinical situation that actually requires it, or is the clinician just checking boxes and doesn't realize we have better tests in-house. Most requests are actually eliminated through that process. The ones where there really is a justification, the clinicians are aware of that and now are giving us a heads-up, saying we have this patient and need to have a culture for X, Y, and Z. So it's a pretty streamlined process."

Acquiescing to clinician concerns about molecular tests being too sensitive is a practice that not everyone endorses.

During the question-and-answer portion of Dr. Newton's AMP talk, Paul Schreckenberger, PhD, rose from the audience to speak.

Dr. Schreckenberger

"As a lab director, I have a real problem with saying, 'Let's use less sensitive tests.' I think that physicians should know what's out there and they should use that information, along with their clinical judgment and with their knowledge of what's going on with the patient," said Dr. Schreckenberger, clinical microbiology director at Loyola University Medical Center, Maywood, Ill. "To me, it's a slippery slope to say that a molecular test is not good because it results in false-positive test results. It is not a false-positive if the target is present in the sample—for example, herpes virus. It's just a matter of whether it's connected to infection."

In an interview, Dr. Newton says he would frame the issue differently.

“The question is in what clinical scenarios is it most appropriate to utilize molecular,” he says. “It is analytically more sensitive, but I think the issue is specificity from a clinical perspective. And there are a lot of examples where maybe it is analytically too sensitive and you lose some clinical specificity.”

Objections to molecular methods for detecting viral pathogens are not always about sensitivity, Dr. Newton adds. The Michigan clinical microbiology laboratory had discontinued direct fluorescent antibody testing for respiratory virus infections when it implemented molecular, but it maintained DFA for detection of herpes simplex and varicella zoster viruses from lesions.

“As the assays became available and validated in our labs for PCR for herpes and varicella, our desire was to discontinue DFA,” he says. With a desire to avoid the implement-first, ask-later approach, Dr. Newton shared the plan with heavy clinician users of this testing.

“The pushback really revolved around turnaround time,” he says. Accustomed to two-hour TATs with DFA testing, “once-a-day molecular testing wasn’t something they were super excited about.”
In response, Dr. Newton and his colleagues have changed their approach, switching to Focus Diagnostics’ 3M Integrated Cycler, a platform “that is much more amenable to more frequent, small batches during the day. We’re in the process of going live with herpes and varicella on that platform…so we can do multiple runs during the day.”

The 3M Integrated Cycler’s analytical run time for Focus’ HSV and VZV assays is about one hour, Dr. Newton says. The agreement with clinicians is to perform two runs, one in the morning and one in the afternoon, seven days a week.

At the Cleveland Clinic, HSV for lesions is one of the few areas in which the virology laboratory still uses a nonmolecular method, Quidel’s ELVIS HSV Test System. Gary W. Procop, MD, MS, who directs molecular microbiology, virology, mycology, and parasitology at Cleveland Clinic, says they still do traditional culturing for enterovirus other than cerebrospinal fluid and for CMV other than blood.

“That’s about it,” Dr. Procop says. “Every once in a while, we’ll do a test-of-cure culture, particularly in an immunocompromised patient whose symptoms have not resolved.”

“The real paradigm shift,” he adds, “is not only the multitude of molecular virology tests available, but that many of them are available for platforms that are very simple to use, platforms that can be used for a variety of different pathogens, and that can be implemented in 200-bed hospitals. In the past, tests that could not be done locally were referred out. Now, many of these tests can be performed locally in smaller-sized hospitals with high-quality results.”

Unlike Michigan, Cleveland Clinic does not send out all test orders requesting culture.

“We’ve retained some ability. Many places would just make it a send-out,” says Dr. Procop, professor of pathology at the Cleveland Clinic Lerner College of Medicine. “Some of these, like the influenza culture, have been retained as a lab-order only. It’s only going to be placed if the doctor calls us, explains the clinical need and rationale, and then it may get approved. If we put all the testing possibilities on the test menu order, some busy person is going to check all the boxes. There’s a lot of utilization management that goes into these efforts.”

Dr. Procop

While lacking hard data on how far laboratories performing virology testing across the country have gone in giving up traditional testing methods, Dr. Procop says commercial development is making the biggest difference in speeding the transition.

“The more turnkey that vendors make their product, the wider the distribution it will have,” he says. “For many of these tests that we have been doing for years—not just here but at other academic medical centers—you had to have people to design the primers and the probes and construct the assays. But poor old St. Elsewhere hospital didn’t have that. They also couldn’t sustain the cost infrastructure.

“What’s really been a change in the development and marketing from numerous manufacturers is that many of these companies followed Cepheid’s lead of having single-use cartridges. You do this, and you throw it away. It all comes prepared. You don’t need basic scientists there, and it’s FDA approved.”

“The traditional virology laboratory,” Dr. Procop concludes, “has been transformed to a molecular virology laboratory.”

Navigating this sea change, Michigan’s Dr. Newton insists, requires a cooperative style from the laboratory.

“There’s very little in the way of things that we can’t do [technologically],” he says. “If you have the resources, you can do a lot, but you have to have a willingness to keep patient care at the front of your decision-making process. It’s about what’s best for the patients, not what’s convenient or easy for the laboratory.”

“Here I feel fortunate,” Dr. Newton adds, “that I don’t have to battle too much with administrators, and I don’t have to battle too much with our clinical colleagues. I have a great relationship with my colleagues. I don’t always get what I want. And they don’t always get what they want.”
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