When to fire up large multiplex PCR?

Kevin B. O'Reilly

January 2016—Multiplex PCR panel tests for viral and gastrointestinal pathogens as well as the rapid identification of bloodstream infections can detect more pathogens more quickly than traditional microbiology methods. The question that continues to bedevil is how to offer this newer breed of tests.

The panels, offered by manufacturers such as BioFire, Luminex, and Nanosphere, come with hefty price tags that have prompted difficult questions about their appropriate use. Should multiplex PCR panel tests be restricted in some way, reserved for the sickest patients or those whose immune systems are compromised? Or should the door be open for clinicians to order them as they see fit?

Multiplex PCR panels are used first-line at Loyola, and an evaluation of outcomes is ongoing. "We're going to be looking at everything we possibly can, and we'll report it," Dr. Paul Schreckenberger says.

One fierce advocate of the open-door approach is Paul Schreckenberger, PhD, director of the clinical microbiology laboratory at Loyola University Medical Center, Maywood, Ill. He made his case for first-line use of multiplex PCR panels before a standing-room only crowd during a point-counterpoint session at the November 2015 Association for Molecular Pathology annual meeting.

Multiplex PCR panel testing "has a huge impact in patient care," Dr. Schreckenberger tells CAP TODAY. "It's what our physicians want, and what they've always wanted, and it's what they get in all the other laboratories. You send the specimen and you get a result back in a couple of hours. It's only microbiology that has had two-, three-, and four-day delays."

At Loyola, clinician response to the introduction of a respiratory panel was jubilance, Dr. Schreckenberger says.

"The physicians loved it, and they said, 'When are we going to have more of these types of panels? We need this for meningitis, blood culture.' There's tremendous pent-up demand for these types of things."

Were the economics of the situation different, there would be no debate about using these panels as the first-line testing option, he says.

“The only reason it’s even controversial is because of the expense. If it were no more cost to the lab than what we currently do, everyone would just be on board. It’s because the labs get pushback because they’re asking for more in their supply budget. The instruments don’t cost that much. It’s the supply costs that can kill you, and run into the millions of dollars a year.”

Seven-figure laboratory expenses tend to raise eyebrows, but leaders at Loyola have so far been keen on Dr. Schreckenberger’s aggressive approach. He and his colleagues in the Loyola microbiology laboratory first got the budget to bring on BioFire’s FilmArray respiratory panel. They added the blood-culture identification panel on that platform last spring and plan to go live with the FilmArray GI panel in February.

“When I asked for these tests, the question I was asked was not how much it costs, but, one, will it decrease patient stay and, two, will it increase patient satisfaction,” Dr. Schreckenberger says. “Those are the two huge drivers for hospital administration. If the answer is yes to those questions, then you can look to answer the cost-benefit question. If the answer is no, then it doesn’t matter what it costs. The hospital is not likely to approve it.”

Dr. Schreckenberger has relied on medical literature stretching back to the introduction of MALDI-TOF to illustrate to administrators the general principle of how improvements in microbiology turnaround times can translate into shorter hospital stays and lower total costs. But, he admits, he is under the gun to show that multiplex PCR panels produce similar results.

“At some point they [administrators] will come to me and say, ‘So, Dr. Schreckenberger, do you have some data to show us?’ The pressure is on me to produce and show that, so we have people working on that. It’s not so easy for us because, in the laboratory, those aren’t statistics that we keep. We have to get people involved who can review charts and look at outcomes.”

“When we evaluated systems in the past, we looked at the sensitivity, the specificity, the turnaround times,” Dr. Schreckenberger adds. “Those are the things we were asked about in the past. Now we’re being asked, what’s the patient outcome? No one ever asked me that before. How do we find that out? These are great questions that need to be answered, and we need to work with our administrators to do this kind of stuff.”

Monthly respiratory testing volume and % positive
Loyola University Medical Center, Oct. 1, 2013–Sept. 27, 2014

Month	Flu A/B		Rapid respiratory panel					% Rapid respiratory panel
	No.	% (+)	No.	% (+)	Location for rapid respiratory panel (%)			
					Inpatient	ED	Outpatient	
October 2013	17	6	291	41	Data not collected			94
November 2013	20	5	230	38	↓	↓	↓	92
December 2013	136	42	404	48				75
January 2014	151	32	411	38	44	37	20	73
February 2014	76	20	313	39	49	28	23	80
March 2014	39	13	231	35	50	36	14	86
April 2014	33	24	258	44	48	35	17	89
May 2014	43	30	388	36	50	37	12	90
June 2014	10	20	190	36	55	33	13	95
July 2014	7	0	222	28	Data not collected			97
August 2014	1	0	204	31	↓	↓	↓	99.5
September 2014	8	0	351	42				98
Total	**541**	**28**	**3493**	**39**	**49**	**35**	**17**	**87**

Adapted from Nov. 5, 2015 AMP annual meeting presentation by Paul Schreckenberger, PhD: "First-Line Use of Multiplex PCR Panels for Pathogens: Full Speed Ahead."

In his AMP talk, Dr. Schreckenberger identified the outcomes that should be measured, and the areas where one could expect to see the impact of multiplex PCR panels. They include faster access to treatment, shorter duration of symptoms, less time off work or school, reduced emergency department times, shorter hospital and ICU stays, better implementation of infection-prevention methods, lower pharmacy costs, and lower laboratory costs due to less need for follow-up tests such as antibiotic peak and trough levels. Other outcomes amenable to improved testing include fewer side effects from inappropriate use of antibiotics, such as for *Clostridium difficile* infections, and lower total costs for the given medical encounter.

Quantifying some of these costs is notoriously difficult, Dr. Schreckenberger acknowledges.

"It's hard to get your arms around the data. It's especially hard when you try to look at costs, because nobody knows how much anything really costs."

During an earlier transition to PCR for *C. difficile*, Dr. Schreckenberger and his colleagues discovered that in one month the faster results helped avoid 362 days of unnecessary patient isolation.

"So I'm saying we can save isolation days. And the administration says, 'How much does an isolation room cost?' How can you run a business this way?"

The outcomes evaluation of the multiplex PCR panels implemented at Loyola is ongoing. "We're going to be looking at everything we possibly can, and we'll report it," Dr. Schreckenberger says.

With regard to respiratory testing, Dr. Schreckenberger shared Loyola's results from the 2013–2014 flu season, both in his AMP talk and in a heavily downloaded point-counterpoint published in the *Journal of Clinical*

Microbiology (Schreckenberger PC, et al. 2015;53[10]:3110–3115). Loyola offered Cepheid's influenza A/B test, as well as the FilmArray respiratory panel, with the latter being $73 more expensive per test. Dr. Schreckenberger advised Loyola clinicians to choose one or the other. That is because payers might consider a panel order after negative results on the flu PCR to be duplicate testing for which payment would be denied.

Clinicians responded by overwhelmingly opting for the respiratory panel, which accounted for 87 percent of the orders, while the remaining 13 percent were for the flu A/B PCR. And most of the orders for the respiratory panel came for patients sick enough to come to the hospital, as 84 percent of orders were for inpatients or patients in the emergency department. And while just 28 percent of the flu A/B tests yielded a positive result, 39 percent of the respiratory panel tests were positive for at least one pathogen.

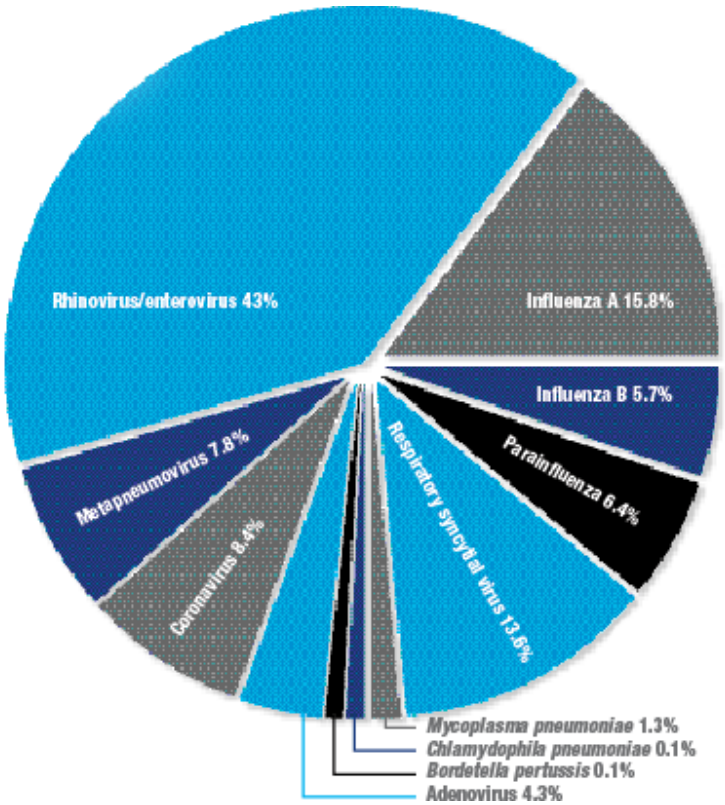
The greater ability to deliver a definitive diagnosis using a respiratory panel helps avoid empiric treatment, or "guess therapy," as Dr. Schreckenberger puts it. That diagnostic specificity also is increasingly important during this age of patient-experience surveys, Dr. Schreckenberger told the AMP crowd. (He disclosed financial relationships as a speaker, consultant, and researcher for more than a dozen diagnostic manufacturers.)

"People don't usually go to the ER for a runny nose. They're usually sicker than they have ever been. It's not satisfying to sit in the ER for a few hours and be told, 'We don't know what's wrong with you. It's not the flu.' For us, only 15 percent of patients had a positive test for the flu, so for 85 percent it's possibly something else. If you're only testing for the flu, you're missing that 85 percent, and you're sending those patients home without a diagnosis. When they get that survey, they'll say, 'I spent six hours in the Loyola ER and they couldn't find out what was wrong with me.'... If the diagnosis is possible, you not only want to get that diagnosis, but you want to treat the patient quickly, and that will lead to patient satisfaction."

Dr. McAdam

Alexander McAdam, MD, PhD, associate professor of pathology at Harvard Medical School, was Dr. Schreckenberger's interlocutor during the point-counterpoint session at the AMP meeting as well as in the pages of *JCM*. He tells CAP TODAY he is not persuaded that multiplex PCR panels will yield a great improvement in patient satisfaction.

"To me, that's a relatively small gain—telling a patient that they're infected with a virus they've never heard of, and for which there's no treatment. It's of some value because they know they don't have something worse," says Dr. McAdam, director of the infectious diseases diagnostic laboratory at Boston Children's Hospital.



Incidence of viruses in respiratory specimens
Loyola University Medical Center, Oct. 1, 2013–Sept. 27, 2014
Percentage total exceeds 100 because some samples contained multiple viruses. Adapted from Nov. 5, 2015 AMP annual meeting presentation by Paul Schreckenberger, PhD: "First-Line Use of Multiplex PCR Panels for Pathogens: Full Speed Ahead."

"The emergency room visit can be very valuable if the clinician tells the patient, 'Based on your history and physical exam, you have a respiratory virus. You're going to get better, and you're not going to get desperately ill. If you get really sick, come back and we'll be here for you,'" he says. "There's tremendous value in that patient-physician interaction. And there's only a little bit added by naming the specific pathogen."

Laying out his views before the AMP crowd, Dr. McAdam said, "Will multiplex PCR panels achieve certain ends—improve patient satisfaction, reveal mixed infections, etc.? Yes, yes, yes. I don't like these tests; I love them. The question is whether to use them as first-line tests."

He noted, for one, that the tests are expensive. The cost per cassette is between $80 and $130, and laboratories also must account for other costs such as testing controls, capital expenses, and service contracts. He estimates that annual expenses for multiplex PCR panels as first-line tests at Boston Children's would be about $200,000 for stool pathogens, $180,000 for respiratory pathogens, and $160,000 for blood-culture identification.

Dr. McAdam says his objection to first-line use of multiplex PCR panels is not entirely about cost.

"That's certainly part of it," he says, "but it's also about the clinical utility of the tests and the difficulty that clinicians may have appropriately utilizing these tests and interpreting the results. The diagnostics have jumped ahead and we're now detecting organisms that might or might not be true pathogens. People will struggle to understand the results of these tests. It's important that normal microbiota not be treated as pathogens."

His biggest concern is not that physicians will prescribe antibiotics to treat a viral pathogen. Rather, Dr. McAdam worries that physicians receiving a positive result for *C. difficile* on a GI panel may wrongly interpret that information.

"*C. diff.* is an important pathogen but it's also found as a member of the normal flora. There's a risk people will treat based on a positive test result when *C. diff.* may not be the cause of the patient's symptoms."

Boston Children's Hospital will implement a rapid respiratory panel this year, but is holding off on GI and blood-culture identification panels for now.

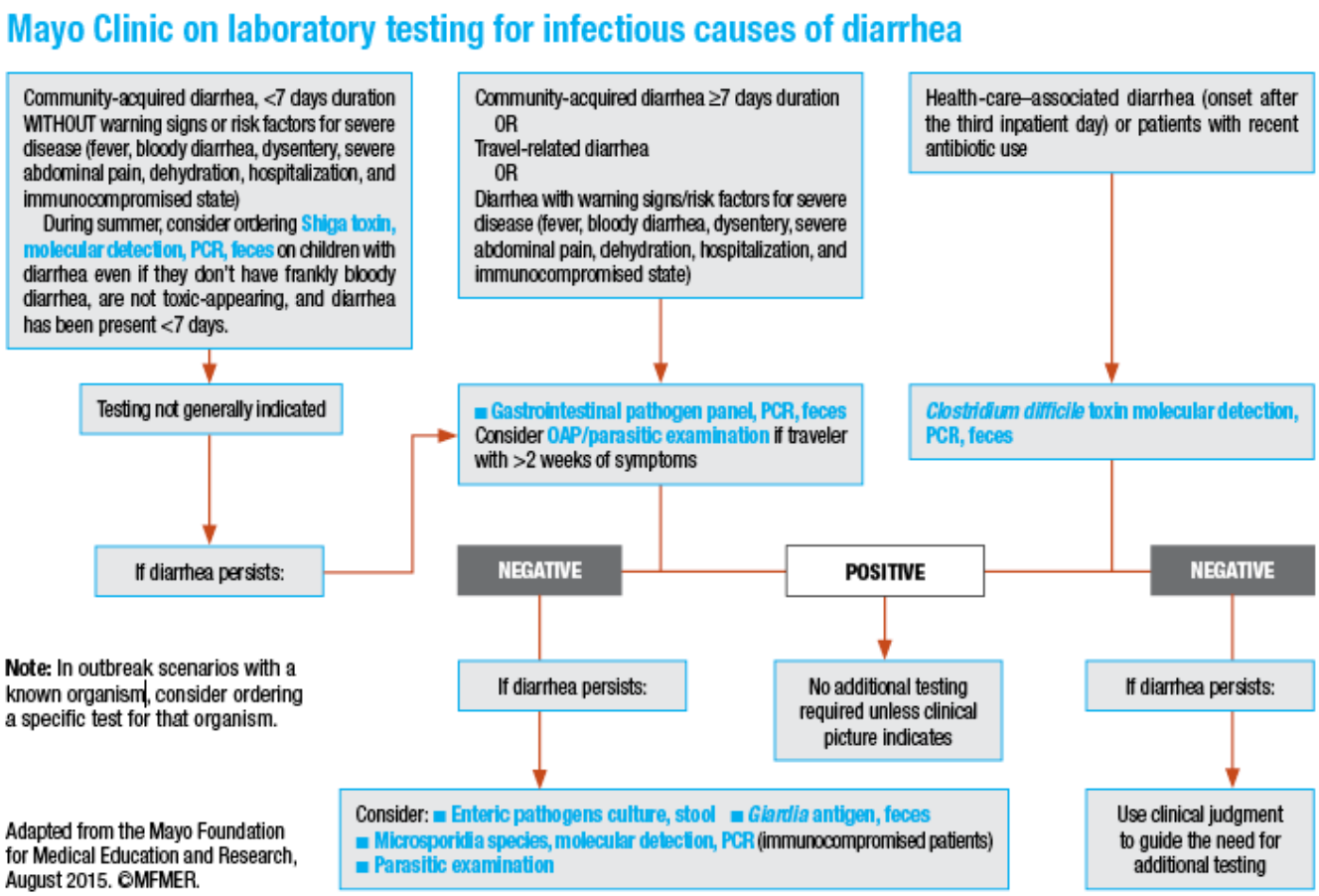
"The big mistake," Dr. McAdam added, "would be to introduce a large multiplex PCR test for syndromic diagnosis without having a careful conversation with the clinicians beforehand, so they understand what organisms the tests will detect as well as the clinical sensitivity and specificity. The goal is that they be prepared to deliver appropriate care when they get the results of the test."
Without doing that necessary legwork with clinicians, it is possible that unintended outcomes, such as more misuse of antibiotics, could be seen.

"There's no data either way," he says. "There aren't data on outcome studies based on these tests. We don't know what actions clinicians take as a result of these reports, and we don't know what effect there is on patients. It's a real hole in the literature."

Robin Patel, MD, says she is excited about the availability of multiplex GI panels but shares Dr. McAdam's concern about their cost and the potential for unintended consequences. She chairs the Division of Clinical Microbiology at Mayo Clinic in Rochester, Minn., and presented data on the performance of panels from BioFire, Luminex, and Verigene. At Mayo, Dr. Patel and her colleagues evaluated the Luminex and BioFire GI panels.

"We found that they were both very good," she says. Mayo opted for BioFire's GI panel (which went live Oct. 12, 2015), in part because the laboratory already uses the FilmArray platform for blood-culture identification.

Despite excellent analytical performance of the GI panel, Dr. Patel said her laboratory encourages first-line use of the panel in only certain patients.



She cautions about the diagnostic uncertainty they can create. “These tests pick up targets that we haven’t been able to detect in the past,” Dr. Patel says. “That sounds like it should be an incontrovertibly good thing, but it’s not necessarily always so—when you detect something that you couldn’t detect before, it can be hard to know what to do with that result.”

The FilmArray GI panel can detect 22 pathogens in stool.

“Stool contains a large number of different organisms, some of which can be pathogens but most of which are beneficial for us,” she says. “There can also be a transient presence of pathogens or organisms that could be pathogens in one person and not in another, depending on what’s going on with them.” This situation wouldn’t necessarily warrant treatment, she says.

Dr. Patel offers as a hypothetical the case of a patient who tests positive for *C. difficile*, and whose stool also tests positive for enteroaggregative E. coli.

“That’s an organism we’ve not had a routine assay for in clinical microbiology,” she says. “So we have to look at the literature to try to figure out what the significance of this finding might be. Now we have a situation where the clinician knows how to handle *C. diff.*-associated diarrhea, but they have to deal with a report telling them that the patient also has enteroaggregative E. coli.

We’ve added confusion because we don’t necessarily know what the role of this E. coli might be in this patient. The clinician has the option of not changing the patient’s management based on this result, either because they don’t know what it means or they don’t think it should change their patient’s management. Or they may decide they need to treat the enteroaggregative E. coli, potentially using an antibiotic which, when given to the patient, may worsen their *C. diff.*-associated disease. Or they may decide to perform further testing. Overall, this situation shows that GI panels may add confusion to clinical care,” Dr. Patel says. The hypothetical patient case could unfold with repeat tests to see whether the enteroaggregative E. coli has resolved.

“This is because sometimes results of GI panel testing provide too much information and this is not a good thing, at

least until we determine what actions should be taken or not taken based on the results."

To help clinicians navigate this potential minefield, Mayo Clinic has developed a testing algorithm for infectious causes of diarrhea that recommends the GI panel only for cases of community-acquired diarrhea that have persisted for more than a week. For patients with health-care–associated diarrhea, Mayo recommends physicians order a *C. difficile* toxin PCR test alone. Mayo Clinic also provides interpretive comments in its laboratory report when certain targets are detected by the GI panel.

Kimberle Chapin, MD, director of microbiology and infectious diseases molecular diagnostics at Brown University-affiliated Lifespan Academic Medical Centers in Rhode Island, agrees in part with points made in the AMP session. "Multiplex technology has provided a solution to issues the lab has been screaming for help with—time-consuming, costly, and nonsensitive techniques for diseases such as viral respiratory pathogens and detection of stool pathogens. Now that we have syndromic panels, a few more issues have emerged that were not fully anticipated," she says.

"Does this mean we should not use the technology? No," she insists. "But it does mean we might have to find the best fit and be willing to adjust as we learn more after implementation."

Right now, all labs are using a workaround solution to address their own issues with current multiplex systems as they relate to lab or patient costs or both, interpretation, volumes, and provider ordering, Dr. Chapin says. "Respiratory panels were the first multiplex panels to be cleared, and we have gained immense knowledge from our experiences."

For some health care organizations, use of a rapid respiratory panel as a first-line test is not feasible because of the high volume of testing. Dr. Chapin says Lifespan expects to see about 5,000 acute respiratory cases during the flu season. "That volume cannot be handled by the only truly rapid respiratory panel where the provider could have clinically impactful results, the BioFire instrument, because a single instrument can perform only one test at a time, and I would need several instruments. That assay is not going to work for every patient, unfortunately," says Dr. Chapin, who spoke at an AMP corporate workshop titled "What's Missing in Molecular Diagnostics," sponsored by GeneWeave, which was recently acquired by Roche. "While other truly rapid RVP diagnostics—two hours or less—are pending, the technology is lacking for another, faster, higher-volume RVP that could be clinically helpful in our setting."

To address some of what laboratories face, Dr. Chapin says she wants to see the capability for flexibility, if necessary, from a multiplex panel from one specimen, from the same vendor. "One test panel performed a single time based on provider requests, but with the ability to pull additional results if needed." That might be to reflex from a narrow panel to a broader panel, to increase the number of pathogens based on the severity or immune status of the patient or if a patient is admitted and infection control needs to know the true pathogen for isolation or cohorting, she says. "I can't do an RVP assay on every single respiratory disease patient currently as test systems are set up, basically because of the cost to the patient in the outpatient setting and the time it takes to report the assay to be clinically useful. So what do we do? And what do most places do?

"We come up with a workaround. A rapid influenza test, and then potentially a reflex to an RVP if the patient gets admitted and the flu was negative. And it would be really nice if a company or our information systems could do both of these things together so we would not have to run a second assay." Maybe Luminex—a single vendor with Magpix and Aries—will be an answer, she says. "Maybe there's something else out there that will be the answer. But, essentially, I have gone to two different vendors to accomplish our clinical needs, and this makes things a little bit difficult for our lab as well as confusing to providers."

Dr. Chapin argues that more outcomes data should be collected at the time the trials are conducted to secure FDA approval or clearance. That would enable a more informed comparison of the clinical and financial costs and the benefits of new molecular diagnostics.

“There’s a major disconnect, now, between trying to get the higher-quality test for someone but not being clear on what benefits some of the results will actually provide, either in the care of the patient or for the overall health care system. For outpatients, where panels might be used because they are more sensitive and less expensive for the lab, it ends up being really costly for the patient if they are paying out of pocket for lab testing,” she says. “Providers will want to know and be able to tell patients that there is a real benefit to the test.”

But, Dr. Chapin notes, device manufacturers lack the “deep pockets” of pharmaceutical companies. The vast majority of expenses associated with the outcome data-collection process involve patient enrollment, the informed-consent process, and follow-up, she says, where a lot of the outcome data would need to be collected prospectively at the time of the trial. “That’s the unfortunate component, and that’s where the diagnostic companies are not going to be able to really do this on their own,” Dr. Chapin says. “Unique partnering of diagnostics with NIH or other foundations, and/or changes in how trials are performed to gather this information, has started to address this need on outcomes from the get-go.”

“As we learn more about the pathogenesis of syndromic disease and pathogens that we are identifying, then we are going to find value, absolutely, in multiplex methods,” she adds. “The diagnostics are ahead of the clinical picture.”
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