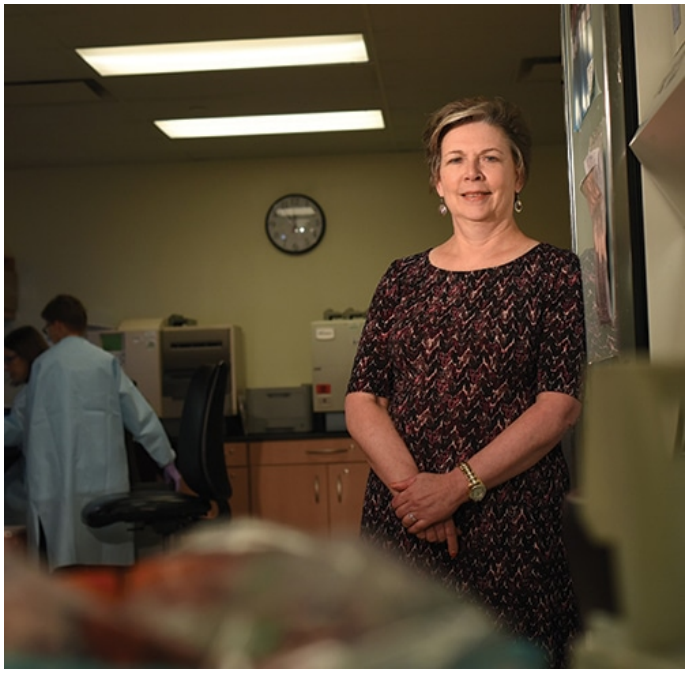
Rapid PCR rules as labs ready flu arsenal

Anne Paxton

December 2018—With the memory of the 2017–2018 “high-severity” influenza season fresh in mind—49 million cases, 960,000 hospitalizations, a marginally effective vaccine, 79,000 deaths—clinical laboratories have been bracing for the customary annual surge in emergency room, outpatient clinic, and physician office influenza test orders. Although flu admissions have been rising somewhat, it is too soon to know how the season will play out, but laboratories are hoping for a season closer to average.

Avoiding a repeat of last year’s travails—lengthy turnaround times, supply shortages, and the need to triage patients for testing—is a must, many laboratory directors say. “We had difficulty keeping up with last year’s demand. It was extremely time-consuming,” says Mary Kay O’Connor, national laboratory director at Summit Health Management, the management arm of the Summit Medical Group, an 800-provider practice on the East Coast.



Mary Kay O’Connor of Summit Health Management. The core laboratory of Summit Medical Group performed the influenza testing in the 2017–2018 season. Now rapid PCR instruments are being put into all of the locations that do strep and influenza testing. [Photo:Jennifer Altman]

It was SMG’s core laboratory that performed the group’s influenza testing last season: about 285 tests a day during the height of the season. “At that time we did not utilize point of care because we did not believe the antigen tests were accurate enough,” O’Connor explains.

In midseason, O’Connor and colleagues realized that SMG would need to switch instruments due to high volume. “We had already been evaluating the Roche Diagnostics Cobas Liat and we could get reagents from Roche, so we switched to the Liat. But even with 10 analyzers running 16 to 18 hours a day straight, we still had difficulty keeping up with an efficient turnaround time.”

Now, SMG is poised for a more sweeping change. “We are putting Roche Diagnostics rapid PCR Liats in all of the

testing locations that do strep and influenza testing, so they will do the molecular test on site."

SMG is just one of the large physician groups that have made significant new instrument purchases, particularly for CLIA-waived rapid PCR tests, and have no plans to return to rapid antigen testing.

Training at SMG's pediatric offices, which are slated to get eight Liats each, and urgent care centers started Dec. 4. "Once we have rolled out those sites, we will go out into the other offices. We'll be installing about 100 Liats in multiple locations for internal medicine, family medicine, and several other service areas," O'Connor says.

One problem she expects to avoid with the Liats is running out of reagents. "We have sequestered all of our reagents with our supplier for the entire year, and we have one lot number. Last year, we ran 15,243 flu tests, so we've sequestered about 16,000 tests for the coming year."

The turnaround time of rapid PCR is a major selling point. "Obviously we were doing it in the core lab in less than a day, but it's better if it's done at point of care because the doctor can give a prescription or not give a prescription."

As SMG integrates new physician groups that perform in-office antigen testing, they will be set up with Liats for immediate results. "This will be particularly helpful for pediatric practices, where they have a high volume of patients with upper respiratory and pharyngitis symptoms," O'Connor says. Since the Liat testing has been linked to the laboratory information system and electronic health record via Roche's IT 1000, the Liats will ease a lot of the offices' paperwork burden, she adds.

Five-hospital Norton Healthcare in Louisville, Ky., is in the midst of an even larger change at its 32 primary care locations, 14 immediate care centers, and 21 pediatric offices, says Joshua Honaker, MD, MBA, chief medical administrative officer of Norton Medical Group. Until this season, the system had been using traditional rapid antigen tests for respiratory syncytial virus and flu as well as strep, with follow-up culture if negative. After comparisons of rapid PCR instruments, testing at pilot sites, and correlation studies, Norton Medical Group purchased 250 Liats. "Now we have rolled out Liats across the board in the last month, and we're in the process of educating and moving our team and changing our culture to using the rapid PCR."

Easing the shift is that the hospitals within Norton Healthcare have been doing the PCR testing for more than a year. "So they gave us really good guidance about heading in that direction as well," Dr. Honaker says. The Food and Drug Administration's recent reclassification of traditional rapid flu tests, mandating that they address poor sensitivity by meeting higher standards, was another factor behind Norton Medical Group's decision to move to rapid PCR.

During the transition to rapid PCR, the rapid antigen tests are still playing a part. "We have old tests still in inventory so we will use them as needed if capacity is an issue with the rapid PCR this first flu season," Dr. Honaker says. But this year, "We also wanted to make sure we had residual inventory for peak times. If an immediate care center that can see up to 40 patients an hour found they all came in with flu and we only had 10 instruments there to run it, they can go back and use the antigen test to help. But that is only for this year." They will not buy more rapid antigen tests next year, he says.

Dr. Honaker

With the cost of rapid flu PCR about three to four times as much as the antigen test, and the rapid strep test about three times as much as its antigen counterpart, a move to rapid PCR does require careful analysis of

reimbursement by commercial insurers and government payers, Dr. Honaker notes. But he thinks payers are recognizing the value of rapid PCR because its accuracy will reduce antibiotic prescribing. “Whether it’s a vaccine or lab test or new technology, anything that comes out is always higher cost to begin with, but I believe the price will come down as our health care systems, providers, and labs see the value and utility in it.”

Clinicians’ response has been favorable in part because of the increased clarity and confidence they have from the results they are providing. “They love to be able to look at their patients and say definitively, ‘you have this’ or ‘you don’t have it.’” Another plus: Sample volume is not an issue, as the Liat will not run a test if there is not enough sample present. “Sometimes with the antibody tests, you will question whether you have enough specimen or it was not a good swab,” Dr. Honaker says.

The rapid PCR turnaround time, about twice as long as the rapid antigen test TAT, means patients need to wait on site a little longer for a result. “But we’ll have a better answer. It ties up the room longer, but I can tell you as a clinician that all the time you spent talking about what may be happening, prepping a culture for a strep that was negative, all that time saved on the back end balances it out. So the wait is worth it.”

From a global standpoint, the business of flu testing occupies a tiny space and a flu season is a relatively insignificant event. Diagnostics is a roughly $65 billion industry; all infectious disease testing represents less than $10 billion of that, and flu testing would be a subcomponent of that, says Steve Beuchaw, executive director of Morgan Stanley and a Wall Street health care analyst for 14 years, the last five focusing almost exclusively on diagnostics.

Beuchaw would place influenza testing in the top 10 categories of respiratory and infectious disease testing that people care about, and for some companies flu is “absolutely huge,” he says. “There are companies out there that could maybe have a 10 percent growth variation from one year to the next as a function of whether we had an acute flu season, as we did last year, or a particularly mild flu season, which we hope to have this year just for our own personal well-being.” But “for a lot of diagnostics companies, flu is really not a focus at all.”

In infectious disease diagnostics, the level of competitive intensity is high, and influenza testing too is a highly competitive space, Beuchaw says. “It’s because the core detection methods—flow and PCR—are largely commodities now. In the case of Cepheid, they have a really clever bit of engineering around the PCR detector to make it exceptionally user friendly.” He believes that is why the company has a large customer base and why the research company Danaher recently opted to acquire Cepheid.

The important factor on the business side of infectious disease, he says, “is more about who has a good menu and whose test is user friendly,” which still requires engineering development and shepherding a product through regulatory agencies. “Getting each one of these tests approved costs tens of millions in the U.S. just for the FDA process.” In fact, he notes, Cepheid terminated development of an HPV test because it estimated the FDA process would cost $60 million and the company didn’t believe it would have a sufficient return on investment.

The higher quality of molecular testing over antigen testing, Beuchaw notes, has been known for a long time. Lesser known is that there are many more test alternatives out there. “To some extent influenza is single disease testing and to some extent it’s panel testing, because you might use a product that looks at a lot of different disease strains at one time.”

One diagnostics company that he follows, Qiagen, has estimated that the infectious disease testing through molecular panels is a billion-dollar business on its own, and reimbursement is pretty favorable—“a lot better than what you have seen for single target tests,” he says. “So you have a number of companies that have entered the space. The technology has made these very efficient, comprehensive panels more attractive” as a business proposition.

For purposes of business strategy, there is no real difference between an intense flu season and a more moderate season, Beuchaw says. “Companies are going to expect there will be tough flu seasons and easy flu seasons, and when they are going through product development and commercialization efforts, they take at least a five-year

and probably a 10- or 20-year view, depending on what they want to accomplish with the technology."

Worldwide, he says, infectious disease is a priority and there is an awareness of the need for high-quality detection of a number of different types of infectious disease, though flu is probably not at the top of the list because for most people it is not lethal. Test technology for infectious disease is an important focus in emerging markets, particularly in developing regions, Beuchaw notes.

Compared with drugs, which are easy to transport and require little space, "Detection technologies are a little trickier because they're bulkier and using them is more complicated than giving someone a pill." Nevertheless, he says, companies that are developing diagnostic hardware that is more portable, more user friendly (through battery power, for example), and more useful in remote areas are more likely to be competitive in worldwide markets.

Dr. Samuel

The core microbiology laboratory at Henry Ford Health System in Detroit is a busy one. It receives microbiology samples 24/7 from the system's six hospitals and 30 associated medical centers. But two years ago, the laboratory decided to decentralize influenza testing to nine of the system's stat labs, says Linoj Samuel, PhD, division head of clinical microbiology. "We have EDs all over southeast Michigan and all these urgent care centers, and they need timely results for things like influenza."

During the decentralization process, the rapid antigen tests at almost all these locations were replaced with 20 to 25 Roche rapid PCR Liat instruments, and the laboratory knew this switch would require careful groundwork. "We put a lot of work into educating clinicians about the new technology. We made sure to convey to the emergency department physicians the advantages of having the new technology operating closer to them. And that it was on them, first, to order testing only in patients where it was required because the molecular test was more expensive, and, second, to only order the test in patients for whom we knew it would make a difference in management."

"Before we even went live with the new rapid PCR installation," Dr. Samuel says, "the ER clinicians told the laboratory the Liats would have a dramatic impact in terms of better antiviral usage, better antibiotic usage, and potentially reduced admissions." Dr. Samuel's team reported at the American Society for Microbiology Microbe meeting, after extensive data collection, that between the 2015–2016 season (running the antigen test) and 2016–2017 season (running the rapid PCR test), there were 40 percent fewer tests due to the impact of clinician education, but a 25 percent increase in the number of flu cases detected.

"We also had data showing that patients who were tested with PCR and shown to be positive were actually less likely to be admitted using these molecular tests." A separate study the team presented at the Infectious Diseases Society of America IDWeek showed that in the ED setting, "We reduced antibiotic usage from about 14 percent in the base group of patients getting antigen testing to eight percent in patients tested by PCR. We also reduced our 30-day revisit rate for patients with respiratory symptoms from 10 percent to four percent.

"So this is one of the few cases where you predict what will happen with new technology and the prediction actually works out in the manner you expected," Dr. Samuel says.

One of the early challenges of transitioning from rapid antigen tests to molecular testing, his laboratory discovered, was that there are more bottlenecks because the instruments run only one test at a time. "With the Liats, the limiting factor is the number of machines at each location. So early on, we had to increase the number of machines," and that drove up the laboratory's capital expenditures.

Another challenge came from early instrument problems that took a little time for the company to fix. This required an adjustment by the clinicians, who were not used to relying on a machine. “Unlike with the influenza antigen, which was a manual test, with PCR when the machine went down your testing was not happening. So we had a lot of frustrated clinicians at the time. But we worked through it and the instrumentation issues were solved. The second season we were live with the machines and we did not see that problem at all.”

In a heavy flu season like 2017–2018, the benefit of using stat PCR was seen at Henry Ford: It freed up isolation rooms faster than when traditional PCR was performed once or twice a day. “The availability of a stat influenza PCR 24/7 that can rule out influenza definitely allows you to take patients out of isolation and free up the rooms,” Dr. Samuel says.

“Over time, in addition to that, we have shown that we have reduced the length of stay in patients by bringing in the stat PCR tests available 24/7. At our main campus, we reduced length of stay by one day of incubation. If you factor that in, at a cost of $750 per room per day, that adds up to a lot of money, and it goes quite a way toward compensating the cost of bringing in this testing.”
Rapid PCR flu testing doesn’t offer any improvement in turnaround time compared with rapid antigen. “In some cases, it might be a little slower, especially if you have a high volume of samples and only so many instruments to run them on. But I think those delays are offset by having a much more reliable result.”

As of mid-November, “sporadic” was the adjective the microbiology laboratory and New York State public health officials have been using to label this flu season, says William Jerome, MLT, point-of-care coordinator for St. Peter’s Health Partners in Albany, a large multihospital system with many owned medical practices in upstate New York.

Jerome is happy with the performance of the benchtop Quidel Sofia fluorescent immunoassay instruments that St. Peter’s 60 physician offices have been operating since March 2017. In some cases the offices have multiple instruments running the Influenza A+B assay.

Jerome

In October 2017, the practice’s 60 physician office labs performed 130 flu tests with 10.7 percent positive. In October 2018, “we did 350 flu tests at the 60 sites and our percent positives were only 3.9 percent. It seems the doctors are testing a lot more than they should be, considering the percent positives so far we are seeing this year,” Jerome says. He speculates the increase is due to apprehension about a repeat of last year’s spike in influenza infections. As a benchmark, in all of New York for the week ending Nov. 10, there were seven patients who tested positive for influenza A and one for influenza B.

User error with the rapid antigen test is small, he says. The instrument is “almost foolproof,” and his laboratory has found that false-negatives are not an issue. The core laboratory at St. Peter’s Hospital uses the Cepheid GeneXpert Infinity System PCR assay for confirmation testing with a turnaround time of 24 hours. For strep testing, following testing on the Sofia, a second swab is sent to the microbiology lab for culture. However, the lab is considering discontinuing that practice because it rarely turns up a positive.

At Jacobi Medical Center in the Bronx, one of 11 New York City hospitals, the priority in the run-up to flu season has been readiness, says Stephen Apfelroth, MD, PhD, director of clinical laboratories and assistant professor, Department of Pathology, Albert Einstein College of Medicine. “So far this season is very slow, but we went to a lot of effort to get prepared after the big season we had last year.” Among the problems: not having capacity or money to do PCR testing on everybody. “In the beginning where we were triaging, only patients to be admitted

would be tested by PCR, and patients who weren't sick enough and were going to get sent home would be done by rapid antigen testing."

"But once we got comfortable with the PCR testing, doctors wanted the right answer on everybody." So this year the laboratory has already increased the capacity of its Cepheid GeneXpert from four modules to eight. "On a busy day in the ER, you can easily get 10 to 15 people coming in within an hour or two. With four modules it was a struggle. We did manage, but with eight modules it is a lot more comfortable."

Jacobi Medical Center's patients are particularly susceptible to flu. "We have more patients with comorbidities and a big proportion of our admitted patients are nursing home patients. The Bronx is one of the counties with the highest incidence of diabetes, and that also makes patients with the flu more likely to be hospitalized," Dr. Apfelroth says.

Dr. Apfelroth

Cepheid is also marketing its point-of-care PCR for influenza, but Jacobi Medical Center is not using it. "The volume is enough that they can send their samples to the main laboratory," he says. Antigen testing is still available but largely phased out. "You know everyone in the ED knows they want PCR. When we were doing rapid antigen, a positive on either test would lead the clinician to initiate antivirals, but they would also treat some of the negatives if they still had a strong suspicion of flu. Now they are satisfied with the predictive value of the negative with the PCR, so they are only treating the ones that come out positive."

In general, the budgets of health care systems for flu testing have to increase significantly because PCR costs more, Dr. Apfelroth says, but in terms of patient management and sometimes discharging patients who don't have the flu, "molecular testing definitely pays for itself."

Facing a flu season of unknown intensity, "We're in a better position than we have ever been," Dr. Samuel says of clinical laboratories. When he first started training 10 or 15 years ago, influenza culture performed by centralized facilities required seven days. Later, rapid culture made that a two-day process. "We then transitioned to core lab molecular testing, which was a much better test but still centralized. And now we've pushed this complex, highly sensitive test out to point of care." It's only a matter of time, he says, before CVS, Walgreens, and Walmart are offering these tests. "But in the past, when patients would be sent home and treated empirically, people were getting antibiotics they didn't need or not getting the Tamiflu they did need. Now, with these rapid tests, the patient can wait at the ED, get the appropriate drug, and then be sent home."

Anne Paxton is a writer and attorney in Seattle.