New contender speeds ID with susceptibility testing

Anne Paxton

May 2018—If a seismic shift were to happen in microbiology, the technology behind the Accelerate Pheno system and PhenoTest BC test kit, which won FDA approval last year as a rapid pathogen identification and antimicrobial susceptibility testing (AST) system for blood cultures, could well be the cause.

Like Secretariat, leaving the entire field of other racehorses 31 lengths behind to win the 1973 Belmont Stakes, Accelerate Pheno has won recognition for blazing speed. It handily outstrips the turnaround time of traditional ID and AST for microorganisms causing bloodstream infections. Providing both phenotypic minimal inhibitory concentration (MIC) and categorical AST results from positive blood cultures in seven to eight hours—versus the customary 48 hours—the system from Accelerate Diagnostics is changing how quickly clinicians can provide optimal therapy to patients with bacteremia and sepsis, microbiology laboratories report.

The BC kit simultaneously detects and identifies multiple microbial targets—about 92 percent of the most common bacteria and *Candida* species in a positive blood culture. Where it pulls ahead is with its unique ability to then immediately perform susceptibility testing on the organisms detected.

“From the moment a patient’s blood is collected to the time we can release an ID with susceptibilities—from vein to the electronic medical record—we can do this in about 24 hours instead of three or four days,” says Eric Rosenbaum, MD, MPH, assistant professor of pathology and medical director of clinical microbiology at the University of Arkansas for Medical Sciences. “That has never been possible before—nothing even close.”

Dr. Humphries

“It really is a paradigm shift in how we manage patients who have bacteria in the blood,” says Romney Humphries, PhD, D(ABMM), MT(ASCP), former section chief of clinical microbiology at UCLA Health System, now chief scientific officer at Accelerate Diagnostics. “The traditional approach is that those patients are ‘rounded on’ by a medical team based on data that comes out day by day. Now we’ll have data that’s coming out hour by hour. And we’ll be much more able to modify and manage treatment in a matter of hours.” Multiple sites are already using the Accelerate Pheno system, and “there are over 100 more that are looking at the system as we speak,” Dr. Humphries says.

Dr. Rosenbaum’s laboratory was one of the first to complete system verification studies, successfully design the interface of the Accelerate system with both the laboratory information system and the institution’s EMR, and fully integrate the system and test into patient care. Since becoming medical director in 2011, Dr. Rosenbaum has been on a quest to modernize his laboratory.

“We started off with a MALDI-TOF mass spectrometer, then a GeneXpert. When we began investigating rapid blood culture ID systems, the Accelerate system had just arrived on the market. It challenged our initial plan to evaluate the well-established and successful FilmArray and Verigene systems. The added ability of the Accelerate system to produce rapid susceptibilities was exciting,” he says, “but it was also very new technology.”

In blood culture diagnostics, FilmArray and Verigene employ molecular methods like PCR or nucleic acid testing for finite pathogen identification, while Accelerate, instead of amplifying DNA, uses fluorescence in situ hybridization probes that also target a finite number of bacteria and yeasts. “All these instruments aim to target the most common organisms that cause sepsis and those are the pathogens to which they direct probes, whether they be primers or, in the case of Accelerate, FISH targets,” Dr. Rosenbaum says. Accelerate is able to detect a panel of 16 pathogens: 14 bacteria and two *Candida* species.

A 2017 study of the accuracy and workflow of ID/AST using Accelerate Pheno compared its performance with routine standard of care. The authors found, for identification, overall sensitivity of 95.6 percent and specificity of 99.5 percent. For AST, overall essential agreement was 95.1 percent and categorical agreement was 95.5 percent compared with routine methods. There was one very major error and three major errors. Time to identification using Accelerate was decreased by 23.47 hours, and time to AST was reduced by 41.86 hours, with reduction in hands-on time of 25.5 minutes per culture (Charnot-Katsikas A, et al. *J Clin Microbiol.* 2018;56[1]:e01166-17).

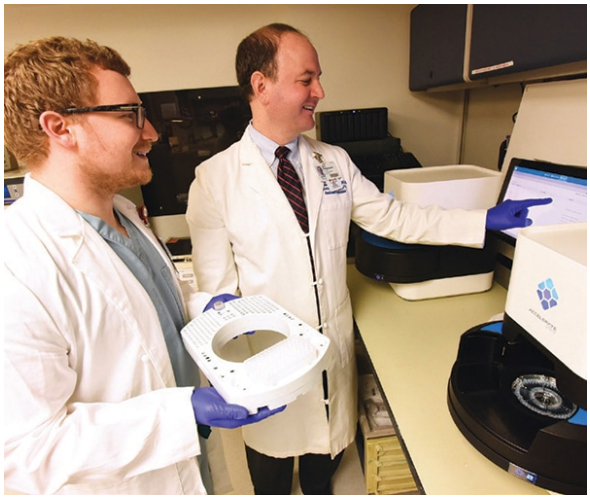
Clinical trials of the Accelerate Pheno showed that if a patient’s positive blood culture is monomicrobial—i.e. has only one target pathogen—the instrument has a 99.6 percent positive predictive value when evaluated in combination with the Gram stain, Dr. Rosenbaum says. However, use of a universal probe along with FISH gives Accelerate the additional ability to indicate the likely presence of off-panel organisms. “So if a blood culture grows something off panel, the Accelerate Pheno should generally be able to tell the user, ‘There’s something in this culture; I just can’t identify it.’ This is the first instrument to offer this valuable feature.”

A logistical advantage of the Accelerate approach is that all reactions and analyses are automated, and microbiology bench experience is not needed to run the test 24 hours a day. It is simple to operate and takes about one minute to set up, Dr. Rosenbaum says. “You aliquot half a cc of the positive blood culture into a sample vial, snap the vial into the cartridge, and insert it into the machine. The Pheno system also frees technologist time that would have been spent processing blood culture identifications and susceptibilities from agar plates.” He estimates that the Accelerate saves at least 30 minutes per specimen.

His laboratory has not stopped using the Gram stain, which is run simultaneously with the Accelerate Pheno. The manufacturer says results are intended to be interpreted in conjunction with Gram stain results. “Once a blood culture bottle goes positive, in about 15 minutes we can say, for example, ‘Gram-positive cocci in clusters’ or ‘Gram-negative bacilli.’ These results are released into the medical record and can begin to direct treatment. Then, to the surprise of our clinicians, within hours they have ID and susceptibility results with MICs.” For many organisms, “we are able to de-escalate antimicrobial therapy after just 24 hours.”

The Accelerate Pheno system has freshly emerged from a favorable multicenter evaluation, with the study authors, in an April 2018 article, describing it as unique and a “first of its kind diagnostic system” (Pancholi P, et al. *J Clin Microbiol.* 2018;56[4]:e01329-17). Clinical impact studies have not yet been completed, but another new study looks retrospectively at patients with Gram-positive bloodstream infections. The study reports on the system’s performance in Monte Carlo simulations, finding that, “coupled with stewardship personnel (either 24/7 or Monday to Friday)” the new approach “would have allowed unnecessary therapy to be stopped and active/targeted therapy to be started ≥24 hours sooner in >50 percent of patients” (Sofjan AK, et al. *Ann Pharmacother.* Epub ahead of print March 20, 2018. doi:10.1177/1060028018765486).

Dr. Rosenbaum points to striking case-based evidence that his institution’s clinical use of the system is changing treatment of sepsis for the better. The recent case of a 22-year-old kidney transplant patient presenting with fever, chills, and rigor is illustrative, he says. Clinicians suspected sepsis of unknown etiology, so they prescribed piperacillin/tazobactam (Zosyn) plus vancomycin. “With use of the system, the clinical team knew within 24 hours that the blood cultures collected on presentation were growing a pan-susceptible *E. coli*, so the team de-escalated to ceftriaxone monotherapy immediately.”



Dr. Eric Rosenbaum (right) and pathology resident Jonathon Gralewski, DO, in the University of Arkansas for Medical Sciences clinical microbiology lab with the Accelerate Pheno. All reactions and analyses are automated, Dr. Rosenbaum says, and bench experience is not needed to run the test 24 hours per day. *Photo credit: John Paul Jones, UAMS*

This patient was also spared the cumulative risk of acute kidney injury caused by an extra two to three days of broad-spectrum Zosyn and vancomycin—the time it would have taken conventional methods to produce antibiotic susceptibility results. “Nephrotoxity is one of the greatest downsides of using antibiotics like these,” which can significantly increase the odds of acute renal injury, Dr. Rosenbaum notes. Complications of AKI can prolong hospital stays from days to a week or more, even in patients with no preexisting renal compromise.

Dr. Rosenbaum also points to a 64-year-old patient with myeloma and febrile neutropenia who presented to the emergency department, triggering use of a broad-spectrum antimicrobial. “The clinical team started the patient on meropenem, concerned about an infection resistant to something like cefepime.” His laboratory was able to run the sample on the Accelerate Pheno and find out in 24 hours that the organism was, again, a pan-susceptible *E. coli*. “So the patient could be switched quickly from meropenem to narrower-spectrum cefepime, which is a win for antibiotic stewardship,” Dr. Rosenbaum says.

Getting such a significant head start on appropriate treatment has to be factored in when considering the cost of the test, Dr. Rosenbaum says. “There is a price difference. But the resources we spend on Pheno are captured back exponentially by the prompt clinical action this instrument enables. For example, switching from daptomycin—used against enterococci—to ampicillin is great not only for antibiotic stewardship but also for fiscal accountability. A patient may not need to be on a drug that is 10 times the cost, and we are now able to know this information days earlier.”

Before moving Accelerate Pheno to clinical use, Dr. Rosenbaum says, his laboratory put it through rigorous challenges, some exceeding physiologic conditions required for verification studies. Equally important was surveying how clinicians would react to the dramatic change of receiving ID and AST results finalized within hours. “Before we signed the contract, I gathered clinicians together throughout our hospital who frequently order blood cultures. We talked about what they would do with a call from the laboratory in the middle of the night with an Accelerate Pheno result. It’s very easy to stay the course, but switching the patient to a more appropriate antibiotic as fast as possible is crucial to making the Pheno a success.” Because this is such a major change, there is a learning curve, he notes. The lab must recruit help from the antibiotic stewardship and infectious disease teams to move things along.

With microbiology data, it's easy for clinical staff from a resident on up to understand when a patient is on the wrong antibiotic for a particular bacterium, says Dr. Humphries, who led the clinical study of Accelerate Pheno at UCLA, one of 13 trial sites. "Conversely, when a patient is being treated unnecessarily broadly, we all appreciate that overtreatment is bad too. But the same urgency isn't typically placed on de-escalating treatment. So the most effective use of our Accelerate Pheno system in conjunction with the antibiotic stewardship team is to help physicians understand that and help with the de-escalation."

Molecular testing has improved AST, but it has limitations. "Bacteria are very creative beings," she notes. "Usually their resistance, especially for Gram-negative blood cultures, is very complex. So it's very difficult to do a PCR for a single gene and predict antibiotic susceptibility or resistance. Even if we have the entire genome, today we don't know enough about it to be able to look at all the genes and say, 'That bacteria is susceptible to the antibiotic I want to use.'" Since genotypic approaches to AST can't fully predict susceptibility or resistance, if a target is detected, the result must report resistance, Dr. Humphries explained in a presentation at ASM Microbe 2016.

In diagnostics, there's been a steady progression in the movement toward more rapid identification of bacteria and susceptibility testing, she says. "The big, big difference with our system, compared to others on the market or that are standard of care, is the very, very fast susceptibility testing result, which tells physicians what drug to treat the patient with."

"Even if the bacteria have mutated and there is brand-new resistance, it doesn't matter; the system will still detect it. And that's really the Holy Grail of doing fast susceptibility testing."

When Beth Prouse, MS, MT(ASCP), clinical microbiologist at Peninsula Regional Medical Center, Salisbury, Md., a freestanding community hospital, first heard about Accelerate Pheno in summer 2016, her laboratory was immersed in building its new Epic Beaker LIS. But soon after the FDA approval of Accelerate, she went for training on the instrument and began the verification process. "We were already using rapid technology for identification of bloodstream infections for a positive blood culture, using the Verigene. We wanted to see what impact getting susceptibility results in such a rapid time frame would have on our patient care and antimicrobial stewardship."

The morphokinetic analysis that underpins Accelerate's susceptibility testing involves the instrument taking pictures of the isolate growing in a certain concentration of an antibiotic, Prouse says. "Then the system looks at how the organism either grows or dies off, and compares those photographs to a library." Dr. Rosenbaum describes this morphokinetic cellular analysis as "an ingenious merger of computer science with medicine.

"About 148 billion data points are analyzed per run," he says, "generating growth patterns that are compared to an extensive database of known growth behavior correlated to broth microdilution methods in order to produce MICs."

At Peninsula Regional Medical Center, with susceptibility results available to physicians 48 hours sooner than when they were performed directly on the blood culture bottle, brisker communication between the clinical pharmacists and clinicians is one of the major impacts so far. Says Prouse: "We page our clinical pharmacists several times during the process, letting them know when the patient sample is going on the Accelerate Pheno system, when the ID is done, and when susceptibilities are completed. At that point, they communicate with the clinicians, and antibiotics can be de-escalated. With Verigene, we would let the clinical pharmacists know if there was a resistance marker present, but we didn't contact them if it wasn't," so that communication was primarily related to escalation of antibiotics.

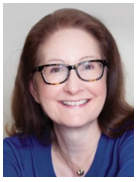
In the emergency department, Peninsula Regional has always had a fairly aggressive approach to identifying patients with sepsis early, Prouse says. "With the introduction of the Verigene in 2013, we've tried to provide our clinicians with as much information as we can, as soon as possible. Our administration has been very supportive of finding the best technology to do that."

At a list price of about $250 per test, the PhenoTest BC kit is probably one of the more expensive technologies on the market right now, she notes. "But there's really not anything else like it on the market. I think it's a wonderful

technology—that's why we were an early adopter. We're not an academic center, we're not a teaching hospital. We're a community hospital. But I believe this technology can be done in a lab that has good medical lab scientists working in it. It's not something you have to have a lot of specialized training to perform. But it's definitely a team effort to make sure patients are getting better care based on the results."
Beginning in May, Prouse says, Peninsula plans to conduct a formal six-month study to confirm the clinical outcomes relating to length of stay, mortality, and antibiotic use.

Margie Morgan, PhD, professor of pathology and laboratory medicine and director of microbiology at Cedars-Sinai Health System in Los Angeles, first heard of Accelerate when she was asked to attend a focus group discussion of a new type of technology described as "divergent." Soon after, Cedars-Sinai became another site for the clinical trial.

Using the system from Accelerate, she says, "we can take an aliquot from the positive blood culture, inoculate the Accelerate Pheno, and within one hour and 20 minutes, be able to alert the clinician to what organism has been identified, and about five and a half to six hours later, report the final susceptibility."


Dr. Morgan

Before using Accelerate Pheno, Dr. Morgan's microbiology lab was using molecular resistance markers to rapidly determine antibiotic resistance information to aid with antimicrobial stewardship. "One of the issues with resistance marker determination was that some clinicians didn't fully understand what was being reported to them. The stewardship pharmacist would discuss the resistance marker findings, but the physician would be reluctant to trust the findings and want to wait for the susceptibility. This led to a significant percentage of unsuccessful interventions."

With use of the Accelerate Pheno system, she says, "the clinician has the final antibiotic MIC results, so that discussion goes more smoothly." The pharmacist places a call to the clinician, relays the identification and antibiotic susceptibility of the pathogen, and discusses the appropriate de-escalation or escalation of therapy. The clinician almost always agrees to make the antimicrobial change.

Cedars-Sinai closely monitors its stewardship efforts, collecting data on interventions and whether physicians make the change suggested to them. "We were averaging 88 percent successful interventions when using resistance marker testing for Gram-negative rods. Now that we've switched to Accelerate, we're at 100 percent acceptance," Dr. Morgan says.

Cedars-Sinai is a large tertiary care multispecialty medical center that cares for large numbers of elderly, transplant, and cancer patients. "With such a complicated patient population, we have found the rapid susceptibility information generated by the Accelerate Pheno to be invaluable," she says. "I think any hospital of moderate size that treats sepsis could make use of Accelerate's system, and results are made even more meaningful with an active stewardship program in place."

Cost is an issue, she admits. "It is more expensive than the resistant marker testing and susceptibility testing method that was used previously." She and colleagues worked with the stewardship committee to help justify the increase in laboratory cost by demonstrating how the information would be used to improve antibiotic use and patient care.

There are a few potential drawbacks, one of which is the limited list of pathogens reported by the BC kit. The system was developed to capture the most common organisms isolated from patient blood cultures. “We do isolate unusual organisms from patient blood cultures that are not included in the Accelerate panel on occasion, so you have to be aware that you will have a small percentage the system will not identify or provide a susceptibility.

“In addition, some have commented that there is a good deal of biohazardous waste generated due to the size of the testing cartridge. But when you add all the waste of plates and susceptibility testing panel materials you’re not using versus the cartridge, it’s possibly somewhat equal.”

When University Health Care System in Augusta, Ga. was considering the Accelerate Pheno, it was before the FDA approval was issued, says Christa Pardue, MBA, MT(AMT), director of laboratory services, and the company was offering a verification program to allow labs to run the test—“not clinically, but to sort of let you kick the tires for a while before the FDA clearance came out. And clearly, with the numbers we had seen and discussions we had had, our laboratory utilization committee said, ‘Yes, see if we can prove that Accelerate will do what they say it can.’”

Pardue

The microbiology lab had the Accelerate Pheno running in parallel with its installed instruments from September 2016 to March 2017 with notable results. “As soon as we went live the first week, we saw several cases where it had a dramatic impact on patient outcomes. It had a very strong correlation with our current technology, which is the gold standard in microbiology: 99 percent sensitivity and 98.7 percent specificity. And our categorical and essential agreements were great with our phenotypic MIC. So the biggest impact was that we had the same quality results but we were getting it 42 hours faster. That was huge to us.”

Later, when the laboratory obtained more clinical information, “we were also able to retrospectively look back at mortality rates. We had been seeing a decline in our mortality rates on blood-culture-positive sepsis patients anyway, but these were even steeper declines,” Pardue says. “It was dramatic to the point that we doubted it for a while, until we revalidated all the data.”

Ioana Chirca, MD, infectious diseases consultant and head of the antimicrobial stewardship program at University Hospital, presented clinical data from her institution at the Society of Critical Care Medicine’s 47th Critical Care Congress in February. From 2016 to 2017, after implementation of Accelerate Pheno, the rate of multidrug-resistant-organism infections in the ICU decreased 12 percent for methicillin-resistant *Staphylococcus aureus* infections and 10.8 percent for vancomycin-resistant *Enterococci* infection, Dr. Chirca reported.

In inpatient settings, rates of MRSA infection dropped from 50 percent and 49 percent in 2014 and 2015, to 41 percent in 2016 and 2017. VRE infection rates declined from 7.50 percent, 6.20 percent, and 6.50 percent in 2014, 2015, and 2016, respectively, followed by a 4.20 percent reduction in 2017. The data also confirmed a reduction in mortality rates of blood-culture-positive sepsis, from 14 percent in February 2017 to four percent in September 2017.

Pardue stresses that the advanced technology is only part of the reason her institution has benefited. “No matter how fast I can get that result, if nobody is looking at it, or knows it’s ready, or is doing anything with it, the test won’t improve outcomes.” So her laboratory developed a workflow to make the best use of the system.

“Under our current process, a positive blood culture is a critical value and we’d call physicians and let them know

we had a positive. We have a protocol now so that we wait one hour for that ID to come off the Accelerate Pheno system, we call if we have a positive blood culture, and we can also tell them what bacteria it is. And our doctors were shocked at first, but now they expect it. We let them know that in six hours we'll have full drug sensitivity in the medical record, and we copy our antibiotic stewardship pharmacist and ordering physician with that, so the pharmacist can call the ordering physician immediately and make recommended changes to therapy."

"We put patients on the right antibiotics for the bacteria that's causing the issues. That's had a huge impact on our outcomes," Pardue says. There hasn't been a major impact on length of stay, which they've also been monitoring. But "there are tons of journal articles out there that will tell you antibiotic exposure is directly related to mortality rate, and our outcomes study has shown that antibiotic exposure matches up with our reduced mortality rate."
The test also detects positive blood cultures that are polymicrobial. "If there are two different bacteria present, it will identify them unless there's an extreme difference in volume of one over the other. In that case, it will identify the one that is most prominent and will also tell you 'there's another one here; we just couldn't identify it.'"

The Accelerate Pheno system provides true phenotypic drug resistance results, Pardue notes. "This means that the physicians can use the results to de-escalate their antibiotic prescription, in contrast with genotypic drug resistance, which is DNA-based and provides likelihood of reaction to a particular drug but does not indicate the actual behavior of that bacteria, so physicians can escalate on a genotypic result but they will not de-escalate."

Although blood is the only specimen type cleared on the system (the company is looking at other specimen types and some are already approved in Europe), it's a very important one, Pardue says. "Every hospital deals with bloodstream infections, and that is one of the most critical infections to be working with."

Further studies of Accelerate are ongoing, including one going more deeply into clinical impact, Dr. Humphries says. "We are looking at doing a registry trial, which would be a quasi-experimental before-and-after implementation to look at clinical impact. Through its antibiotic resistance leadership group, the National Institutes of Health has also funded a randomized, controlled trial of the Accelerate Pheno system and test. So we're anxious to see what that shows."

Several companies are developing different technologies to produce rapid susceptibility testing, she notes. These include morphokinetic cellular analysis (Accelerate Diagnostics), pathogen-specific bioparticles (GeneWeave/Roche Diagnostics), laser light scattering (BacterioScan/Fisher Scientific), microbial weighing (LifeScale), and CLSI's rapid disk-diffusion method. "None of the commercial methods, as far as I know, are near clinical trial," she says.

Accelerate Diagnostics is also developing an assay for respiratory specimens, to test lower respiratory tract secretions for some patients with severe bacterial pneumonia. "So we're taking our technology that we developed for blood and harnessing it for this alternative infectious disease, so that it could have an impact on different populations." The goal is to initiate clinical trials this year, Dr. Humphries says. Accelerate's respiratory product is already CE marked in Europe.

As a pathologist, Dr. Rosenbaum appreciates hearing the excitement of clinicians who receive their blood culture AST results days sooner than they expect. "This is a big change for the lab—we are all familiar with calls asking for faster results. But to hear, 'The AST results are in the chart already; is this possible?' That's a call any lab would love to receive."
Strong evidence of the benefit to patients continues to emerge. Microbiology labs should take the lead in evaluating these new technologies, Dr. Rosenbaum says. "We do this on behalf of our patients who don't know to ask, 'Does this hospital have a rapid ID/AST system?'"—which, he says, can "save lives and reduce the budget."
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Anne Paxton is a writer and attorney in Seattle.