Procalcitonin passes automation hurdle

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December 2016—Matt Damon in *Interstellar*. Julia Roberts in *The Player*. Gene Hackman in *Young Frankenstein*. When movie stars appear in uncredited parts, it's usually for a cameo, not a leading role. But in diagnostics, an uncredited or off-label use of an assay might be its main use—possibly even its most clinically important use.

Procalcitonin should be viewed as a complementary test, not as a competitor to testing of lactate, Dr. Stefan Riedel says. "Both laboratory tests are important for the diagnosis and management of patients with symptoms suggestive of sepsis."

Such is the case with the sepsis biomarker procalcitonin (PCT). It's not a new biomarker; clinicians in Europe have ordered it for the past two decades and in the U.S. for at least seven years. PCT assays, developed by German biotechnology company Brahms and later licensed to Thermo Fisher Scientific, as well as the Vidas enzyme-linked fluorescent immunoassay developed by BioMérieux, have been approved by the Food and Drug Administration since 2008 to assess the mortality risk of patients with suspected sepsis.

Last March, the FDA expanded the clinical claims that PCT diagnostics manufacturers can make to include a comparison of PCT measures over four days after admission as a gauge of the patient's response to therapy. But PCT's official FDA-approved uses are still only one facet of the assay's actual role in addressing sepsis.

By many accounts, it is procalcitonin's unadvertised, unofficial applications, more than the approved uses, that have been drawing clinicians in many hospitals to order the assay in increasing numbers. Study after study shows that PCT—when results can be obtained speedily—is a highly effective biomarker for the differential diagnosis and for managing antibiotic treatment as well.

Given this background—even though automated PCT assays were already available in the U.S. on the Brahms Kryptor and BioMérieux Vidas platforms—the FDA's decision in June to approve an automated PCT Brahms assay

for Roche Diagnostics' Elecsys platform could significantly expand clinicians' use of PCT. Requiring no reagent preparation or hands-on testing, the new test could make quick results more widely available, increasing the practicality of PCT's off-label applications and reinforcing PCT's increasingly central role in ameliorating sepsis

"The literature coming from colleagues, especially those in Europe, makes it pretty clear that PCT has value in the management of sepsis," says Joshua A. Hayden, PhD, assistant director of the central laboratory at New York-Presbyterian Hospital–Cornell Campus. "And now, with the FDA approval of Roche's test, making this analyte available on a random-access platform which many labs are going to have already, there is a real opportunity to start offering this testing to clinicians without undue operational burdens on the laboratory."

In interviews with CAP TODAY, pathologists and clinicians who have extensive experience with PCT explain how it has become so pivotal a test and why this new choice in automated platforms could be a milestone for managing sepsis.

The FDA drew attention to sepsis diagnostics on June 23 when, based on findings of the U.S. Multicenter Procalcitonin Monitoring Sepsis Study (MOSES), a trial designed by Thermo Fisher Scientific, the agency authorized marketing of both Roche Diagnostics' and BioMérieux's Brahms PCT test, following a three-month review. (According to Roche and Thermo Fisher, the MOSES trial design leveraged the same patient samples to enable a "universal analysis" approach to demonstrate substantial equivalence to the FDA, resulting in the clearance of the Elecsys Brahms PCT assay.)

Changing regulatory requirements have also intensified hospitals' concern about best approaches to suspected sepsis. Beginning with October 2015 discharges, the Centers for Medicare and Medicaid Services adopted a Severe Sepsis and Septic Shock Management Bundle of measures for hospitals to follow for fiscal year 2017 payment determination, including measures hospitals must take within three hours of admission of a suspected sepsis case.

Dr. Newton

"We're all having to meet those standards or metrics," says James Newton, MD, infectious disease specialist and antibiotic stewardship director at Washington Regional Medical Center, Fayetteville, Ark. But every institution handles treatment somewhat differently. At his hospital, clinicians aim to administer a large fluid bolus of 30 mL/kg plus levofloxacin, vancomycin, and meropenem within the first hour, providing a broad spectrum of coverage. Then there's an effort to narrow the spectrum with laboratory tests. But traditional lactate is inadequate to help with the narrowing. "If you see someone with a lot of vague symptoms and check their lactate, it can be elevated for lots of reasons," Dr. Newton notes.

With a one-hour turnaround, this is where a PCT assay can begin to help with a diagnosis. Studies including a meta-analysis of 30 earlier trials have found that PCT can differentiate effectively between true sepsis and systemic inflammatory response syndrome of noninfectious origin (Wacker C, et al. *Lancet Infect Dis.* 2013;13[5]:426–435).

PCT levels can also help predict whether the patient is responding to antimicrobial therapy, Dr. Newton explains. With most bacterial infections, unlike viral or parasitic infections, a handful of proinflammatory cytokines are released and raise PCT levels. If an antibiotic is killing bacteria, the patient's PCT levels will fall in accordance with the protein's defined half-life. If PCT starts at 100 and is still at 80 in 24 hours (rather than 50), "that tells me it's time to make a change in the antibiotic regimen."

Washington Regional is evaluating whether switching from the Brahms/BioMérieux platform to the Elecsys Brahms PCT test will be helpful. “We’re doing a month-long test with the Roche product, running both platforms in parallel on specimens, and it’s up to the laboratory director to decide whether we want to switch. I’m looking for whether it will give me the same information we’re used to getting.” With turnaround time now at one hour, “if we get it down in half that time, it helps for sepsis, but for the everyday routine follow-up that we use PCT for, it’s not going to make a difference whether we get a rapid return or not. We’re just looking for the pattern.”

PCT levels have their quirks. “In the first two days of life, PCT is usually high, and people who have had severe trauma, including major surgery, have high levels, sometimes transiently,” Dr. Newton says. In some thyroid cancers, PCT is also high. There are sometimes conflicting data in the literature relating to other symptoms, Dr. Newton notes. PCT is reliable for diagnosing septic arthritis and meningitis, but it’s clearly not a good test for things like cystitis and cellulitis, which are common infections but don’t produce high PCT levels. “We don’t know why. It’s one of those things that comes with experience of using the test and treating patients,” he adds.

“We’re trying to use our database to look at all these patients and disease processes, and look for both positive and negative predictive value. With a particular symptom complex, is the negative predictive value of PCT high enough where I could honestly say I don’t need antibiotics for this patient? Is the PCT test accurate enough to identify a cystitis versus a pyelonephritis?”

Those questions remain to be answered, and Dr. Newton thinks it’s too early to say whether the Roche platform will expand the use of PCT. “It will allow people to get experience with the test, because if it’s part of an automated platform, then it will end up like tests for calcium or magnesium—things you’d like to see but don’t necessarily use every day. PCT is probably going to be thrown in that category at first.”

Bronson Methodist Hospital in Kalamazoo, Mich., now runs 800 to 900 PCT tests a month, says Jeff Pearson, MD, laboratory medical director at the 404-bed hospital. For about four years, the laboratory has been using the BioMérieux Vidas immunoassay system, but it recently switched its PCT testing to the Roche Elecsys platform, mainly due to the level of automation offered.

“The Vidas works quite well and the test runs in roughly the same amount of time, but it has to be loaded manually. Our Roche system has front-end automation, so you can have your tubes of blood barcoded, you run your PCT, results are interfaced to the LIS, and it’s more efficient.”

Dr. Pearson

As Dr. Pearson points out, the FDA cleared PCT for managing sepsis; the multicenter MOSES study looked at how critically ill patients progressed from severe sepsis and shock and evaluated their 28-day mortality risk. The study found that if a patient’s PCT level dropped by more than 80 percent, that added up to a twofold reduction in mortality risk after 28 days.

In real life, Dr. Pearson says, PCT has been used at Bronson for many years as a guide to diagnosing sepsis as well as prescribing antibiotic therapy for both sepsis and lower respiratory tract infection. “While the laboratory doesn’t promote these off-label uses, the ICU clinicians do order the test for these purposes.”

The literature is quite strong, he adds. When one study looked at ICU patients for whom PCT was used to guide antibiotic therapy, the author reported that mortality was significantly reduced (Carr JA. *J Intensive Care*.

2015;3[1]:36). “So while PCT is approved as a guide to monitoring sepsis patients, within the hospital the test’s uses are much broader.”

Mayo Clinic in 2014 developed a sepsis “sniffer” algorithm (an automated surveillance algorithm) for early detection and treatment, and it laid the groundwork for the 63 pages of CMS guidelines that hospitals are now required to implement, Dr. Pearson notes. “It sets standards for treatment and intervention—when to start IV fluids, when to start broad-spectrum antibiotics.”

“The algorithm makes quite a big deal out of lactate levels, which can indicate inadequate oxygen to tissues. There is severe sepsis when lactate is greater than 4 mg/dL. But if lactate is greater than 2 mg/dL, you need to repeat it. The problem with lactate is its sensitivity. A 2 or 2.5 is within our normal range.” A research letter published in *JAMA* in July 2014 showed that at Kaiser in California, 26.3 percent of sepsis deaths had lactate <2 and 29.6 percent between 2 and 4 (Liu V, et al. 2014;312[1]:90–92).

To evaluate PCT and lactate levels in concert, Dr. Pearson believes, would give much more helpful information, “because lactate is really a metabolic measure, whereas PCT can be used as an early marker of sepsis and also gives a pretty good idea of the degree of severity. If it’s above 10, the patient is probably going down into septic shock.”

“Everyone knows it’s a constellation of symptoms that indicates sepsis. It requires good clinical acumen to make that diagnosis.” Of particular importance are serial measures of PCT to track change. But the lack of FDA approval for those serial measures poses the same problem with PCT that it does with high-sensitivity troponin. “By determining the delta—the change over time—of high-sensitivity troponin, you can get much better information on a true myocardial infarction.” But setting the correct cutoffs has been difficult, he admits. “It’s a hang-up for the FDA. So it’s a trickier process getting approval for serial testing.”

Roche’s new platform shifts the competitive landscape for PCT, Dr. Pearson says, because it ends BioMérieux’s four- or five-year corner on the market. “Siemens has talked about delivering PCT on an automated platform but never got there, so Roche is kind of the second one in the door.” He also does not consider the benefits of Roche’s automated platform to be limited to larger institutions. “We’re a moderate to somewhat bigger lab, but I believe Roche’s Cobas systems are scalable. A smaller-sized lab could buy a smaller version that doesn’t have quite the same throughput but can still run PCT off the system.”
Given these factors, he expects use of PCT to grow over the next couple of years.

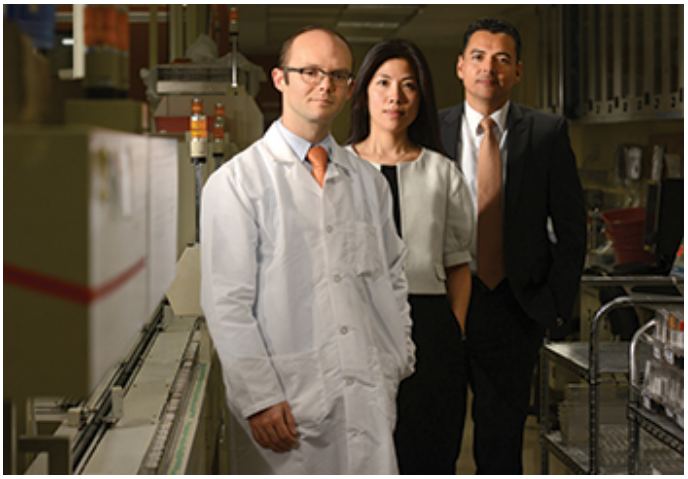
“When we first started, the cost of a PCT test was pushing close to $100. Now there is more competition in the market, prices are going down, and more labs can afford to run the test to get the benefits of early identification and management, and to prevent the adverse outcomes to the patient of too much antibiotics.”

At New York-Presbyterian Hospital–Cornell Campus, the negotiations to switch to Roche are being finalized. “We are now in the process of moving to the Cobas e411 for PCT on a Roche random-access platform,” says Dr. Hayden, central lab assistant director, “and we’ll realize turnaround times under one hour.” For PCT to meet clinical performance requirements as a biomarker, he says, rapid TAT is needed.

Europe has been far ahead in adopting PCT as a sepsis biomarker because of the wider availability of platforms. “There are more options in Europe, which reduces the cost of tests and allows labs to bring in instruments that meet their needs. Here in the U.S., if you wanted to do the test, you used the BioMérieux Vidas instrument whether or not it really worked for your lab workflow. That was a huge barrier,” Dr. Hayden says.

With that history, he was surprised by how quickly the FDA moved to approve Roche’s submission. “Ordinarily it takes a lot longer for them to make sure everything is in order. Perhaps Roche’s submission packet was so thorough and complete it didn’t require as much back and forth. The FDA is prioritizing management of septic patients, so there is more focus on how to deliver the best possible care for our patients and on evidence-based practices that can help facilitate that.”

The availability of PCT on the Roche platform should expand its use, in his view. “The same instrument that runs Roche’s PCT can run troponin and hCG, so this is a matter of adding an analyte to an existing platform rather than purchasing a platform just to run the analyte.” The Vidas platform, although automated, is better set up for batch-mode processing, Dr. Hayden says. “It’s not the same as just putting a tube on the instrument and walking away; it’s not what I would call true automated random access.”



Dr. Joshua Hayden (left) at New York-Presbyterian Hospital with
Su-Chieh Pamela Sun, MPA, MT(ASCP), central lab program manager, and Juan Garcia, MBA, BSMT, central lab program director. With procalcitonin on the Roche platform, Dr. Hayden foresees expanded use and lower prices, and he hopes to someday see an approved indication for PCT in guiding antibiotic use.

Price has also been an obstacle to adoption of PCT. “It’s a very expensive test to run on the BioMérieux panel, but I expect the price points will be coming down now that there is competition.”

Dr. Hayden hopes that the manufacturers will follow up their recent FDA submission to pursue an approved indication for PCT in guiding antibiotic use. “There’s a definite need to have sort of a systematic evaluation of that.” But he joins other experts in cautioning that sepsis remains a complex diagnosis. “I don’t see PCT replacing some of the other lab values such as lactate, and I would never expect a clinician to stop an antibiotic just because of a PCT level, if their clinical suspicion and the patient in front of them says otherwise. However, I do see PCT as being an additional data point that can factor into their decision-making.”

Some laboratories that are continuing to perform Thermo Fisher’s PCT assay are also witnessing rising test volumes. At 350-bed El Camino Hospital in Mountain View, Calif., the laboratory has seen a steady growth in PCT volume and now does about 400 PCTs a month on the Thermo Fisher Kryptor Brahms platform, says Kelly Abbott, MT(ASCP), CLS, chemistry lead. “We thought it was mostly for the ER, but it’s actually the whole house that is using it.” On the rare occasions when routine instrument maintenance delays performance, “the doctors really notice.”

Abbott

In Abbott's region, it's becoming more common, for TAT reasons, for hospitals to offer PCT themselves rather than send it out. A smaller hospital within El Camino's system sends its PCT specimens to El Camino's laboratory, which aims to return a result in 60 minutes. "It's a 23-minute test and we try for a 45-minute turnaround time. That's our goal. Inside our hospital, 90 percent of test results are reported within 45 minutes."

While the Thermo Fisher system performs a broad menu of automated tests, El Camino uses it only for PCT. "That's why we brought the instrument in here." Abbott, too, foresees a rise in the volume of PCT tests: "I would say anytime a test becomes more automated, people are more likely to run it, especially if they can do other things on the same platform."

That advocates are pressuring to get PCT built into sepsis protocols is a strong indication of the assay's importance, she adds. El Camino, which produced its own video on sepsis awareness, has a nurse in charge of sepsis protocols who attends conferences and does other outreach to raise awareness. According to the hospital's nurse educator, Jackie Keane, RN, a survey of nurses showed their No. 1 most desired topic for education was sepsis.

At Beth Israel Deaconess Medical Center in Boston, PCT is currently a send-out test, and for Stefan Riedel, MD, PhD, associate medical director of clinical microbiology, bringing PCT in-house is a priority. He has considerable experience as an early user of PCT at Johns Hopkins Bayview Medical Center (JHBMC). There, he worked on the initial studies validating the Brahms test, starting before Brahms' 2009 partnership with Thermo Fisher.

The emergency department at JHBMC was using PCT to help guide the diagnosis of sepsis and the procurement of blood cultures, instead of doing pancultures and blood chemistry tests on all patients who looked septic. This practice led to a slight decrease in the "overuse" of blood cultures, Dr. Riedel notes, which in turn reduced the number of blood cultures contaminated by skin flora, since blood cultures were then collected in an aseptic fashion separate from routine blood draws. At JHBMC, "PCT was on the laboratory test menu and it was built into our diagnostic algorithms. It was part of the order sets for certain patients presenting with symptoms suggestive of sepsis."

Basically, the FDA has approved PCT for diagnosis of severe sepsis and this year broadened the original indication a little bit, again with the focus on sepsis. "But PCT has potential utility for other infectious diseases—for example, to help differentiate between viral and bacterial pneumonia. I am certain there are clinicians, hospitals, and practices in the U.S. that probably use PCT this way, and there is enough evidence in the literature to support it," Dr. Riedel says. "However, the current FDA approval for this test focuses on sepsis."

Hospitals that already have an existing Roche Elecsys platform may now be more likely to adopt PCT onto their laboratory testing menu. "The initial platform that came from Brahms/Thermo Fisher was the Kryptor analyzer. While it is still considered the gold standard test method, it is a very specific and complex instrument, not in mainstream use in the U.S. for the typical chemistry lab." The Vidas by BioMérieux is likely to be more commonly used in microbiology labs, Dr. Riedel points out. "It may not be as widely used in chemistry labs, and that is where the PCT assay, which is a serum or plasma test, would usually be performed." Having PCT available on the Elecsys analyzers may lead to an increased use of PCT in the U.S., he believes, because it gives more labs the ability to offer the PCT test.

Growing awareness of the seriousness of sepsis may speed up adoption of PCT, Dr. Riedel says. "There has been a lot more emphasis over the last 10 or 15 years on the pathophysiology of sepsis that gave us a deeper understanding of the complexity of this illness, and in conjunction with that, the recognition of various biomarkers and the immune response associated with them." Worldwide, sepsis is among the top five causes of death, and studies are now showing that the long-term sequelae, particularly among the elderly, include reduced life expectancy and significantly higher rates of hospital readmissions, he notes.

"If you see a lot of patients with sepsis in your hospital, whether you are in a community-based hospital or a large

academic center, the test has a utility for the diagnosis and management of sepsis. If it's a send-out test, then by definition the earliest result you can get will be the next day, but the utility of PCT lies in having a test result available within an hour or two to make an impact on patient care."

This is true even of the newer FDA-approved clinical uses of PCT differential calculators, which require tests be performed four days apart. "You want results back shortly after your test order because the idea is that clinicians are able to make decisions for treatment and management as soon as you have the result available. I don't think a 24-hour TAT is feasible."

Dr. Riedel thinks that rapid PCT results could have a significant effect on antimicrobial stewardship programs as well. "Studies in Europe have shown this is certainly the case. At the moment in the U.S., such impact will still require studies and investigation. And it depends on how strong the stewardship management team at an institution is. It will take some work to pull all these players together. The first step will be to actually have the test available."

But he also stresses that among the various laboratory tests used for sepsis diagnosis, PCT should be viewed as a complementary test rather than as a competitor to currently used tests such as lactate. "Both laboratory tests are important for the diagnosis and management of patients with symptoms suggestive of sepsis. Lactate aids in the assessment of organ dysfunction, while PCT is a marker to describe the state of the pathophysiology of sepsis and inflammation."

The experience of Eric Gluck, MD, director of the ICU at Swedish Covenant Hospital in Chicago, extends back over several years of work validating PCT assays. His hospital and another one in Florida published data in *Critical Care* in 2013, based on a preliminary study showing the ability of PCT measurements to prognosticate outcomes (Schuetz P, et al. 17[3]:R115). "That was a precursor of the definitive, multicenter MOSES study, which the FDA used to approve additional claims about PCT," Dr. Gluck explains.

At Swedish Covenant, PCT has been offered for about seven years throughout the hospital—on the floor and in the ED as well as in the ICU. "We use it as a means of differentiating patients who have viral infections from bacterial and non-infections. PCTs show significantly more sensitivity and specificity, when you have clinical suspicion, than previous tests we have used. They're also a means of determining whether therapy is effective; if PCT levels don't disappear, we can question whether or not we are adequately treating the patient. And third, PCT sometimes allows us to stop antibiotics early when the levels normalize," before the prescribed course of antibiotics ends.

About 25 percent of admissions to the Swedish Covenant ICU are patients with sepsis, and the vast majority of those patients get one, or possibly two, PCT measures. Some get daily PCT tests for three or four days. But many more patients on the floor throughout the hospital—probably 500 a year—also have PCT tests. "We have realized that we were probably underdiagnosing infection in many people because the findings we used to use were relatively nonspecific. And we have much more aggressive treatments that are likely to result in better outcomes. With an aging population, we have more patients who get ill and require hospitalization, and many of those patients have sepsis."

The potential market for Roche's new platform is broad, Dr. Gluck says, noting that the PCT assay is available on multiple platforms and that "Roche's is the most important.

"If you have Elecsys, the additional cost is zero, except for reagents, and I believe the reagents are relatively cheap. So the actual cost for the test is in the $20 to $35 range."

More important, Dr. Gluck notes, "Sepsis is something everyone has to treat. It could be a presenting symptom for somebody in the community or it could be a postoperatively acquired infection or some other reason. So I don't think the size of the hospital is as important as the fact that most hospitals do have a significant portion of patients who are septic, and this test does help diagnose and see that the infection is responding appropriately to antibiotics."

PCT testing on an automated platform has a tremendous cost-benefit, in Dr. Gluck's view, because of the ability to get data quickly and to halt antibiotic use in patients who are responding more rapidly than expected. "Although to the clinicians, PCT might appear to be more expensive than what they usually order, such as CBCs or electrolytes, with PCT many patients who would have gotten full courses of antibiotics will not, many who would have had adverse events will not, and patients will not develop critical care infections as often."

"The clinical signals with sepsis are not as sensitive and specific as we'd like, and PCT allows the antibiotic stewards to have a lot more confidence that they're not going to cause patients harm by stopping antibiotics. So PCT also plays a very strong role in antimicrobial stewardship," Dr. Gluck adds.

Dr. Riedel says the U.S. health care system has not yet taken full advantage of how PCT can help in the effort to stem the tide of sepsis. "The lack of availability of a suitable platform hampered the recognition and utilization of PCT in the U.S. The fact that we now have the Roche platform for doing PCT testing will afford many more hospitals the opportunity to offer this biomarker."
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