Next-gen troponin: out of the gate, into labs

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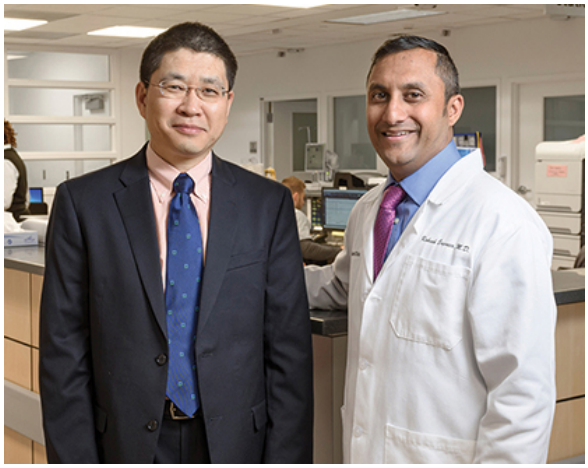
November 2017—The story of highly sensitive cardiac troponin, as written by Dr. Seuss, would provide a small twist. In this version, the Grinch doesn't steal Christmas. Rather, he keeps delaying it, quarter after quarter, year after year.

"I remember maybe seven years ago, Roche told me their assay was coming. It's coming, it's coming, it's coming," laughs Sihe Wang, PhD, medical director and section head, clinical biochemistry, Cleveland Clinic, and clinical chemistry professor, Cleveland State University.



The Cleveland Clinic went live with Roche's TnT Gen 5 Stat assay in June. "The only way to make a smooth transition is to have a team composed of all the stakeholders," says Dr. Sihe Wang (left), here with emergency medicine physician Rakesh Engineer, MD.

"It was a long journey," agrees Elsie Yu, PhD, system director of clinical chemistry, toxicology, and point-of-care testing, Geisinger Medical Laboratories, recalling the impatience with which she awaited FDA approval of a next-generation troponin assay. "And it wasn't only me," she says. "It was also cardiologists and the ED."

At Brigham and Women's Hospital, Boston, Petr Jarolim, MD, PhD, is familiar with the any-day-now chorus, having uttered it to his colleagues for eight long years. "I started making promises to my clinicians in 2009," he says, laughing.

Finally, however, laboratories and their clinical colleagues can start unwrapping the package. The FDA cleared Roche's TnT Gen 5 Stat assay earlier this year, and now physicians are implementing it, or at least considering whether to do so, as a way to more quickly manage patients presenting with chest pain.

Interestingly, for all the anticipation leading up to approval, the FDA asked the company to refer to its test as a "next-generation" assay, rather than a "high-sensitivity" assay.

That has made little difference to Dr. Yu. She had already assembled a team of physicians from cardiology and emergency medicine, as well as the laboratory, and was ready to act. (In hindsight, she says, her team should have included hospitalists as well.) "As soon as we heard the FDA approved it, we said, 'OK, let's see how we can

implement this.'" Geisinger went live with the assay in September.

Her laboratory had two primary reasons for making the switch from the fourth-generation assay, says Dr. Yu. One was to shorten the rule-out algorithm for myocardial infarction. Using the previous assay meant taking measurements at zero and six hours, or using zero and serial measurements.

With a more sensitive test, the zero/three-hour algorithm "looks pretty solid," she says, based on studies from Europe. (High-sensitivity cardiac troponin testing has been available outside the United States for about seven years.) Physicians are contemplating zero/two-hour or even zero/one-hour algorithms as well, she says. "Regardless, it's a lot shorter algorithm for the ED to see if a patient has an MI."

First of two parts

Next month: How emergency medicine physicians and cardiologists view next-generation troponin testing

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The other attraction, Dr. Yu says, is that the newer assay will be more sensitive in detecting micro-MI. Aside from MI, she adds, the new troponin will have the advantage of detecting other types of myocardial injury. "It is a much better marker for cardiac function, so it gives more confidence in rule in/out. That's something that excites our ED."

Her cardiologist colleagues are excited as well. Even if the new assay translates into a heavier workload, in the form of more cardiology consults—a common fear with this test—she says they relish the thought of identifying patients in need of treatment sooner rather than later.

At Brigham and Women's Hospital, Dr. Jarolim and colleagues were hoping to go live with the

Gen 5 in November. In his view, "It is clearly a better assay" compared with earlier generations of tests. "No question about it," says Dr. Jarolim, director of clinical chemistry and the biomarker research and clinical trials laboratory, and professor of pathology, Harvard Medical School. "We will definitely shorten the [testing] intervals," he says. "We are even considering moving to a one-hour rule out/rule in."

The Cleveland Clinic Health System beat others to the punch, going live with the assay in June. Dr. Wang, too, worked with a team of providers, which in addition to the usual suspects—lab, cardiology, ED—included nursing and internal medicine. "The only way to make a smooth transition is to have a team composed of all the stakeholders. Making a change is not easy," says Dr. Wang.

He also benefited from a C-suite team, he acknowledges. The Cleveland Clinic Health System's executive team essentially ordered the switch from on high, convinced it would improve patient care and save money, as well as possibly enhance the institution's reputation for providing high-quality cardiac care. "When your CEO tells you to do it, guess what?" Dr. Wang says with a laugh. It likely helped that the CCHS' chief medical operations officer is the interim chair of pathology and laboratory medicine, he adds.

Dr. Wang recites the aforementioned reasons for the lab wanting to adopt the new assay, then adds an unexpected benefit. Laboratory medicine isn't always the most visible specialty among clinicians, he says, but moving to the newer assay gave him and his colleagues a reason to team up with clinicians. Thanks to the ongoing collaboration and a smooth transition, he says, "We've gained a lot of respect. We already had a good relationship, but it's gotten even better." Indeed, he jokes, the laboratory has become sort of a rock star—no small thing in Cleveland, given its proximity to a certain Hall of Fame.

Dr. Fitzgerald

Discussions are also underway at the University of California, San Diego, but for Robert Fitzgerald, PhD, professor of pathology, UCSD Center for Advanced Laboratory Medicine, the talks are merely the latest in a decades-long dialogue about troponin. He recalls his work with the first-generation assay, and the same arguments—his word—that unfolded back then continue to echo today. When the laboratory looked to replace CK-MB with that first troponin, physicians raised the same worry they're raising now: It's too sensitive—we don't know what to do with it.

That's why he has proceeded cautiously with the Gen 5. Though he considers the assay to be "very solid analytically, with good accuracy and good precision," he wanted to make sure his colleagues' concerns were addressed.

"Before we tried to make the switch," Dr. Fitzgerald says, "we had a conversation: Are we interested in looking at it? And there clearly was interest from cardiology as well as the ED." (The transition team also includes general practitioners, he notes.) The next question was, "How do we look at it in our patient population?" Its relatively long use in Europe didn't mean instant familiarity with it here. "So we wanted to get our stakeholders involved in the initial discussions about how to evaluate it."

The laboratory has now begun a thorough evaluation of the assay, and Dr. Fitzgerald sounds pleased. From the earliest days, troponin "has allowed medicine and treatment protocols to evolve. This is just another step in that same direction."

Like other laboratory professionals, Dr. Fitzgerald is eyeing uses beyond the rule-out/rule-in scenarios. "I am excited about the possibility of detecting minor myocardial necrosis in a variety of settings that we couldn't do previously, like cardiotoxic drugs. It's a bit low, but analytically and biochemically, there's a signal there. If we get a little smarter, we can figure out how to use it. Eventually, we will be able to address some of these more clinically interesting questions."

The long run-up to FDA approval could be a boon or a bust. In theory, it meant plenty of time to get ready, including wider adoption of the universal definition of MI. On the other hand, out of sight can mean out of mind—how much can physicians be expected to remember about a test they're not using?

"You would think," Dr. Wang says, "that when it finally came down to using it, after such a long wait, it would be easy to start. But it's not."

Dr. Yu gained a toehold when some of her clinical colleagues remembered hearing about higher sensitivity troponin at their own specialty meetings. That gave her "enough clinician support to get the ball rolling," she says.

Dr. Yu

She and a group of clinical colleagues met monthly to review the literature. "One thing we got right: Instead of me

telling them what to do, which I don't think they would have appreci-
ated, is we had the cardiologists look up the literature they wanted to share, and the ED group looked up the literature they wanted to share," Dr. Yu says. She provided the lab-oriented literature. "So it wasn't just me feeding information to them."

Dr. Yu works with all seven hospitals in Geisinger's system, which is located in rural Pennsylvania. "Not all the ED directors were aware of it," she recalls. Though the topic has been prominent in the literature, she says, questions from colleagues have revealed a mixed understanding of the biomarker. "So it's important that everyone start at the same level before going into too much detail."

Case in point: "A lot of people don't know what high sensitivity means," Dr. Yu says. "They also don't always know what testing algorithm they're using" even with the older troponin assay. Dr. Yu speculates that as clinical routines develop, the lab's role in overseeing algorithms sometimes retreats into the background. "So one ED would tell me they were testing at six hours, and another would say, 'No, we're doing three—we thought that was OK.' I think they were fundamentally mixing up the literature, even though everyone meant to do the right thing."

The troponin literature is a cup runneth over, as Dr. Yu and her transition team quickly discovered. Part of her job, she says, was to help her colleagues focus on literature related to testing algorithms.

But that can lead to another hiccup. The vast majority of literature, unsurprisingly, focuses on the European experience with the assay. Those established algorithms may be different in FDA-approved settings.

Once the literature review was well underway, Dr. Yu and her colleagues began hammering out a testing algorithm.

At first blush, it didn't seem all that complicated an issue—why not adopt and adapt the European protocol, using, for example, the FDA-approved gender-specific cutoffs?

But like a road trip across Montana, the trip turned out to be longer, and with more dreary patches, than one might have predicted at the start. "We spent a lot of time working on our algorithm," says Dr. Yu. One reason was each hospital took a different approach to handling patients in the so-called gray zone—those who may not have an MI but who aren't well enough to discharge. "What do we do with them?" says Dr. Yu, asking troponin's eonian question.

They arrived at an answer after several months of discussion. Wanting to make matters as straightforward as possible for providers, she set up the electronic health record using four categories: undetectable level, detectable (but normal) level, elevated level, and critically high level. Anyone under the 99th percentile is considered normal (females = 14 ng/L; males, 22 ng/L).
She calls these details "little things," but insists their impact is big. "It helps that they can just look at the chart and don't have to remember the exact cutoff."

As with any good product launch, she also had to get the word out. One hospital used grand rounds to let physicians know about the upcoming change; others used department and medical staff meetings to spread the word. Finally, right before the assay went live, "I blasted everyone with a one-page communication in Epic," Dr. Yu says, "just as a final reminder."

Yes, it's a lot of communication, she says. "I know it sounds like overkill. It really is not, at the end of the day." Every medical institution, it seems, has its version of a not-listening spouse. "There's always a few people who, when we go live, ask, 'What's going on?'"

At Brigham and Women's, Dr. Jarolim has watched with interest as these particulars play out.

From the laboratory perspective, says Dr. Jarolim, the switch shouldn't be too challenging. As with any assay, validation is critical, but it's not particularly unusual or difficult. But as Adam soon learned on a certain primordial

garden show set in Eden, the process of naming matters. Says Dr. Jarolim: “Our cardiologists quite correctly point out that if we call it Gen 5, most clinicians won’t understand what the big deal is. So we will include some sort of designation that it’s a higher sensitivity assay.”

He’s also concerned that the new assay, which measures troponin in nanograms per liter, could sow added confusion among clinicians, who have become used to using micrograms per liter—the standard measurement with earlier assays.

And, naturally, there’s the issue of cutoffs. “Shall we use the specific ranges as recommended in the package insert?” Dr. Jarolim asks. “They may not be quite valid for the patient population at Brigham and Women’s. We think what is currently recommended is, actually, relatively high.” Consequently, he says, “We are near a decision to be more conservative, with lower cutoffs for both women and men.”

Dr. Jarolim

Continues Dr. Jarolim: “Obviously this whole issue of high sensitivity or not is complicated.” In contrast to most clinical lab assays, where the sensitivity is defined by the capability of detecting a certain standard with sufficiently high precision, “in the case of troponin, the high sensitivity is defined somewhat arbitrarily” as the test’s capability of detecting the biomarker in at least 50 percent of the reference population. “If you use this reference, it makes things quite subjective,” he says. How do you select your reference population? How do you define healthy? What is your age distribution in the reference population? Troponin levels increase with age, even in healthy people, and it may vary depending on gender. “That’s why we think we should suggest, in the designation of the assay, that it’s a higher sensitivity than the previous, fourth-generation assay.”

The manner of rolling out the test, unsurprisingly, has varied by institution. Those with multiple sites had to think big but didn’t necessarily want to start big. The Cleveland Clinic Health System, for example, began with a pilot implementation of the assay on its main campus as well as at Hillcrest Hospital, a large community hospital, followed by a stepwise rollout at all regional hospitals and family health centers.

Brigham and Women’s is part of the Partners HealthCare system, which also includes Massachusetts General Hospital, North Shore Medical Center, and multiple other facilities. While Dr. Jarolim saw advantages to rolling it out systemwide on the same day, in the end, it seemed to be so logistically complicated that the Partners’ leadership decided Brigham and Women’s would go first. Others will eventually go live based on the hospital’s experience.

At UCSD, the rollout, like Ravel’s “Bolero,” is unfolding quietly but steadily. For two months the laboratory will run both the fourth-generation and Gen 5 tests (it had been doing so for about a month at the time Dr. Fitzgerald spoke with CAP TODAY) while reporting results only from the fourth-generation test. Since it’s an IRB-approved protocol, Dr. Fitzgerald and colleagues will be able to collect data on a variety of clinical parameters. One area of particular interest: looking at low-end cutoff points and whether treatment might have been different if based on a Gen 5 test result.

(While it’s too soon for any formal data analysis, Dr. Fitzgerald has noticed one difference between running Gen 5 and its predecessor. “We had problems when using the Bio-Rad control for the Gen 5 assay, so we switched to the Roche control. Since switching to the Roche control, we’ve had no problems,” he says.)

Once the data are collected and summarized, Dr. Fitzgerald says, results will be presented at grand rounds in an open forum, with representatives from the lab, the ED, and cardiology present. “We’ll break it into an overview of

the analytical performance of the test, then review some of the cases where there might have been differences in how we initially treated patients."

Following that, he continues, the laboratory will continue to use both tests, reporting results from both but using the units of ng/L for the Gen 5 test. "That way people can start to understand that the units have changed while still getting their old results. We'll do that for a couple of months, and then, provided things go well, we will switch to Gen 5." For now, however, the clinicians are blinded to the results from the Gen 5 assay.

The best-laid plans still invite questions, naturally.

The questions Dr. Yu heard most consistently centered on so-called false-positives. To those in the laboratory, it's not an endearing term. "I don't like it, because these are not actually false-positives," she says. "Those patients are truly positive for troponin; they just don't have MI." But she knows she's fighting a losing battle, and has raised the white flag on the term favored by her clinical colleagues.

Her ED colleagues feared using the new assay would lead to delays in discharging patients from the observation unit. Dr. Yu helped mitigate those concerns by sharing with them a European study (Twerenbold R, et al. *Eur Heart J.* 2016;37[44]:3324–3332) that showed use of the test lowered ED length of stay and costs without an increase in coronary angiography or stress testing. Furthermore, she says, "We're talking about implementing the zero and one-hour rule-out protocol," although she'd like to see clinicians become more comfortable with the zero/three-hour protocol first.

She knows of institutions that are using both those protocols simultaneously. It's a move she and her colleagues considered initially, "but when we drew the whole thing out, it was too complicated to follow." Better, they decided, to let one solid approach sink in before attempting to refine it. As for using the zero/one-hour rule in, "We don't like it," Dr. Yu says. "We don't think it's specific enough."

Dr. Yu suspects there is a role for testing at six hours (albeit not in Geisinger's current algorithm) for some patients in the so-called gray zone (another term favored more by clinicians than laboratory professionals). CTA isn't always an appropriate option, she says; even when it is, not every institution (including Geisinger) has it available 24/7.

Geisinger chose to use the gender-specific cutoffs, a decision mostly driven by literature that suggests doing so will benefit women patients. "When I describe the physiology to providers, none of them question it," says Dr. Yu. While other studies conclude there's no advantage, "physiologically, I think it makes a lot of sense," she says, suggesting that differentiating between genders is "the first step to make this more accurate."

At UCSD, emergency medicine physicians are worried they'll be inundated with positive results, says Dr. Fitzgerald. The cardiologists, in turn, are fearful they'll be swamped with consults on cases with low-level positives.

He regards both scenarios with sanguinity. "I think in practice that's not going to bear out," he says, looking to the Canadian and European experience with the Gen 5.

Dr. Fitzgerald also anticipates the laboratory will use sex-specific cutoffs, noting, "There's pretty good data to show there are differences at the low end." But he and his colleagues are still trying to determine a critical value for the Gen 5. Ideally, he says, they will be able to do so after the first phase of the rollout.

Dr. Wang says the primary worry was that referrals to cardiologists would increase. "But in reality, I don't think it is the case due to a triage structure put in place by emergency, cardiology, and internal medicine." The one-hour rapid rule-out algorithm using the higher sensitivity troponin T has meant more low-risk patients can be discharged. In the past, they may have been put in observation beds for further workup, with three to four cardiac biomarkers, stress testing, and frequent consults to cardiology. In fact, he says, the vice chair of the cardiology institute has been pushing for a systemwide rollout of the rule-out algorithm. "He said he's received zero complaints. Which is very unusual," Dr. Wang adds.

Despite their relatively limited experience with the Gen 5 test, laboratories say the early reviews are positive.

So far, says Dr. Yu, the only hitch has been with a few ED providers, during the initial go-live, who were struggling with what to do with elevated troponins when the value remained unchanged at the three-hour retest. She traces the confusion back to so-called false-positives. “Things have gotten a lot better since then, and they are getting more comfortable with the new test, especially with discharging patients.” Cardiologists, she says, are not getting as many consults as they thought they would.

Dr. Yu anticipates having to make adjustments to the algorithm. As with anything new, there are growing pains. “But this is something we need to do. We’re already so far behind our European colleagues.”

It’s too soon to have measured clinical outcomes, of course, but Dr. Yu (who says this is now the focus for the Geisinger groups) already sees some success, even if it falls short of Christmas miracle status. “My providers have been tremendously supportive. Everyone is really excited about this.”

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