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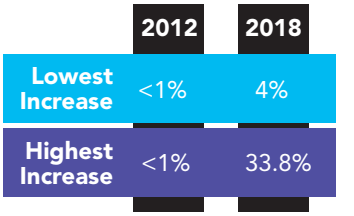
Tough Choices on Syphilis Screening

REGIONAL VARIANCES IN ADOPTING PROSTATE CANCER GENETIC TESTING



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A New Troponin Strategy

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Features

Departments

With the election of former Vice President Joe Biden, there may be a more coordinated, comprehensive federal approach to managing the COVID-19 pandemic.
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Federal Insider

AACC Urges Biden to Work With Lab Community on SARS-CoV-2 Testing

In a letter to President Biden's Coronavirus Advisory Board, AACC is calling on the Biden administration to collaborate closely with laboratory medicine professionals and to give the federal government a stronger role in helping laboratories respond to the COVID-19 pandemic.

AACC outlines four key areas the Biden administration should act on, beginning with manufacturing and distribution of laboratory supplies. In a survey of laboratories in September, AACC found that 57% of respondents reported ongoing problems obtaining supplies needed to perform coronavirus diagnostic testing. Nearly 70% of the laboratories said they cannot obtain needed test kits and reagents, and 36% cannot get the swabs needed to collect specimens.

Second, AACC is asking the Biden administration to repeal a Centers for Medicare and Medicaid Services (CMS) decision to tie lab payments to turnaround time. "Many laboratories are completing their testing within the timeframe specified by CMS," the letter says. "For those laboratories not meeting this timeframe, it is often for reasons outside of their control."

Third, AACC is calling on the Biden administration and Congress to work together to rebuild public health infrastructure, noting that federal expenditures for the Centers for Disease Control and Prevention, when adjusted for inflation, remain at fiscal year 2008 levels.

Finally, AACC urges the Biden administration to include a laboratory professional on the administration's Coronavirus Advisory Board. "A laboratory expert on the Board can suggest strategies for expanding access to testing in the face of surging coronavirus cases," the letter says.

CMS RELEASES 2019 HEALTHCARE COST DATA

Data from the Office of the Actuary at the Centers for Medicare and Medicaid Services shows that before the COVID-19 pandemic, U.S. healthcare spending was growing at a moderate pace of 4.6%, and that a suspension of the health insurance tax—a major tax under the Affordable Care Act that Congress repealed in its December 2020 spending bill—played a significant role in slowing the growth of private health insurance costs.

Overall, national healthcare spending in 2019 grew 4.6%, which was similar to the 4.7% growth in 2018 and the average annual growth since 2016 of 4.5%. While personal healthcare spending rose somewhat faster—5.2% in 2019 versus a 4.1% increase in 2018—the net cost of health insurance declined by 3.8% because of the tax suspension.

Notwithstanding these moderating factors to overall healthcare spending, Medicare spending continues to grow at a significantly higher pace, increasing by 6.7% to reach $799.4 billion in 2019, faster than the 6.3% rise in 2018 and despite enrollment growth holding steady.

REPORT: HOSPITAL EXPENSES CLIMB AS REVENUE FALLS

Hospitals face rising expenses and falling revenue as COVID-19 continues to stretch healthcare business models, according to a report by Kaufman Hall. The report found that revenues and volumes were down across most metrics, yet inpatient volumes rose as the number of patients hospitalized with coronavirus infections doubled in December.

The report underscores the importance of federal funding. Hospitals' median operating margin was -1.1% year-to-date based on November data with federal funding not included, a 11.6% decline compared to 2019. With CARES act funding, the median operating margin was 2.5%, still down 8.3% year-over-year.

The additional relief bill Congress passed in September adds $3 billion to the government's Provider Relief Fund. As of December, the Centers for Medicare and Medicaid Services had distributed about $125 billion of the $175 billion allocated under the CARES act.

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Bench Matters

Total Lab Automation: What Matters Most

Systems added to lean processes bring efficiencies, new opportunities.

Alexander B. Leichtle, MD

In this second of a two-part examination of total lab automation (TLA), I explore what TLA can and can't do, as well as prerequisites for and considerations in installing TLA systems.

Expectations are very high when it comes to TLA, but I offer a few words of caution based on our experience here at Inselspital–Bern University Hospital in Bern, Switzerland. In relocating the routine laboratory, we decided to simultaneously renew the core lab instrumentation and install a TLA solution. We did so to reduce unnecessary manual work and gain high standardization and documentation for the clinical lab and the institutional biobanking by joining and automating the workflows. The main point we learned from these efforts is that if introducing a TLA system is seen as a trigger and leverage to lean lab processes and IT structures, eliminate unnecessary variability, introduce binding standards, and consider all the deviations of standard processes implemented over decades, then it will be a success story. One that would have been possible without installing even a single TLA module.

Conversely, TLA deployed solely to render existing, complicated processes faster and less laborious will fail. TLA is not necessarily faster or more flexible than a committed worker. Moreover, TLA definitely isn't a must for every laboratory. The more diverse samples and requests are, the less efficiency automation brings. The mantra hence must be simplify, then automate. And, as everywhere, the Pareto principle applies: Labs that connect 20% of their instrumentation that processes 80% of their samples already have an efficient solution. The difficulty is in deciding which processes should reasonably be automated.

Greg Gibson

PREREQUISITES

Introducing TLA in a lean, highly standardized lab environment is much easier than mirroring complex procedures based on manual workflows, making upfront standardization an inevitable prerequisite. A good starting point is a lab's table of all analyses. Labs should scrutinize all tests and consider which are obsolete, whether specific tube types or more common ones will work for an analysis, if separate aliquots are needed, and other similar considerations. Working through the table will reveal areas of improvement to tackle early on.

Following this process, I recommend that labs critically review their system's master data, with a hard look out for dependencies that might have been introduced previously to ease manual processing but that now hamper straightforward automated workflows.

If possible, labs also should reduce the variety of sample types, as having many different tube formats renders automation technically challenging. This effort could be combined nicely with a patient blood management initiative and lead to overall smaller sample tubes. If a lab defines (and orders) the sample tubes to be used, this process can be fast and simple. However, making this change could be more challenging if a lab depends on external submitters.

Another major TLA change concerns lab employees. TLA—a highly technical process that needs staff to manage robotics and embedded IT—is not yet as user-friendly as fully automated analytical instruments. In contrast, if a TLA system does not properly work for any reason, its emergency processes at least have to be maintainable manually, depending on the service-level agreement with the TLA vendor. This requires considerable flexibility in staff knowledge and planning.

Cost is of course a key factor in planning to buy and install a TLA system. TLA doesn't save staff expense, but it brings standardization and documentation at a very high level.

A QUESTION OF SPACE

TLA needs considerable space. A large space without walls and

columns offers the easiest setup, but other possibilities exist. Narrow wall openings enable sample transport to other rooms, and sample escalators let samples climb or descend to other floors.

Different types of conveyors allow flexibility in rearranging due to new modules or analyzers. Notably, conveyors are convenient for sample transport, but not necessarily to reach maintenance openings and the like. Hence accessibility concerns should be a priority, and it might be more efficient to let samples drive a few meters more, to make daily maintenance accordingly easier. It might even be reasonable to split automation lines if one sample type is processed only at one specific analyzer or if the analytical solution consists of large connected instruments that are so huge they don't fit in the dedicated area. A secondary benefit of conveyor systems is, nevertheless, that cables, tubes, IT connectors, etc. can be guided through the base of the conveyor system and reach the respective module and analyzers so that they are easy to access and maintain. If a laboratory has remote premises, optimal sample retrieval points can be designated.

Middleware is another important aspect of TLA. Some TLA applications enable direct links between the laboratory information-management system and routing engine without having to intercalate a middleware. This frees labs from depending on the routing engine provider to attach instruments of another company, resulting in much more flexible and independent solutions.

Labs handling samples of a certain biological security level will need to think through contamination and decontamination issues that affect planning of the TLA.

Although TLA systems are set up to run smoothly and without manual errors, labs have to have procedures in place for emergency breakdowns. This means analyzers should be loadable manually, and sufficient centrifugation capacity should be easily accessible.

SIDE BENEFITS

In providing high process quality and extensive documentation, TLA also offers several side benefits. Having time stamps and in some cases photos of samples enables labs to track and document preanalytical errors in a way that fosters discussions with sample submitters, like when barcodes are not attached properly or samples are underfilled or contaminated. For laboratory customers, TLA automated sample storage significantly improves how labs handle new requests from already processed and stored samples. Last, but not least, TLA is a big leap towards healthcare integrated biobanking and enables on-the-fly generation of aliquots for cryostorage in research and routine.

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The Sample

SARS-CoV-2 Test Frequency, Turnaround Time Outperform Sensitivity in Curbing Virus Transmission

A mathematical modeling study concluded that when it comes to COVID-19 surveillance, test frequency and turnaround time are considerably more important than test sensitivity (Sci Adv 2020;10.1126/sciadv.abd5393).

The investigators determined that testing 75% of individuals every 3 days using a rapid test with a limit of detection (LOD) of 10^5 copies/mL and same-day results in an environment with 4% SARS-CoV-2 prevalence and a reproduction rate starting at R_O 1.5 would "drive the epidemic toward extinction within 6 weeks and reduce the cumulative incidence by 88%." In contrast, a similar testing frequency using polymerase chain reaction (PCR) with an LOD of 10^3 copies/mL and a 48-hour results turnaround would reduce infectiousness by 58%.

"When it comes to public health, it's better to have a less sensitive test with results today than a more sensitive one with results tomorrow," said lead author Daniel Larremore, in a prepared statement.

Larremore and his colleagues at the University of Colorado and Harvard University hypothesized that given the features of viral increase, infectivity, and decline during SARS-CoV-2 infection, there would be "minimal differences" in effective screening regimens between PCR tests and cheaper, faster tests with higher LODs.

The investigators modeled viral loads and infectiousness curves for 10,000 simulated individuals based on within-host viral kinetics features like latency and growth. They also assessed the impact of repeated screening at different intervals and with tests of different sensitivities in a university-type setting of 20,000 people and in a large city of 8.4 million. In addition, the researchers modeled the impact on transmission dynamics of factors such as delayed results, changed model assumptions like R_O, and the effect of repeated population screening.

Even weekly testing using a test with 100 times lower molecular sensitivity than PCR with just half of a population participating would reduce the peak and length of an outbreak.

Based on their findings, the authors suggested that federal and state governments encourage the development and use of rapid, lower cost, and lower sensitivity tests for public health and repeat population screening.

WIDE REGIONAL DIFFERENCES IN ADOPTING GENE EXPRESSION TESTING FOR PROSTATE CANCER

Amid overall increased use, significant regional variations exist in commercial gene expression testing for prostate cancer, with a greater than 8-fold difference in use between high-adopting and low-adopting regions (JAMA Oncol 2020;doi:10.1001/jamaoncol.2020.6086).

The researchers accessed administrative claims data from Blue Cross Blue Shield Axis for 92,418 men ages 40 to 89 diagnosed with prostate cancer between 2012 to 2018, using CPT codes to identify claims for genomic testing within 6 months of initial diagnosis. During the study period this testing rose from 0.8% of patients to 11.3%.

The researchers analyzed the data according to 217 hospital referral regions (HRR), which reflect regional healthcare markets for tertiary medical care. From this process they identified five distinct regional trajectories of test adoption. Less than 1% of patients were tested in all five groups at baseline, but adoption of this testing increased during the 6-year study period from 4% in the lowest adopting group to 33.8% in the highest.

In comparison to HRRs with the lowest test adoption, those in the highest had higher HRR education measures, household income, and prostate cancer resources, such as density of providers and rates of prostate-specific antigen testing.

The authors did not find a direct link between race and the trajectories but cautioned that this could be due to the study sample of younger,

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commercially insured patients, which might mitigate racial disparities in accessing cancer care. They also didn't have access to patient-level demographics, so couldn't rule-out the possibility of racial differences.

Unrelated geographic regions shared testing adoption trajectories, suggesting similar local level conditions might promote dissemination of new technologies, like access to research-oriented medical centers, relationships with industry, or interest among patients.

SINGLE-PAGE ARTIFICIAL PANCREAS DASHBOARD PROPOSED FOR REPORTING KEY GLUCOSE MANAGEMENT METRICS

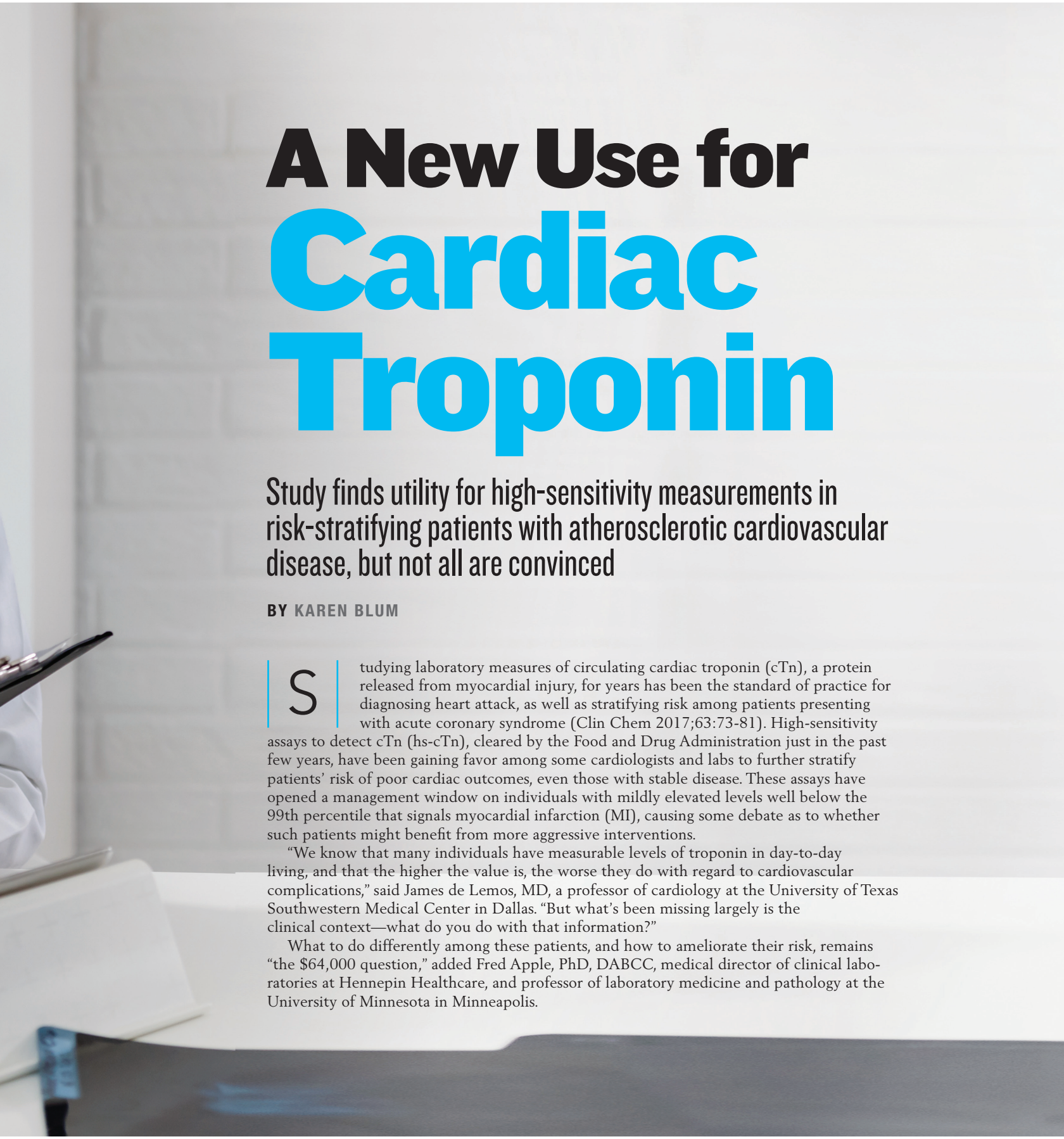
A standardized single-page reporting format for seven glucose metrics across all hybrid closed-loop (HCL) glucose management systems could boost uptake and appropriate use of the systems, ultimately improving patient care, according to the researchers who proposed this report, dubbed Artificial Pancreas Dashboard (AP Dashboard) (Diabetes Technol Ther 2021;23:10.1089/dia.2020.0622). In proposing AP Dashboard, Viral Shah, MD, and Satish Garg, MD, University of Colorado (CU) faculty members and practitioners at the CU Barbara Davis Center for Diabetes, noted that despite advances in therapies and technologies, diabetes outcomes have not improved markedly, and only about one-third of patients achieve optimal glycemic control. While recognizing socioeconomic barriers to accessing newer technologies, the authors also posited that providers' lack of knowledge could be a major barrier. Finding easier ways to interpret glucose and insulin metrics and optimize HCL settings could help, they suggested.

The seven AP Dashboard components would include: glucose metrics; hypoglycemia; insulin; user experience; hyperglycemia; glucose modal-day profile; and insight. The proposed glucose metrics include: mean glucose; standard deviation (SD) and/or coefficient of variation (CV); glucose management indicator (GMI); and a visual graph of continuous glucose monitor (CGM) metrics like time in range, above range, and below range.

Most members of an expert panel in 2012 agreed that mean glucose is a simple metric that both patients and physicians understand.

While CV is more constant and not affected by mean glucose or HbA1c, the authors believe that patients and clinicians find SD easier to understand. GMI is the new logistic regression formula to estimate HbA1c based on mean glucose.

In a break from current practices, the authors propose including in AP Dashboard both level 1 hypoglycemia (CGM glucose <70 mg/dL) and level 2 hypoglycemia (CGM glucose <54 mg/dL). Just reporting level 1 hypoglycemia doesn't provide enough information to develop an action plan for minimizing hypoglycemia, according to Shah and Garg. To avoid over-reporting hypoglycemic events they proposed reporting level 1 episodes that last at least 15 minutes.



A New Use for Cardiac Troponin

Study finds utility for high-sensitivity measurements in risk-stratifying patients with atherosclerotic cardiovascular disease, but not all are convinced

BY KAREN BLUM

Studying laboratory measures of circulating cardiac troponin (cTn), a protein released from myocardial injury, for years has been the standard of practice for diagnosing heart attack, as well as stratifying risk among patients presenting with acute coronary syndrome (Clin Chem 2017;63:73-81). High-sensitivity assays to detect cTn (hs-cTn), cleared by the Food and Drug Administration just in the past few years, have been gaining favor among some cardiologists and labs to further stratify patients' risk of poor cardiac outcomes, even those with stable disease. These assays have opened a management window on individuals with mildly elevated levels well below the 99th percentile that signals myocardial infarction (MI), causing some debate as to whether such patients might benefit from more aggressive interventions.

"We know that many individuals have measurable levels of troponin in day-to-day living, and that the higher the value is, the worse they do with regard to cardiovascular complications," said James de Lemos, MD, a professor of cardiology at the University of Texas Southwestern Medical Center in Dallas. "But what's been missing largely is the clinical context—what do you do with that information?"

What to do differently among these patients, and how to ameliorate their risk, remains "the $64,000 question," added Fred Apple, PhD, DABCC, medical director of clinical laboratories at Hennepin Healthcare, and professor of laboratory medicine and pathology at the University of Minnesota in Minneapolis.

EMERGING AND REINFORCING EVIDENCE

One recent study adds a possible twist to the ongoing dialogue (JAMA Cardiol 2020;5:1255-62). Researchers at Brigham and Women's Hospital in Boston investigated how hs-cTn I measurements would impact risk classification of patients with atherosclerotic cardiovascular disease (ASCVD) from the prior PEGASUS-TIMI 54 trial (N Engl J Med 2015;372:1791-800).

In the newer study, the investigators first assigned patients to groups of very high-risk ASCVD or lower-risk ASCVD based on their cardiovascular history and comorbidities, in line with the 2018 American Heart Association (AHA)/American College of Cardiology (ACC) cholesterol management guidelines criteria (J Am Coll Cardiol 2019;73:e285-350). The researchers further stratified the 8,635 study participants by hs-cTn I level with Abbott's ARCHITECT assay, using cut points of 2 ng/L (the assay's limit of detection) and 6 ng/L (a proposed risk threshold). All patients had had an MI 1 to 3 years before study enrollment, were at least 50 years old, and had at least one high-risk feature.

When patients in the very high-risk ASCVD group were further risk stratified by hs-cTn I level, 9% with levels below the assay's limit of detection had a 3-year event rate of 2.7%, less than the overall rate in the lower-risk ASCVD group. Conversely, 22.6% of those in the lower-risk ASCVD group with an hs-cTn I level exceeding 6 ng/L had an event rate of 9.1%, comparable to the overall rate in the very high-risk ASCVD group. In total, the use of hs-cTn I measurements reclassified about 12% of patients, said lead study author Nicholas Marston, MD, MPH, a cardiologist at Brigham and Women's Hospital.

"Most notably, it upclassified one in four patients in the lower-risk ASCVD group into the very high-risk ASCVD group," he said. "So that's potentially 25% of these lower-risk patients who could or should be getting more aggressive therapies. It adds a clinical application that could provide value in helping manage patients."

The data are showing that cTn "is a powerful risk-stratifying tool, independent of everything else going on there," Apple said. "That's been shown for years now, so this is just another rendition of how troponin independently predicts risk."

A NEW STRATEGY—PERHAPS

An accompanying editorial suggested that cTn levels should not just be viewed as a marker for myocardial injury but also used more frequently for assessing CVD risk in stable patients with heart disease (JAMA Cardiol 2020;5:1263-4). In this way, reclassified individuals potentially could receive more intensive statin therapy or start taking potent PCSK9 inhibitors. Marston said he and his colleagues already monitor patients' cTn levels to help guide their management decisions. Apple said he totally agrees with this approach, and he could see where cTn could be monitored as commonly as cholesterol.

de Lemos, admittedly an early adopter, said he also thinks it's a reasonable strategy that can provide further information on when to be more aggressive with additional therapies in patients with established disease. The readings could be even more beneficial in people who don't have diagnosed CVD, he said.

But others are more cautious.

"I think it's premature to say that we would do this routinely," said Donald Lloyd-Jones, MD, professor of preventive medicine, cardiology, and pediatrics and chair of preventive medicine at Northwestern University Feinberg School of Medicine in Chicago. While the Boston study does shuffle the deck a bit, he would do something different for a fairly small number of patients.

Drilling down on the numbers, the lower-risk group was roughly

"We know that many individuals have measurable levels of troponin in day-to-day living, and that the higher the value is, the worse they do with regard to cardiovascular complications."
—James de Lemos, MD

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Accurate measurement of plasma volume or overall volume status has been notoriously difficult. Thus, many surrogates for volume status have been developed over the years, from simple non-invasive measures such as the history and physical examination, weight, laboratory studies, and radiographic imaging, to more complex and invasive techniques such as CVP or pulmonary capillary wedge pressure measurement. Several formulae based on hemoglobin, hematocrit, and sometimes weight have recently been studied in various patient populations with promising results.

Presenter

Mitchell Rosner, MD, MACP. Henry B. Mulholland Professor of Medicine
Chair, Department of Medicine, University of Virginia Health System

Learning Objectives

- Discuss the importance of establishing the volume status of patients
- Review the clinical decision making affected by a patient's volume status
- Review the concept of "Goal Directed Therapy" in resuscitation and its benefits and pitfalls
- Discuss the implications and adverse outcomes of incorrect assessment of volume status, including acute kidney injury, hypo- and hyper-tension, congestion, etc
- Evaluate the current methods at our disposal for determining volume status and plasma volume including invasive and non-invasive methods, and the pros and cons of each

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20% of the total population from this trial, explained Lloyd-Jones, who also coauthored the 2018 AHA/ACC guidelines and is president-elect of AHA. About one in four of those patients fell in the high cTn group, who would be reclassified upwards.

"In this particular study, it was only about 5% of patients where I would do something different by knowing their troponin level," he said. "It's an important 5%, but it's only 5%. On the flip side, I would not decrease the intensity of therapy for the large group (80%) of higher risk patients just because their troponin is low today. While these data are interesting and point the way to how we might use these biomarkers for the future, I think we need to get a little bit better at figuring out who we need to do this testing on, because I'm not sure running this on everybody all the time is going to be a very cost-effective strategy."

Several caveats would need to be considered before implementing this type of testing wide-scale, cautioned Allan S. Jaffe, MD, chair of the division of clinical core laboratory services and a consultant in cardiovascular medicine at the Mayo Clinic in Rochester, Minnesota. "As you get way down into low laboratory values, where you have a more diverse group who may or may not have underlying cardiovascular disease, some of these patients will end up having values that look like they may have increased risk for disease, and could be misclassified due to the tiny changes that exist between those at risk and those not at risk." Factors like biological and analytical variation can cause such alterations. In addition, he said, things such as exercise can increase cTn modestly, just enough to confuse the results.

"You have to have the sort of study that definitively says this works, before you can worry about these other implementation details," Jaffe said. "That is not a knock on the study, but it's a caution in regard to taking the next step."

Additionally, he said, the study results are only applicable to Abbott's assay. More cutoff points would have to be determined for each hs-cTn assay.

cTn is a marker of interest as a signal of heart damage, but the mechanism of injury has yet to be determined, Apple said. Once that issue has been sorted out, physicians can think about implementing more accurate therapies based on cTn results.

Information like the results of this study will be considered in future guidelines produced by AHA and ACC, Lloyd-Jones said, but they're not strong enough to influence a revision as of now. A clinical trial that compares this testing strategy versus usual care would be interesting evidence but an expensive undertaking, he noted.

"While these data are interesting and point the way to how we might use [hs-cTn] for the future, I think we need to get a little bit better at figuring out who we need to do this testing on, because I'm not sure running this on everybody all the time is going to be a very cost-effective strategy."—Donald Lloyd-Jones, MD

HERE AND NOW

Meanwhile, clinical laboratory professionals can take several actions to help clinicians at their home institutions. One is to be aware of the availability of these tests, Marston said. The field needs to move toward using hs-cTn assays as an overall strategy, Jaffe added. Despite the Fourth Universal Definition of MI, different approaches persist even for diagnosing acute MI. Lab professionals also need to help clinicians understand how to interpret and act on hs-cTn results for individual patients. Verbiage is important here, Lloyd-Jones stressed: It's key to educate clinicians that not everyone with a low cTn level is low-risk, and not everyone with a high cTn level is high risk.

Jaffe concurred: "I think we need to be careful to make sure that the advice we give makes this useful, and isn't just a way of selling testing that doesn't end up really helping."

While both science and laboratory technology evolve, cTn remains an important indicator to watch. "It is a very consistently powerful test for risk assessment for cardiac disease across the spectrum," de Lemos said. "Wherever you measure it, it seems to provide very important additional information."

Labs in the future might be able to generate hazard ratio data from their own populations, Apple suggested. Jaffe said he and others in the field appreciate that more useful cTn measurements are a coming benefit.

"This is eventually going to be applicable to large numbers of patients with and without atherosclerotic disease," Jaffe said. "But we need to do the sorts of studies done here to define what those cutoff values are … Eventually, we will get all those metrics right. And this will work not only for patients with stable ASCVD but in a whole lot of other instances for prevention."

Marston and Lloyd-Jones reported no relevant financial disclosures.

de Lemos has grant support from Roche and Abbott, and has consulted for Siemens, Ortho Clinical Diagnostics, and Quidel.

Apple and the Hennepin Healthcare Research Institute receive research funding from several companies that have cTn assays. Apple sits on the board of directors for Hytest, and on an advisory board for Siemens and Instrumentation Laboratory.

Jaffe has consulted for multiple diagnostic companies that make hs-cTn assays.

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Plasma ACTH: Tales of Diagnostic Misadventure and The Path Forward

Considering the different medical management pathways associated with concentrations of this hormone, providing physicians accurate results is critical

BY ZAHRA SHAJANI-YI, PHD, DABCC, FAACC, NRCC-CC, AND MARI L. DEMARCO, PHD, DABCC, FAACC, FCACB

A DIAGNOSTIC CONUNDRUM

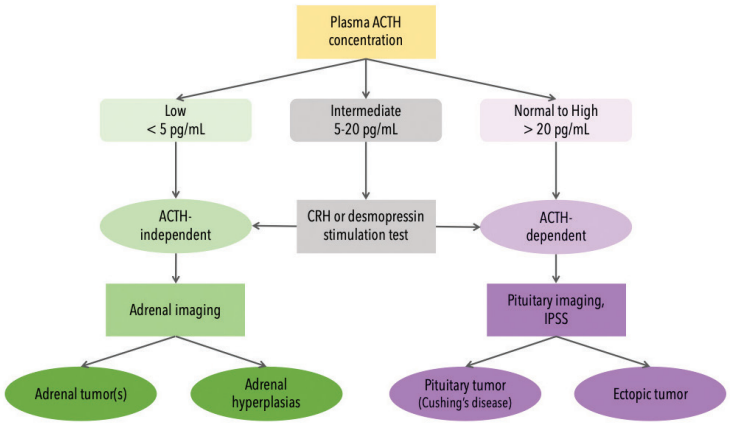
A 74-year-old women was referred to an endocrinologist to assess her for probable Cushing's syndrome. Measurement of the patient's morning serum cortisol and salivary cortisol (elevated), combined with typical signs and symptoms, helped the clinician confirm that she had Cushing's syndrome. To further assess the source of the elevated cortisol, the physician ordered plasma adrenocorticotropic hormone (ACTH) testing. Repeated several times over the course of 3-months, using the Siemens Immulite ACTH assay, these results consistently fell within the assay's reference range (10–18 pg/mL, reference range 6–50 pg/mL). Imaging studies previously identified an adrenal mass (incidentally); however, based on the ACTH findings, additional imaging was undertaken to look for an ACTH-dependent cause, including a pituitary tumor. This second round of imaging did not reveal a pituitary mass. Having previously cared for a handful of patients in which the ACTH results did not fit with the patients' clinical picture, the endocrinologist was suspicious of the ACTH results and contacted the clinical lab to further examine this case. Based on the clinician's suspicion, the lab sent out the ACTH testing to a different lab, which used the Roche Elecsys ACTH assay. The plasma ACTH was undetectable by this alternate method.

Which ACTH results were correct? Did the ACTH results indicate ACTH-dependent or ACTH-independent cortisol secretion?

ACTH AND DISORDERS OF THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS

Plasma ACTH measurements have an essential role in diagnosing and managing patients with disorders of the HPA axis. These measurements help differentiate between primary adrenal insufficiency, characterized by an elevated concentration of ACTH, and secondary adrenal insufficiency, indicated by a low concentration of ACTH. Once a physician establishes a diagnosis of Cushing's syndrome, ACTH concentrations are critical in determining the underlying pathology, discriminating with excellent sensitivity and specificity between ACTH-dependent (pituitary or ectopic) and ACTH-independent (adrenal) forms (Figure 1). While plasma ACTH assays are neither standardized nor harmonized, generally speaking, ACTH concentrations less than 5 pg/mL are considered consistent with ACTH-independent Cushing's syndrome whereas values greater than 20 pg/mL are consistent with an ACTH-dependent cause (*1-2*). Concentrations that fall within the range of 5–20 pg/mL, or "gray zone", are less definitive but are commonly associated with ACTH-dependent causes (*1-2*). Given the divergent diagnostic interpretations associated within this narrow range of plasma ACTH concentrations, measurement precision and accuracy are critical.

F1 The Role of Plasma ACTH Measurement in Determining the Cause of Cushing's Syndrome



CRH, corticotropin-releasing hormone; IPSS, inferior petrosal sinus sampling

DIAGNOSTIC MISADVENTURES

In the case above, the endocrinologist, in consultation with the laboratory, relied on clinical acumen to adjudicate between the discrepant ACTH plasma results. With clinical findings pointing towards an ACTH-independent Cushing's syndrome, only the Roche results were consistent with this clinical picture. The initial ACTH analysis performed on the Siemens system led to numerous repeated laboratory tests, unnecessary pituitary imaging, and a delayed diagnosis of an adrenal adenoma. Fortunately, based on the endocrinologist's suspicion of an erroneous ACTH result and involvement of the clinical laboratory, unnecessary higher-risk procedures were avoided.

There are numerous other cases in the scientific literature detailing similar incidents where plasma ACTH was measured to clarify the etiology of disease and the result was discordant with the patient's clinical presentation (*3-7*). In these cases, re-analysis of plasma ACTH on an alternate platform indicated that the initial ACTH result was likely inaccurate, eventually resulting in a revision of the diagnosis (*3-7*). Moreover, these cases highlight the impact on patients ranging from unnecessary additional routine lab tests to costly imaging and invasive testing such as inferior petrosal sinus sampling, and even to surgery (*3-7*).

As an example, in a case of a 21-year-old woman with consistently elevated plasma ACTH via the Siemens Immulite assay, the elevated ACTH finding led both physician and patient on a diagnostic misadventure that ultimately resulted in this young woman undergoing pituitary surgery (*7*). This surgery turned out to have been unnecessary; extensive investigations including ACTH analysis using alternate methods revealed that the patient had neither elevated plasma ACTH nor Cushing's syndrome (*7*).

APPROACHES TO TROUBLESHOOTING ACTH IMMUNOASSAY RESULTS

After ruling out pre-analytical issues, the first steps in investigating cases of suspected spurious immunoassay results generally include repeat analysis, including repeat analysis after sample dilution and use of heterophile blocking reagents, and testing on an alternate platform. In a majority of cases in the literature, investigations of potential heterophile antibody interference in ACTH immunoassays rarely yielded informative findings, which begged the question: What exactly are the ACTH assays actually measuring?

In clinical ACTH sandwich immunoassays, the signal is proportional to the concentration of ACTH in the sample. For the sandwich, the assay's capture and detection antibodies bind two epitopes (or the immunogen sequence if using polyclonal antibodies) on ACTH. An immunoassay's design can create different susceptibilities and potential sources of interference, that is, 1-step v. 2-step, use of monoclonal and/or polyclonal antibodies, antibody sequence (species), and epitope locations on the analyte, among other considerations. ACTH assays are not harmonized, with no available reference material or reference method to assist in such an endeavor. While modest biases exist between different assays, the discrepancies noted in the published cases and outliers from our own method comparisons exceeded the expected bias between methods.

When a physician orders plasma ACTH, they expect that the result will reflect the concentration of biologically

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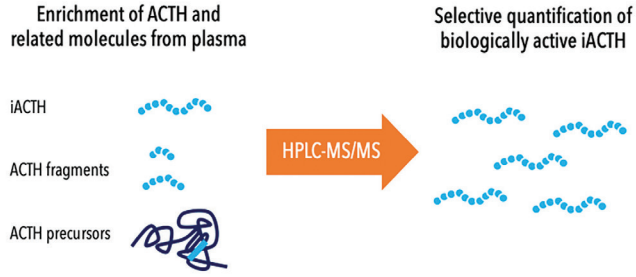
active intact ACTH (iACTH), a 39-residue peptide. ACTH is derived from precursor proteins, pro-opiomelanocortin (POMC) and pro-ACTH. ACTH can be further cleaved by endogenous proteases in tissues to form an N-terminal biologically active fragment, α-melanocyte-stimulating hormone (aMSH, comprising residues 1–13) and a C-terminal fragment termed corticotropin-like intermediate peptide (CLIP, residues 18–39). N-terminal residues 1–24 of ACTH are sufficient for biological activity and thus provocative testing to stimulate the release of cortisol by the adrenal glands uses synthetic polypeptides from this region (cosyntropin/Synacthen). These synthetic analogues, as well as endogenous ACTH fragments and precursors, can result in falsely elevated or falsely decreased ACTH results when measured by immunoassay, and the nature of the interference (positive or negative) can vary by assay for the same interferent (*8*).

SELECTIVE MEASUREMENT OF BIOLOGICALLY ACTIVE, INTACT ACTH

To overcome challenges associated with ACTH immunoassays, we developed a high performance liquid chromatograph mass spectrometry (HPLC-MS/MS) assay to quantify iACTH (*8*). Using HPLC-MS/MS enabled us to selectively detect and quantify various forms of ACTH, most critically the biologically active iACTH (Figure 2). This HPLC-MS/MS assay also enabled us to side-step interferences common to immunoassays including heterophile antibody interference and interference from closely related molecular isoforms—in this case ACTH precursors and fragments. After identifying several cases with discrepant ACTH results as measured on the two immunoassays most commonly used in North America (Roche Elecsys and Siemens Immulite)(*8*), we used the iACTH HPLC-MS/MS assay to help us answer the question: Which, if any, immunoassay result reflects the concentration of iACTH in a patient's plasma sample? Consistent with the previously published literature correlating ACTH assay results with clinical findings, in our series of cases only the Roche assay results were highly positively correlated with the iACTH concentration determined by HPLC-MS/MS (*8*). In turn, these results indicate the Siemens Immulite was measuring something other than the intended measurand.

F2 Selective Quantification of Biologically Active Intact ACTH by HPLC-MS/MS



TROUBLESHOOTING ADVICE AND FUTURE PROSPECTS

When investigating potential causes for assay interferences, laboratorians typically start by repeating analysis using the same assay, followed by dilution studies and the use of heterophile block tubes. Testing on an alternate platform often involves sending out the samples and for this reason is usually one of the last steps. Based on the current available data and our experiences, we recommend that labs investigating an ACTH result prioritize troubleshooting via an alternate assay. This prioritization is driven in part by the limited volume often available for alternate/repeat testing; unlike the majority of analytes, ACTH requires special preanalytical conditions (collection into a chilled tube and frozen immediately prior to analysis) due to rapid proteolytic degradation. The literature supports this approach, indicating that for ACTH, testing for antibody-mediated interference is often uninformative. We also recommend making multiple aliquots (as is reasonable with the volume of plasma remaining), freezing them at -70 C and thawing an aliquot immediately before use when troubleshooting.

Although this is the simplest troubleshooting strategy currently accessible to most laboratories, we have found MS to be the only tool capable of providing empirical evidence of the true iACTH concentration when ACTH results and the clinical picture are discrepant. Development of the iACTH HPLC-MS/MS assay also highlighted the need for a commutable ACTH reference material to support harmonization of ACTH immunoassays and future standardization efforts. Currently, we use the iACTH HPLC-MS/MS assay in our ongoing investigations to determine the specific cause(s) of the observed interference in ACTH immunoassays, with the aim of facilitating analytical improvements in contemporary ACTH immunoassays.

ROLE OF CLINICAL CHEMISTS

One of the ongoing responsibilities for clinical chemists is being proactive in engaging our physician colleagues regarding any factors that could affect how they interpret test results. It can be difficult for a laboratorian to recognize a spurious ACTH result because doing so requires correlation with a patient's complete clinical picture, information which might not be readily accessible. Similarly, physicians might have difficulty deviating from management plans informed by the ACTH result, based on perceived confidence in the lab result (*7*). As such, it is critical to increase awareness of the issue from the perspective of both the physician and clinical laboratorian. In our experiences, we have found success

by engaging with these communities via grand rounds, case conferences, laboratory-focused didactics, and conference presentations.

Ultimately, laboratorians, physicians and assay manufacturer share the same goal: improving the quality of care for our patients.

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Understanding and Improving SYPHILIS

Before implementing a particular algorithm, clinical laboratories need to carefully weigh factors such as their population, instrumentation, and clinicians' understanding of the tests

Syphilis, a chronic bacterial infection caused by the spirochete *Treponema pallidum*, is a sexually transmitted infection (STI). However, syphilis also can be acquired through vertical (mother-to-child) transmission, and congenital syphilis continues to be a global cause of infant mortality. Syphilis has been stigmatized for hundreds of years, and its varying presentations and stages have historically often made this formidable contagion difficult to recognize and diagnose.

Syphilis has early and late stages. Early stages occur within the first year following infection and late stages at greater than 1 year from infection. Early stages include primary (chancre), which if untreated will progress to secondary (rash) syphilis. These two stages are the most contagious. Early latent syphilis is asymptomatic but acquired within the last year and is considered an early stage of syphilis. Late stages occur if syphilis remains untreated and include latent syphilis (asymptomatic) and the symptomatic tertiary syphilis.

Today standard clinical laboratory testing detects syphilis easily, and the infection when detected at an early stage is, generally speaking,

SCREENING

BY SARAH WHEELER, PHD, FAACC

easily treated with penicillin. Yet syphilis infections are rising. The U.S. experienced a more than four-fold increase in the incidence of primary and secondary syphilis cases between 2000 and 2017. This increase occurred disproportionately among sexual and racial minorities, including men who have sex with men (MSM) and Black men (*1*). Among MSM, approximately 50% of syphilis cases have HIV coinfection (*2*). 2016 data from Europe mirror these statistics (*3*).

The U.S. has seen increases in congenital syphilis cases in more recent years owing to increased incidence among females, a trend not observed in the European Union (*1*). Congenital syphilis is of particular concern as it leads to increased rates of miscarriage, stillbirth, and significant birth defects that might not be evident until early childhood or adulthood (*4*). The best treatment for congenital syphilis is prevention by detecting and treating the infection in women early in their disease course.

Only with thorough and effective screening can syphilis be treated and its spread mitigated. Clinical laboratories play a key role in reducing the burden of syphilis through early diagnosis, improved prenatal screening, and enhanced testing availability to all populations.

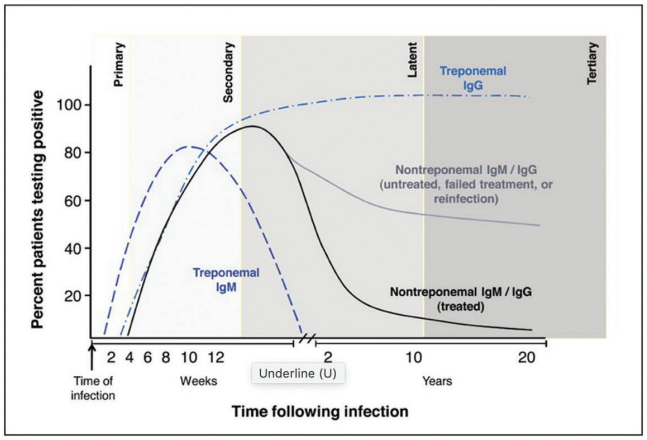
LABORATORY SCREENING FOR SYPHILIS

Most laboratories offer serologic detection of syphilis. Unfortunately, the assays and their interpretation are complex and often misunderstood by physicians and patients. Because no one single test definitively diagnoses untreated syphilis, laboratories rely on testing algorithms. Importantly, the appropriateness of each test sequence can vary based on the laboratory and population.

Serologic assays for syphilis diagnosis fall into two categories: non-treponemal and treponemal (Figure 1). Nontreponemal assays date to 1906, when August Paul von Wassermann in Germany described the first serologic test for syphilis based on complement fixation, later termed the Wassermann test or Wassermann reaction. This test was the basis for refinements that led to the Venereal Disease Research Laboratory (VDRL) test and the Rapid Plasma Reagin (RPR) test.

Nontreponemal assays assess antibodies against antigens released during the cellular damage caused by syphilis infection or released by the treponemes. VDRL assays utilize cardiolipin- and lecithin-coated cholesterol particles as antigens which, when bound with antibodies in the serum, are measured via microscopic agglutination. RPR assesses macroscopic agglutination of cardiolipin-coated particles following binding with serum antibodies. Efforts to standardize the VDRL and RPR assays have led to the use of synthetic antigens for antibody detection, which have replaced the cardiolipin and lecithin that were previously derived from animal tissues with varying purity.

F1 Syphilis Staging and Serology



From Soreng K, Levy R, Fakile Y. Serologic testing for syphilis: Benefits and challenges of a reverse algorithm. Clin Microbiol News 2014;36:195-202.

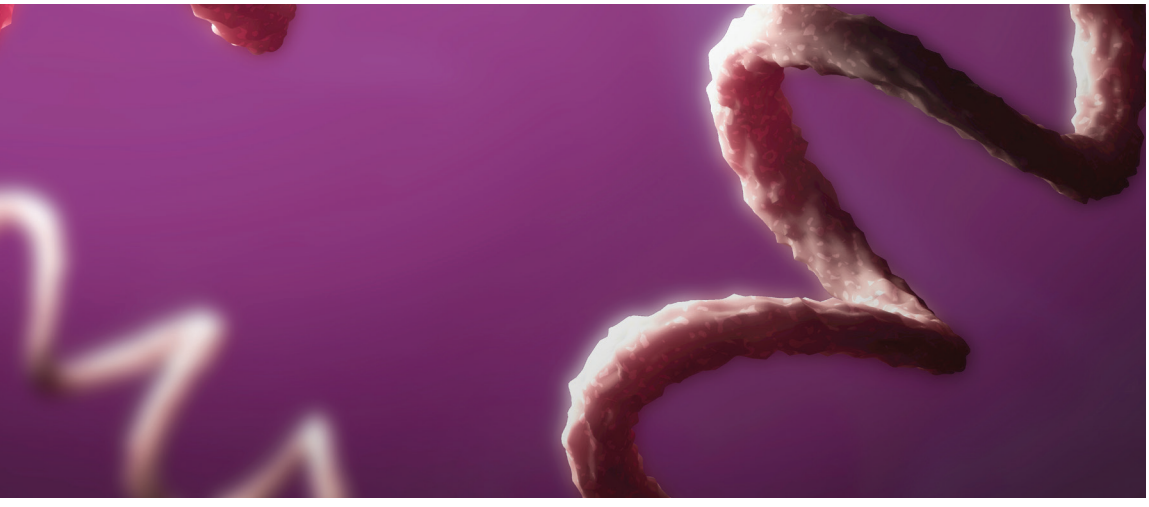
As indirect markers of infection, an important caveat to nontreponemal assays is that other pathophysiological conditions unrelated to syphilis can induce the antibodies they detect. Laboratories refer to these nonsyphilis positive VDRL/RPR tests as biological false positives. Biological false positives are common in autoimmune diseases, chronic liver disease, following acute febrile illness, or during pregnancy.

Despite this nonspecificity, nontreponemal tests remain valuable in assessing active disease because they are semi-quantitative, with results reported as a titer of antibody. This generally is thought to reflect the amount of antibody present and may correlate with the activity of the infection. Titers of nontreponemal antibodies usually fall following successful penicillin treatment for syphilis infection. However, as many as 20% of cases might not see a full decline in titers to seroreversion. These patients, referred to as serofast, do not lose their nontreponemal antibody response even after presumably effective treatment.

Significantly, nontreponemal titers tend to wane over time even without treatment, making these assays of limited clinical utility in later disease stages. The ability to monitor treatment efficacy in earlier disease stages makes these nontreponemal tests of important utility in syphilis treatment regimes.

Treponemal assays, on the other hand, are more specific and detect antibodies against the antigens specifically associated with *T. pallidum*. Treponemal tests are qualitative and do not provide titer information. They are usually reactive earlier than nontreponemal assays and will often remain positive for the rest of a patient's life, even after successful treatment.

The most common treponemal assays are *T. pallidum* enzyme and chemiluminescent immunoassays, which can be specific for immunoglobulin (Ig) G or detect both IgG and IgM. Three manual treponemal



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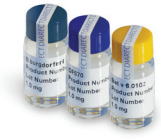

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assays—*T. pallidum* particle agglutination assays (TPPA), microhemagglutination test for antibodies to *T. pallidum* (MHA-TP), and fluorescent treponemal antibody absorbed test (FTA-ABS)—have been in use for decades.

TPPA and automated treponemal assays have surpassed FTA-ABS and MHA-TP in sensitivity and specificity, leading to a decline in the use of FTA-ABS and MHA-TP (5). TPPA is still generally considered the most specific of the treponemal assays, though there is a paucity of information in newer automated assays compared to TPPA (5).

Conventional treponemal tests initially used whole organisms to generate the tests, causing nonspecificity thought to be related to antibodies against commensal microorganisms. Newer specific recombinant proteins and polypeptides have mostly replaced this approach, improving both the sensitivity and specificity of enzyme and chemiluminescent immunoassays.

Due to the unique characteristics of nontreponemal and treponemal assays, laboratories use both for diagnosis of active syphilis infection. A reactive nontreponemal assay might not be due to syphilis specifically, and a reactive treponemal assay might be indicative of past treated infection. The limitations of each assay pose added complexity to this diagnosis for some patients.

Use of the assays also has changed over time. Historically nontreponemal assays were inexpensive and quick, making them a standard first-line screen, followed by treponemal assays when the screen was positive. In more recent decades, the introduction of automated treponemal assays has provided a workflow and often a cost advantage compared to the manual process for nontreponemal assays. Now, the automation of nontreponemal tests (primarily RPR) has inspired debate around the most effective testing algorithm for syphilis screening.

SCREENING ALGORITHMS

In the U.S., the Centers for Disease Control and Prevention (CDC) has two accepted algorithms: the traditional (or forward) and the reverse algorithm. The traditional algorithm calls for a nontreponemal assay to screen patients, with positive screens followed by a treponemal assay to confirm that the positivity is due to syphilis.

With automated treponemal assays came the reverse algorithm that screens patients with a treponemal assay. In this algorithm, positives are assessed for active disease by a nontreponemal assay; discrepancies between the two assays are resolved by an orthogonal treponemal assay in case of false positivity on the first treponemal screen.

The 2014 European guideline on the management of syphilis provides three possible algorithms. The first is the same as the CDC traditional (forward) algorithm. The second involves a variation on the CDC reverse algorithm, with a recommendation that reactivity in the first treponemal assay be confirmed with a second treponemal assay. The third is a combined initial testing of treponemal and nontreponemal assays.

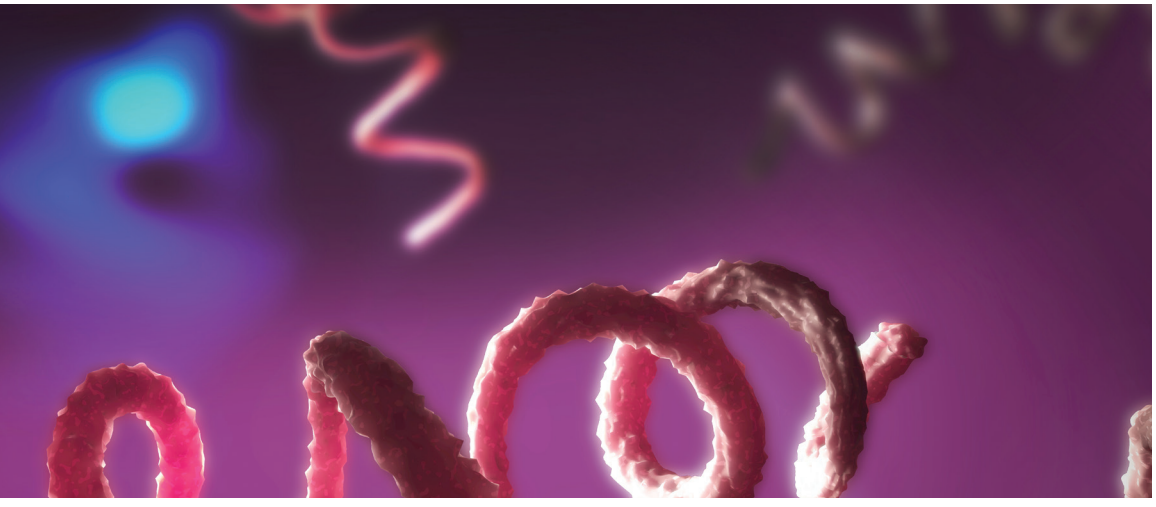
Which algorithm is best? It depends. As a laboratory assesses possible algorithm implementation, the advantages and limitations of each algorithm are important to consider.

Forward testing, that is, starting with a nontreponemal test, has allowed laboratories to perform an inexpensive and comparatively rapid test before confirming positive samples with a more time-intensive and expensive treponemal test. Nontreponemal screening is unlikely to detect early, latent, or treated syphilis cases, as these often do not have nontreponemal reactivity. Laboratories using an IgG specific treponemal test might find that some patients are reactive by nontreponemal testing before treponemal testing due to the inclusion of IgM detection in the nontreponemal tests.

In laboratories and low-resource settings that lack automated testing, nontreponemal tests remain a mainstay of first line testing. Use of the forward algorithm also requires that labs perform only two tests, compared to the three tests needed for CDC's reverse algorithm.

The CDC and European Centre for Disease Prevention and Control (ECDC) reverse algorithms appear to have similar sensitivity, specificity, and accuracy (6). Despite the similarity in detection, the ECDC algorithm notably does not provide a distinction between active and treated or latent disease. This can be problematic for test reporting, as most countries report primary and secondary syphilis rates with laboratory testing being a key component of this determination (7).

There has been concern about increased false-positive results when using reverse-testing algorithms in low prevalence populations. However, with the advent of treponemal testing utilizing recombinant proteins and automated methodologies, the sensitivity and specificity appears to have improved and these assays



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T1 Interpretive Reporting Example*

Syphilis Total	RPR	TPPA	Interpretation
Neg	Neg	NA	None
Pos	Pos	NA	None
Pos or Equivocal	Neg	Neg	The patient had a positive syphilis screen (antibody to *T. pallidum*) and a negative RPR. The syphilis screen was further evaluated by a second test for antibody to *T. pallidum* (TPPA). The TPPA test was negative, therefore the positive syphilis screen was likely a false positive. Clinical correlation is required.
Pos or Equivocal	Neg	Pos	The patient had a positive syphilis screen (antibody to *T. pallidum*) and a negative RPR. The syphilis screen was further evaluated by a second test for antibody to *T. pallidum* (TPPA). The TPPA test was positive. This may represent an adequately treated case, early primary syphilis, late latent, or late syphilis. If primary syphilis is suspected repeat the test in 2 weeks (and if the RPR is reactive, active syphilis infection should be considered) or empirically treat. Clinical correlation is required.
Neg	Pos	Neg	Reaginic antibodies (false positive RPR results) can be encountered in some infectious diseases (chickenpox, infectious mononucleosis, leprosy, hepatitis A, malaria, measles, tuberculosis), autoimmune diseases (the antiphospholipid antibody syndrome, lupus erythematosus) and, occasionally, pregnancy and narcotic addiction. Clinical correlation is required.
Neg	Pos	Pos	The patient had a negative syphilis screen (antibody to *T. pallidum*) and a positive RPR (Rapid Plasma Reagin). The sample was further evaluated by a second test for antibody to *T. pallidum* (TP-PA). The TP-PA test was positive. Thus, untreated or treated syphilis should be considered. Clinical correlation is required.

*From Eric Statz, William J Wertz, Bradley J Wheeler, et al. New syphilis serology testing requires new reporting algorithms. J Appl Lab Med 2020;5:601-4.

are clinically useful for these testing algorithms (*5*).

Due to the large number of automated treponemal tests and the relatively short time that many have been on the market—as compared to the decades of experience with VDRL and RPR by a limited number of manufacturers—there is variability in the reports about increased false positivity in the reverse algorithm (*5*,*6*,*8*,*9*). In this article, the term false positives refers to patients never exposed to syphilis, but some papers in the literature consider past treated syphilis positivity in the screening algorithm to be a false positive as it requires no intervention.

The variability in the literature likely reflects population and assay manufacturer differences. This is one reason for there not yet being a clear answer on which algorithm is best. Laboratories already performing syphilis testing might find a retrospective data review informative in assessing algorithm changes or in implementing additional testing.

Apart from standard screening algorithms, laboratories serving hospitals with labor and delivery or pediatrics populations should consider congenital syphilis testing as well, as it presents unique testing challenges. For example, maternal treponemal and nontreponemal IgG antibodies will pass to the fetus. Serologic testing in the mother is immensely important, and early prenatal detection of syphilis and appropriate treatment is the best way to improve infant outcomes.

CDC recommends only nontreponemal tests for detection of congenital syphilis. Ideally a laboratory would draw a paired specimen from mother and baby and run the samples on the same assay to obtain nontreponemal titers. An infant with a nontreponemal titer fourfold higher than the mother's is considered proven or highly likely to have congenital syphilis, though lack of this finding does not exclude congenital syphilis. CDC does not recommend cord blood testing for syphilis due to maternal blood contamination, and Wharton's jelly

within the umbilical cord is known to cause false-negative results.

MULTIPLEX TESTING: A CASE STUDY

When we at the University of Pittsburgh Medical Center implemented a new multiplex test that allowed for simultaneous assaying of treponemal and nontreponemal antibodies, we assessed how physicians used this testing to determine if a reverse or dual-reporting algorithm would be best. In our chart review we found many questions and misinterpretations of syphilis testing in the reverse algorithm.

For example, patients with a positive treponemal IgG and TPPA and a negative RPR were referred for infectious diseases consults as syphilis positive despite a documented history of treated syphilis years earlier. Meanwhile, for patients with a negative treponemal IgG screen, clinicians subsequently ordered an RPR (inappropriately) that was positive in the setting of active autoimmune processes, requiring further testing and psychological stress. Adding to the confusion, syphilis and other STI testing had recently been converted from a test that required physician review and approval before being sent to the patient portal to an auto-sent test, available within hours of the laboratory resulting the testing.

After discussions with infectious diseases colleagues and assessing the current state of testing, we decided to proceed with dual reporting of total

treponemal antibodies and RPR to be followed by batched TPPA when treponemal and nontreponemal results were discrepant. When we implemented dual reporting, we decided to provide interpretive comments to physicians, and by extension, to patients to lower the confusion that these tests can create. We created the interpretive comments in collaboration with the infectious diseases physicians we serve.

We then performed a retrospective review of the first 3 months of testing to determine the efficacy of our testing algorithm (n=4558) (*10*). We found a low prevalence, 0.4%, of active syphilis and a 1.1% prevalence of treated syphilis. We also chart-reviewed positive screens to help identify false-positive screens as well as early/latent disease.

The dual screening identified five cases of early/latent disease (0.1%) that the forward algorithm would have missed but the reverse or dual algorithms would have identified. We found a false positivity rate in total treponemal testing of 0.26%—0.1% in TPPA and 3% in RPR. Our population has a high number of prenatal screens and autoimmune diseases, both of which are more likely to have biological false positives in the RPR screen, a tendency we observed.

In our institution the dual screen has increased the number of TPPA confirmations we perform, but our physicians prefer having the information from both treponemal and nontreponemal testing. We maintained physicians' ability to order RPR independent of the syphilis screen to allow for congenital syphilis testing as well as disease treatment management. The most important gain, however, has been in providing interpretive comments (Table 1). Both physicians and patients have benefited from the line or two of interpretation included to help clarify results.

IDEAS FOR CLINICAL LABORATORIES

To determine the best algorithm, clinical laboratorians need to assess the technical capabilities of their laboratories, collaborate with infectious diseases colleagues, and review the populations they serve. Interpretive comments will significantly benefit both physicians and patients regardless of the algorithm implemented, particularly as many patients now receive their laboratory test results immediately via secure patient portals. Interpretive comments are also an opportunity to engage with infectious diseases colleagues to improve patient care and population health.

As syphilis rates continue to increase and enable the spread of HIV, it is vital that laboratories take a proactive role in improving syphilis screening to facilitate early detection and intervention.

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BY ELIZABETH WEINZERL, MD

So Many Choices: Selecting Reference Labs Using a Standard Process

LABORATORY STEWARDSHIP FOCUS

Genetic testing is increasingly coming into the mainstream, with genetic and genomic testing now available for thousands of genetic conditions. Many hospital laboratories send out genetic tests to reference laboratories, often at considerable cost.

Numerous publications have demonstrated that specific lab stewardship measures can reduce this burden and simultaneously improve patient care (*1*,*2*). These interventions include reviewing all genetic orders over a certain monetary threshold, using electronic clinical decision support tools, and restricting send-out labs to a select few. We found at our institution that careful preparation and analysis will give us the opportunity to significantly reduce the number of reference laboratories we use while maintaining the quality that clinicians and patients depend on.

Mapping the Problem

Our pediatric hospital system consists of three hospitals and 10 outpatient draw stations throughout the community, and our send-out volume has risen to nearly 100,000 total tests per year. Although a molecular pathologist screens all miscellaneous testing costing more than $2,000, providers can still send testing to their personally preferred laboratories. As a result, our current lab policy includes 80 approved reference labs. Having 80 approved reference labs creates numerous complexities with ordering, result tracking, and financial reporting. It also prevents us from effectively contracting for lower rates.

To maximize value and consolidate our complex genetic testing as much as possible, our newly formed laboratory stewardship committee (LSC) embarked on a request for information (RFI) and subsequent request for proposal (RFP) initiative from 11 established labs performing germline genetic testing. The goal of the initiative was to limit the number of reference labs for genomic testing and to negotiate lab contracts to improve both quality and economy.

Surveying Clinicians

To garner information and provide an inclusive environment, we first surveyed multiple providers throughout the hospital system, focusing on the services with highest genomic testing volumes: neurology, hematology/oncology, cardiology, and medical genetics. We asked providers about their specific needs and preferences for genomic-based reference testing to identify the attributes of reference labs most desirable to the clinical teams. Sample questions included: "What are your top barriers in the ordering process of outpatient genetic testing?" and "What would be most important to you in a genetic lab formulary?"

From this survey, we gathered valuable information about attributes to prioritize in our search, such as the ability of a reference lab to handle testing preauthorization, as well as their overall quality of methodology.

TABLE 1. Distribution of Potential Points Across all Categories in Request for Information

Maximum Possible Ccore	Questions With 0 Point Weight	Questions With 1 Point Weight	Questions With 2 Point Weight	Questions With 3 Point Weight	Total Questions	Maximum Answer Points	Maximum Possible Score
Vendor Profile	0	13	0	1	14	3	48
Financial	0	17	0	0	17	3	51
Quality and Technical	0	17	3	2	22	4	116
Website	0	8	6	1	15	3	69
Customer Service	0	15	3	4	22	3	99
Billing	11	4	0	0	15	3	12
						Total	395

Designing a Quality Screen

We then embarked on an RFI as a quality screen across 11 pre-selected germline genetic testing labs, most of which our providers currently use. We asked each lab questions in the following categories: general vendor information, finance, quality and technical, website, customer service, and billing. Sample questions covered the minimum depth of sequencing the vendor performs for germline testing, and for clinical exomes, the minimum percent coverage of the clinical exome genes sequenced. We also asked whether the lab offered a website custom panel build ability with an appropriate search tool to build panels and whether they helped obtain preauthorization for testing.

Of the 11 labs given the RFI, one failed to respond by the deadline and was eliminated from further consideration. We evaluated the remaining 10 labs as follows. A group of four physicians on our LSC collectively gave each question a relative weight of 1–3, based on the importance of the question. We established this importance based on our own expertise, as well as using feedback from the clinical survey. Examples of high-weight questions included: What minimum depth of sequencing does the vendor perform for germline testing? Are current and compliant CPT codes listed clearly for each test? And, What method of interfacing is used?

We then assigned a grade for each question's response in a standardized process, with a value between 0 and 4, based on the response. We calculated the total score for each question by multiplying the weight by the grade. Table 1 demonstrates the total possible distribution of points across our scoring system.

Note that the billing category contained questions predominantly weighted as zero; this was done purposefully, so as to concentrate the RFI on quality and customer services issues, and to defer billing evaluation to the subsequent RFP.

Request for Proposal

Based on the results of the RFI, we eliminated from further consideration the five labs with the lowest total RFI scores and shared this information with our clinical colleagues in order to keep them engaged. We moved forward with an RFP for the top five scorers.

The RFP was largely geared toward financial and billing considerations, but also incorporated additional questions from our clinical colleagues. In addition, we compiled a list of the testing that we had previously sent to the bottom scorers and asked the top five labs whether they could perform such testing, and for what cost. Although we considered using a scoring system similar to the one we had used for the RFI, we realized after we received the results back that there were a clear top three out of the five finalists, and therefore we unanimously decided to opt out of further numerical analysis.

Next Steps and Complexities

Much of our progress in the later stages of this project, beginning with the RFP, has slowed considerably during the COVID-19 pandemic. Nonetheless we've pressed forward by focusing on incremental progress, rather than admitting defeat for non-COVID-19 initiatives. Currently, we are negotiating on pricing with our final three genomic reference labs, with the goal of redirecting the majority of our genetic test menu to these three labs.

Benefits of a Data-Driven Approach

Since the choice of genetics reference labs tends to be very subjective, a data-driven approach, such as using an RFI and RFP, provides an unbiased selection process that can be adopted organization-wide. To objectively determine value, such an evaluation should include a thorough investigation of testing quality, such as depth of sequencing and quality of reporting, customer service, and billing practices. Once a small number of labs has been selected based on this evaluation, testing can be redirected to these labs to the extent possible to minimize complexity, maximize cost savings, and streamline operations.

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LABORATORY STEWARDSHIP FOCUS


BY JULIE M. EGGINGTON, PHD, AND MEGAN E. GARLAPOW, PHD

Aligning Genetic and Genomic Test Reimbursement With Value of Tests

LABORATORY STEWARDSHIP FOCUS

Very small helms guide very large ships. Similarly, in vitro diagnostics account for only about 2.3% of healthcare expenditures in the U.S. but have an outsized influence on clinical decision-making (*1*). The enormous impact of diagnostics on patient health underscores the critical need to drive quality improvements with those who helm clinical genetic and genomic testing.

Unfortunately, test reimbursement is not well-aligned to promote accurate and useful genetic/genomic tests. Many health insurance companies, health systems, and employer benefit managers are unaware of the National Institutes of Health's warning that "most genetic tests today are not regulated, meaning that they go to market without any independent analysis to verify the claims of the seller… [T]here is no federal oversight of the clinical validity of most genetic tests" (*1*).

In the U.S., clinical genetic and genomic testing labs provide diagnostic, predictive, prognostic, and theragnostic tests with perceived clinical value—a perception is frequently untethered from reality. This means that many patients are inadvertently harmed when well-meaning clinicians use low-value and inaccurate tests in patient care.

Some genetic tests cannot detect the mutations clinicians assume they can, as was recently reported for a Cowden syndrome family (*2*). Others might too readily and with insufficient evidence classify genetic variants as clinically meaningful, a problem featured in a 2019 *Wall Street Journal* report about a child's ongoing diagnostic odyssey (*3*).

While most genetic/genomic test errors and deviations currently go undiscovered, published head-to-head comparison studies between labs often show low concordance, suggesting that fundamental technical issues plague the industry. Researchers at Vanderbilt undertook one such study, showing in 2016 only a 10% concordance in variant detection/classification on 63 persons with interesting genetic variants in only two cardiac genes when samples were tested at three different accredited laboratories (*4*).

T1 Consequences of Errors in Genetic and Genomic Tests' Technical Accuracy

Adherence to personnel and laboratory protocol can drift, often without laboratory/medical directors' awareness. Clinicians can ask a laboratory about the qualifications of lab personnel, and whether director(s) are appropriately focused or are spread across too many laboratories or tests, but but this type of interrogation ought not be necessary as the highest standards should be followed when the stakes are as high as human health.

Test ordering, sample tracking, and quality control encompass a large category in genetic/genomic testing. Approximately 5%–26% of genetic/genomic test orders are incorrect, and laboratories do not always have protocols in place to check for misorders (*6*). Also, mislabeling of samples and sample swap can happen within labs, and not all labs have robust quality control measures.

Analytical validation and bioinformatics are other key areas for technical accuracy. That an analytical validation approach has been peer-reviewed does not guarantee the approach is high quality. In fact, in an in silico "bake-off" assessing 10 different variant calling next-generation sequencing workflows in 2017, just 10 of 22 variants were correctly identified by all 10 workflows, and just three workflows correctly identified all 22 variants (*7*). Validation—and re-validation upon introduction of even minor modifications—is critical to supporting technical accuracy but is woefully adhered to, and labs often use third-party, unvalidated bioinformatic tools.

For tests requiring genetic variant classification, too many classification false positives, even within variants with two stars or more in ClinVar, plague many labs (*8*). Automated classification via artificial intelligence software and/or blind adherence to the American College of Medical Genetics and Genomics 2015 guidelines without watching for edge cases can easily result in excessive false positives, the downstream consequences of which can be dire for patients and costly for the healthcare system.

Test report content and organization also contribute to technical accuracy issues. For example, the most important findings might not be clearly designated, and thus easily missed by clinicians, resulting in inappropriate patient care. Further, for sequencing tests that report on novel variants, laboratories often handle variants of uncertain significance (VUS) in different ways, which might not be obvious to the ordering provider. Some labs do not report VUS at all, while other labs effectively push VUS to Likely Benign with insufficient evidence to reduce VUS rates, since the prior probability of a VUS being pathogenic is often less than 10% in some syndromes (*9*).

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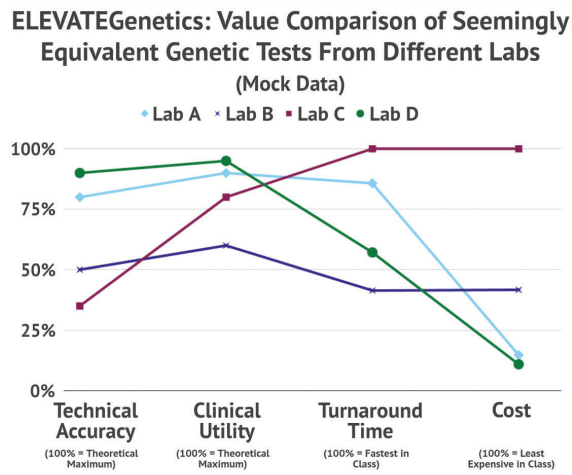

What Is Value?

With mounting examples of genetic/genomic test discordance and failures, key stakeholders have begun looking for solutions to evaluate test value. The formula for measuring value of in vitro diagnostics uses measurements of clinical utility, cost, turnaround time, and technical accuracy (5). Turnaround time and costs can be determined readily, while a growing array of vendors provide as a service different measurements of clinical utility. However, comparative and standardized metrics of technical accuracy have been lacking. While CLIA certification or accreditation from an organization such as the College of American Pathologists is necessary to maintain minimal standards for laboratories, the scope of these accreditations does not consider all the critical aspects of technical accuracy that are important for accurate diagnosis and patient care.

Technical Accuracy

In clinical genetics and genomics, five major categories affect technical accuracy. Each poses for test results its own strengths, errors, and obstacles. The five categories include:

1) personnel and laboratory accreditations;
2) test ordering, sample tracking, and quality control;
3) analytical validation and bioinformatics;
4) variant classification; and
5) test report content and organization.

Errors in any of these can have potentially devastating impacts on patients, including unnecessary surgeries, incorrect medications, misguided family planning decisions, or missed opportunities for early medical intervention. Table 1 offers several examples.

Quality Audits That Include Technical Accuracy

In conjunction with laboratory accreditation or test approval by the New York State Department of Health or the Food and Drug Administration, quality auditing can fill critical knowledge gaps for decisionmakers. The rapid evolution of the genetic/genomic diagnostic landscape outpaces accreditations and guidelines, which do not adequately address technical accuracy.

Therefore, the nonprofit and independent Center for Genomic Interpretation has developed a program that provides auditing services to stakeholders that includes technical accuracy, clinical utility, turnaround time, and cost measurements. This program, called ELEVATEGenetics (Figure 1), addresses the need for standardized and quantified metrics so that stakeholders—including consumers and insurers—have clear metrics by which to understand and compare the value of genetic and genomic tests.

Conclusion

As the clinical genetics and genomics industry continues to focus on making more clinically useful tests and aggressively solves technical accuracy problems, diagnostic value and downstream patient care will improve. We recommend that test accuracy and utility metrics be standardized and transparent, and that test reimbursement be tied to these metrics so that tests of higher value enjoy improved reimbursement rates.

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Regulatory Roundup

GenScript Gets FDA EUA for SARS-CoV-2 Neutralizing Antibody Test

The Food and Drug Administration (FDA) has granted emergency use authorization (EUA) to the first serology test that detects neutralizing antibodies from recent or prior SARS-CoV-2 infection. Developed by GenScript, the test is called the cPass SARS-CoV-2 Neutralization Antibody Detection kit. Neutralizing antibodies are those that have been observed in a laboratory setting to decrease SARS-CoV-2 viral infection of cells. FDA has previously issued EUAs for more than 50 antibody tests, but these other tests only detect the presence of binding antibodies, which target SARS-CoV-2 without necessarily decreasing the infection and destruction of host cells.

It's important to note that the effect of neutralizing antibodies for SARS-CoV-2 in humans is still being researched. The ability to detect these antibodies with GenScript's test could help researchers gain additional insight into what the existence of neutralizing antibodies tells us about a patient's potential immunity. However, FDA cautions patients against using the results from this test—or any serology test—as an indication that they can stop social distancing, wearing a mask, or other steps to protect themselves and others. Like other serology tests, GenScript's test also cannot be used to diagnose an active infection.

FDA RELEASES LIST OF ESSENTIAL MEDICINES AND MEDICAL COUNTERMEASURES

In response to an August 6, 2020 executive order, the Food and Drug Administration has identified and published a list of essential medicines, medical countermeasures, and critical inputs deemed medically necessary to have available at all times in an amount adequate to serve patient needs. This list includes diagnostic testing kits and supplies for rapid test development and processing, personal protective equipment, and devices for managing acute illnesses such as ventilators. The list also includes medicines that are most needed for patients in U.S. acute care medical facilities and active pharmaceutical ingredients of essential medicines and medical countermeasures. The executive order seeks to ensure sufficient and reliable long-term domestic production of these products, and to minimize potential shortages by reducing U.S. dependence on foreign manufacturers. The ultimate goal of this work is to ensure the American public is protected against outbreaks of emerging infectious diseases, such as COVID-19, as well as against any other potential public health emergencies.

FDA APPROVES NEW CLAIMS FOR ROCHE LUNG CANCER CO-DIAGNOSTIC

Roche has received Food and Drug Administration (FDA)

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approval of expanded claims for the cobas EGFR Mutation Test v2 as a companion diagnostic for a broad group of therapies used in the treatment of non-small cell lung cancer (NSCLC). The cobas EGFR Mutation Test v2 uses real-time polymerase chain reaction to qualitatively detect defined mutations of the epidermal growth factor receptor (EGFR) gene in NSCLC patients. It analyzes DNA isolated from formalin-fixed paraffin-embedded tumor tissue or circulating tumor DNA from plasma derived from EDTA anti-coagulated peripheral whole blood. This claim expansion allows clinical laboratories to use the test as a companion diagnostic for all five FDA-approved EGFR tyrosine kinase inhibitor (TKI) therapies targeting the *EGFR* mutation L858R and exon 19 deletions. The group claim will also enable labs to use the test as a companion diagnostic for any EGFR TKI therapies targeting the same mutations that might be approved in the future, without the need to conduct individual clinical studies with the test for each new therapy.

FOUNDATIONONE LIQUID CDX EARNS FDA APPROVAL FOR 4 NEW CO-DIAGNOSTIC INDICATIONS

The Food and Drug Administration (FDA) has approved Foundation Medicine's FoundationOne Liquid CDx test to help identify patients who might benefit from treatment with four FDA-approved targeted therapies. These new companion diagnostic indications are for Piqray (alpelisib), Rubraca (rucaparib), Alecensa (alectinib), and Lynparza (olaparib). Piqray is a kinase inhibitor from Novartis indicated for the treatment of postmenopausal women, and men, with hormone receptor-positive, human epidermal growth factor receptor 2-negative, *PIK3CA*-mutated advanced or metastatic breast cancer. Rubraca is Clovis Oncology's poly (ADP-ribose) polymerase inhibitor for the treatment of adult patients with a deleterious *BRCA* mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer. Alecensa is a tyrosine kinase inhibitor from Genentech indicated for the treatment of patients with anaplastic lymphoma kinase-positive metastatic non-small cell lung cancer. While Lynparza, which was developed by AstraZeneca and Merck, is approved for metastatic castration-resistant prostate cancer patients who carry mutations in homologous recombination repair genes.

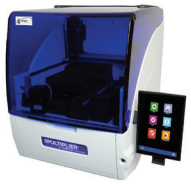
FUJIREBIO SUBMITS TEST FOR ALZHEIMER'S AMYLOID PLAQUES TO FDA FOR CLEARANCE

Fujirebio Diagnostics has filed for 510(k) premarket clearance with the Food and Drug Administration (FDA) for its Lumipulse G ß-Amyloid Ratio (1-42/1-40) test. FDA granted the test breakthrough device designation in February 2019, and Fujirebio expects it to be among the first commercially available in vitro diagnostic tests in the U.S. that aids in the assessment of Alzheimer's disease. The test is designed for use in adult patients age 50 years or older who present with signs of cognitive impairment. It runs on Fujirebio's fully automated Lumipulse G1200 instrument system and measures cerebral spinal fluid concentrations of ß-amyloid 1-42 and ß-amyloid 1-40, which are both major components of the amyloid plaques found in the brains of patients with Alzheimer's. The test then combines these measurements into a ratio of ß-amyloid 1-42 / ß-amyloid 1-40, which can be used to estimate the presence of amyloid pathology and to evaluate patients for Alzheimer's disease and other causes of cognitive decline.

CE MARK GRANTED TO ORTHO FOR TRANSFUSION LAB TESTING PLATFORM

Ortho Clinical Diagnostics has received the CE mark for the semiautomated Ortho Optix reader, an immunohematology platform designed for low- to mid-volume transfusion labs that can't afford to invest in the typical automated platform. When paired with the Ortho workstation, the Optix reader provides a complete semiautomated testing platform. Its high-resolution camera captures color, grayscale, and front and back images of each test without operator intervention, which provides objective data for automated results interpretation and eliminates the subjectivity and discrepancies of multiple operators reviewing images manually. Additionally, the Ortho Optix reader uses the same Ortho BioVue system column agglutination technology as the Ortho Vision analyzer, and features a comprehensive testing menu including antibody panels, selected cells, and dilution series.

AACC CLINICAL LAB EXPO PRODUCT SHOWCASE



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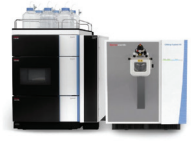

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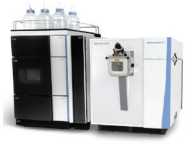

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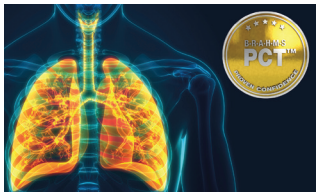

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New smooth-flow FP 150 expands the flow rate range of KNF low-pulse liquid pumps to 0.2-12.4 L/min. New gas pumps include NMP850 HP offering flow from 7-30 L/min with pressure >36 psig and vacuum down to 100 mbar abs. New NPK 06 is part the growing line of compact swing piston compressors now spanning 3-78 L/min flow with pressure to 80 psig.

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StatStrip® Glucose Hospital Meter System

The StatStrip Hospital Glucose System is the only glucose meter system cleared by the FDA for use with critically ill patients and CLIA-waived for use with ALL patients and ALL sample types. Testing critically ill patients with other glucose meters is an off-label use under FDA regulations.

Nova Biomedical Corporation

Stat Profile Prime Plus Critical Care Analyzer

Nova's Stat Profile Prime Plus is a comprehensive, point-of-care analyzer that measures 20 critical care tests including blood gases, electrolytes, metabolites, hematology, and co-oximetry, in a simple, compact device. Test menu: pH, PCO2, PO2, Na, K, Cl, iCa, iMg, Glu, Lac, Urea, Creat, Hct/Hb, SO2%, and Co-Ox.

Nova Biomedical Corporation

Thermo Fisher Scientific™ Amplitude™ Solution

The Amplitude Solution is a highly automated molecular diagnostic testing system that can analyze up to 8,000 COVID-19 specimens in 24 hours, helping laboratories quickly scale COVID-19 testing to volumes. This solution offers maximum throughput with minimal hands-on time, equipment, and staffing.

Thermo Fisher Scientific

Applied Biosystem™ TaqPath™ COVID-19 Combo Kit

The TaqPath™ COVID-19 Combo Kit is a fast, highly sensitive in vitro diagnostic solution that contains the assay and controls needed for the real-time PCR detection of RNA from SARS-CoV-2. It is a single, high-throughput kit for use with applied Biosystems real-time PCR instruments and COVID-19 Interpretive Software.

Thermo Fisher Scientific

BS-430

BS-430 is a perfect solution for the middle to high workload laboratories looking for a one-stop solution for routine chemistries and also COVID parameters

Shenzhen Mindray Bio-Medical Electronics Co., Ltd.

BS-600

BS-600 is a reliable chemistry solution for mid-end labs

BS-600 is a random access and fully automated chemistry analyzer, with throughput of 600 tests per hour for routine chemistry and up to 770 tests per hour including ISEs.

Shenzhen Mindray Bio-Medical Electronics Co., Ltd.

BS-800M

BS-800M is a reliable chemistry solution for mid-high-end labs

BS-800M is a random access and fully automated chemistry analyzer, with throughput of 800 tests per hour for routine chemistry and up to 1200 tests per hour including ISEs.

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CAL 6000

Mindray CAL 6000 defines a new generation of cellular analysis line, which supports flexible configurations with 1-2 units of BC-6000/ BC-6200 and 1 unit of SC-120, the throughput of CAL6000 is up to 220 blood test per hour and 120 slides per hour.

Shenzhen Mindray Bio-Medical Electronics Co., Ltd.

CAL 8000

CAL 8000 is Mindray's flagship cellular analysis automation system, which can integrate hematology analyzer, slide maker and stainer, CRP analyzer and HbA1c analyzer. It is flexible in configurations and can combine different testing modules depending on customer needs.

Shenzhen Mindray Bio-Medical Electronics Co., Ltd.

CL-1200i

CL-1200i Chemiluminescence Immunoassay Analyzer aims to fulfill the need of laboratories with small-to-medium daily test volumes, providing efficient design, robust performance and more importantly, reliable results.

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CL-6000i

CL-6000i Chemiluminescence Immunoassay Analyzer is an outstanding roof-top immunoassay analyzer with industrial-leading throughput as 480t/h, a perfect choice for laboratories with large daily test volume.

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Applied Biosystem™ TaqPath™ COVID-19, Flu A, Flu B Kit

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Thermo Fisher Scientific

Applied Biosystems™ TaqPath™ COVID-19 Pooling Kit

Detect the presence of SARS-CoV-2 in up to 5 samples simultaneously with the TaqPath™ COVID-19 Pooling Kit, a highly sensitive real-time PCR multiplex test that enables high throughput population testing and pathogen detection.

Thermo Fisher Scientific

Sysmex XF-1600 Flow Cytometer

The XF-1600 integrates a multilaser optical layout with Sysmex's proven fluidics design for reliable performance in a flow cytometer. It uses innovative technology and fluidics to provide high detection sensitivity. Like Sysmex's clinical testing platforms, the XF-1600 flow cytometer is backed by exceptional service and reliability.

Sysmex

Sysmex UN-Series Automated Urinalysis System

The Sysmex UN-Series provides an innovated workflow solution while offering scalable and customizable instrumentations to meet a variety of needs. Using fluorescent flow cytometry for quantitative results and digital images for particle identification allows for fewer manual microscopy reviews, leading to improved turnaround times.

Sysmex

Visby Medical COVID-19 Test

The instrument-free COVID-19 rapid PCR Test from Visby Medical is the diagnostic solution you have been waiting for. Lab-quality PCR testing from a single-use device that never goes down, requires no cleaning, no maintenance and no difficult-to-source cartridges. Results within 30 minutes empower your lab to make informed decisions in minutes and not days.

Visby Medical

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Industry Playbook

Companies Team for CRISPR-based SARS-CoV-2 Test

Mammoth Biosciences announced a partnership with MilliporeSigma and Hamilton Company to commercialize its CRISPR-based SARS-CoV-2 test. The three companies say their collective effort can help increase testing capacity as COVID-19 cases continue to spike across the globe.

The Detectre Boost SARS-CoV-2 assay is a nucleic acid test that uses CRISPR-based detection for high specificity and sensitivity. The companies plan for the test to use both nasal swab and saliva patient samples and run on Mammoth's Detectre Boost platform, which can run 1,500 tests in an 8-hour span with minimal user interaction. The test will be contract manufactured by MilliporeSigma and will include automated liquid handling equipment manufactured by Hamilton Company to increase sample processing.

"In order to begin reopening more aspects of society, we'll need a robust testing infrastructure that can rapidly scale up capacity as needed," said Trevor Martin, co-founder and CEO of Mammoth Biosciences. "By combining CRISPR-based diagnostics with the proven manufacturing and product leadership of MilliporeSigma and Hamilton Company, we're confident this solution will be a gamechanger for labs."

Production for the Detectre Boost SARS-CoV-2 test will take place in MilliporeSigma's Life Science Center in St. Louis and will be commercialized across the United States if approved by the Food and Drug Administration.

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CENTOGENE, FUJIREBIO PARTNER FOR RAPID ANTIGEN TESTING IN AIRPORTS

Centogene and Fujirebio Europe have partnered to advance rapid SARS-CoV-2 antigen testing in airports throughout Germany. Using Fujirebio's Lumipulse G SARS-CoV-2 test on the Lumipulse G automated system, Centogene—which has laboratory centers in several airports—will administer the test to passengers and send results to their digital devices in 40 minutes.

Fujirebio's Lumipulse G technology is a fully automated platform that can run 120 tests per hour. The Lumipulse G SARS-CoV-2 test is the first of its kind that uses a chemiluminescent platform. Currently, the SARS-CoV-2 test is being used by Japanese authorities to screen individuals when they return from travel. Through the deal, Centogene has partnered with Lufthansa airlines to provide testing for all passengers free of charge.

"With our test strategy, we are pursuing the goal of using the data obtained to collect important knowledge in dealing with antigen tests. We are convinced that it is the only right way to further expand the established test infrastructure at the airports." said Christoph Leffers, head of task force testing for Lufthansa Group.

RGC, UCLA ADVANCE IN WHOLE EXOME SEQUENCING RESEARCH

In an effort to advance personalized healthcare, UCLA Health and Regeneron Genetics Center (RGC) have teamed to provide whole exome sequencing for UCLA Health patients.

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Whole exome sequencing analyzes thousands of protein-coding genes which can help researchers pinpoint genetic abnormalities and potential changes in DNA sequences. UCLA will add on to RGC's existing genetic database that pairs the sequenced exomes with the private health records of more than 1 million patients from health centers across the world. Ultimately, the database is intended to enable analysis of genetic factors that can influence diseases.

With UCLA's healthcare expertise, the diversity of the health system's population, and RGC's genetic sequencing, the companies see a promising future for their work in genomic medicine.

"Genetic data that better represents the entirety of the human population will lead to better-informed treatment options for all people, which is why we continue to expand this unique drug discovery and development tool, while our collaborators utilize verified information in patients' daily care," said Aris Baras, MD, senior vice president and head of RGC.

UGENTEC AND MOLGEN MATE AI AND CHEMISTRY PLATFORM FOR SARS-COV-2 TEST

UgenTec and MolGen announced a collaboration for an end-to-end SARS-CoV-2 test that analyzes a patient sample and provides results in 90 minutes. The companies will combine UgenTec's artificial intelligence-based software platform, FastFinder, with MolGen's instrumentation and chemistry platform, PurePrep, to deliver a low-cost analysis with what the companies say will be highly accurate results.

Through MolGen's PurePrep program, the companies will be able to efficiently transport samples from testing tubes to plates, then use the automated PurePrep 96 system to extract RNA for testing. UgenTec's FastFinder platform will perform data analysis using its three leading products: FastFinder Analysis for interpreting data; FastFinder Workflow for sample and instrument tracking; and FastFinder Insights for monitoring metrics and instrument performance.

"As demand for testing is spiking, labs are under pressure to ramp up volumes with personnel under strain. More than ever, labs need rapid SARS-CoV-2 testing, but workflows that heavily rely on molecular biologists to manually call results just do not scale," said Steven Verhoeven, CEO of UgenTec.

Both companies intend to begin commercialization of the test in the Netherlands and hope to expand production in other geographical areas. The partners have also mentioned expanding testing workflows to include other infectious diseases and oncology assays.

LABCORP, BML, TEAM FOR COMPANION DIAGNOSTICS ADVANCES IN JAPAN

LabCorp, which is increasingly focused on developing and commercializing companion diagnostics, and Bio Medical Laboratories (BML), a clinical diagnostic testing firm, have signed an agreement to increase development and delivery of companion diagnostics in Japan.

The partnership builds on a previously established relationship between the companies. Through LabCorp's drug development business, Covance, BML, and LabCorp have collaborated on laboratory testing services for more than a decade and developed the Covance-BML Trial Laboratory to support drug development and clinical trials for pharmaceutical companies. The partners stated that they will begin developing clinical assays that target oncology and aim to expand commercialization of future assays through Covance.

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"Our combined ability to bridge the time gaps between the development phase and drug approval through to national reimbursement, along with the benefit of having a centralized laboratory testing facility, gives our respective customers the advantage of early adoption of their drug. BML's experience with local testing requirements, quality standards, and logistical expectations will ensure instant access to high-quality testing," said Kensuke Kondo, MD, president of BML.

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Ask The Expert

How the 2020 Election Could Impact Labs

EXPERT
Patricia Jones, PhD, DABCC, FACB

How could the election results affect the U.S. response to the COVID-19 pandemic?

A: With the election of former Vice-President Joe Biden, there may be a more coordinated, comprehensive federal approach to managing the COVID-19 pandemic. One of Biden's first acts as president-elect was to create an advisory board to develop a national plan for addressing the pandemic. To date, the incoming president has also stated that he plans to double the number of drive-through testing sites, mobilize 100,000 people to conduct more contact tracing, and use the Defense Production Act to increase the availability of much-needed supplies. In addition, he has urged the adoption of a national mask mandate to limit the spread of the coronavirus.

Now that the election is over, what does the U.S. government need to do to get the pandemic under control?

As COVID-19 cases surge to record highs, the demand for testing is also increasing, and while labs have the capacity to keep up with it, the supply chain as it stands does not. The federal government therefore needs to improve the coordination and distribution of laboratory testing supplies. While each state has a coordinator to distribute supplies to labs in need, few labs actually know about the existence of these coordinators or what supplies their states have in stock. In addition, the government also needs to find a way to help ramp up supply production in order to increase the number of available kits, reagents, and other materials that laboratories need to conduct SARS-CoV-2 tests.

Do you think we'll see any further changes with laboratory developed test (LDT) regulation?

The incoming administration is likely to be sympathetic to expanding Food and Drug Administration (FDA) oversight of LDTs, so I would not be surprised to see the agency attempt to expand its authority in this area. However, there is significant congressional opposition to such a move. Earlier this year, Senator Rand Paul (R-Ky.) introduced legislation, the Verified Innovative Testing in American Laboratories Act, which would codify the existing LDT regulatory approach under CLIA. AACC supports this measure. There is also a possibility that Senator Paul might become the next chair of the Senate Health, Education, Labor, and Pensions Committee—the panel that has jurisdiction over this issue—which might further limit congressional action in this area.

Are there other ways in which the election results could affect labs or the healthcare system?

With the Democrats controlling the White House and the House of Representatives, there might be renewed interest in increasing funding for the key health agencies, such as the National Institutes of Health, the Centers for Disease Control and Prevention (CDC), and FDA. Thus, patient safety might get renewed attention. President-elect Biden has also stated a desire to expand Medicaid and the Affordable Care Act to reduce the number of people without health insurance. On a narrower issue, Biden expressed support for eliminating surprise billing, which occurs when a patient receives a higher than anticipated charge because the provider was out-of-network.

What are the top concerns for AACC advocacy efforts moving forward?

AACC continues to focus its attention on improving pediatric reference intervals (PRI), harmonizing clinical laboratory test results, preserving patient access to LDTs, and reducing cuts in lab reimbursement set forth under the Protecting Access to Medicare Act. In 2020, AACC increased the number of organizations supporting the PRI initiative to 34 and brought the American Academy of Pediatrics on board. The association hopes to obtain federal funding for the PRI effort in 2022, as well as to increase the federal money allocated to CDC to harmonize test results. AACC will also continue to work with its allies to prevent duplicative regulation of LDTs by FDA and to identify a new payment methodology for determining a fairer reimbursement model for outpatient tests under Medicare.

Patricia Jones, PhD, DABCC, FACB, is chair of AACC's Policy and External Affairs Core Committee, a professor of pathology at University of Texas Southwestern Medical Center, and medical director of laboratories at Children's Medical Center in Dallas.
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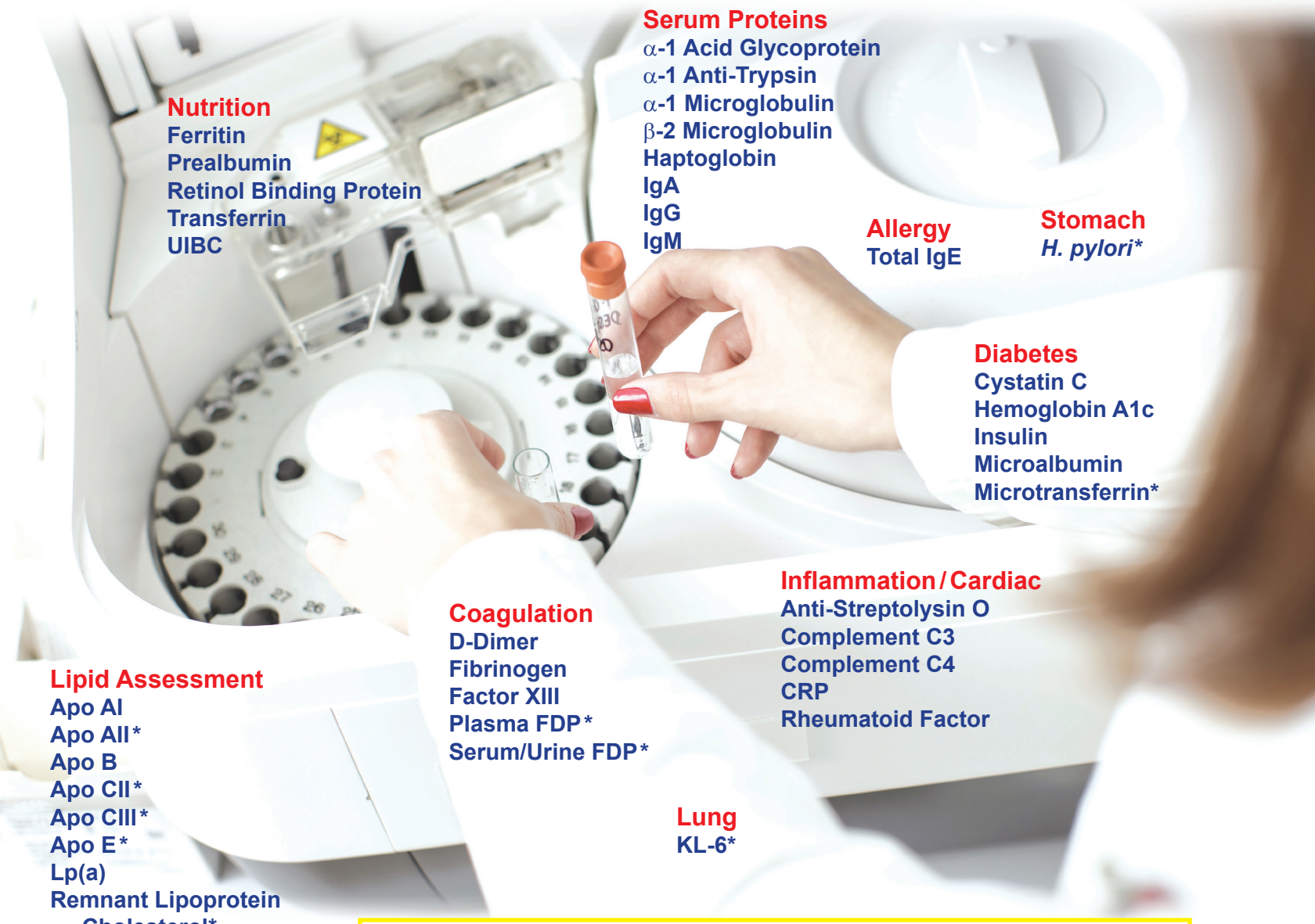

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