October 2018

CLN Clinical Laboratory News

An AACC Publication | Volume 44, Number 9

A THREE-TEST RISK SCORE FOR ACS

GLUCOSE < 100

EGFR ≥ 90

HS-CTNI < 4

Clinical Chemistry score for predicting ACS risk

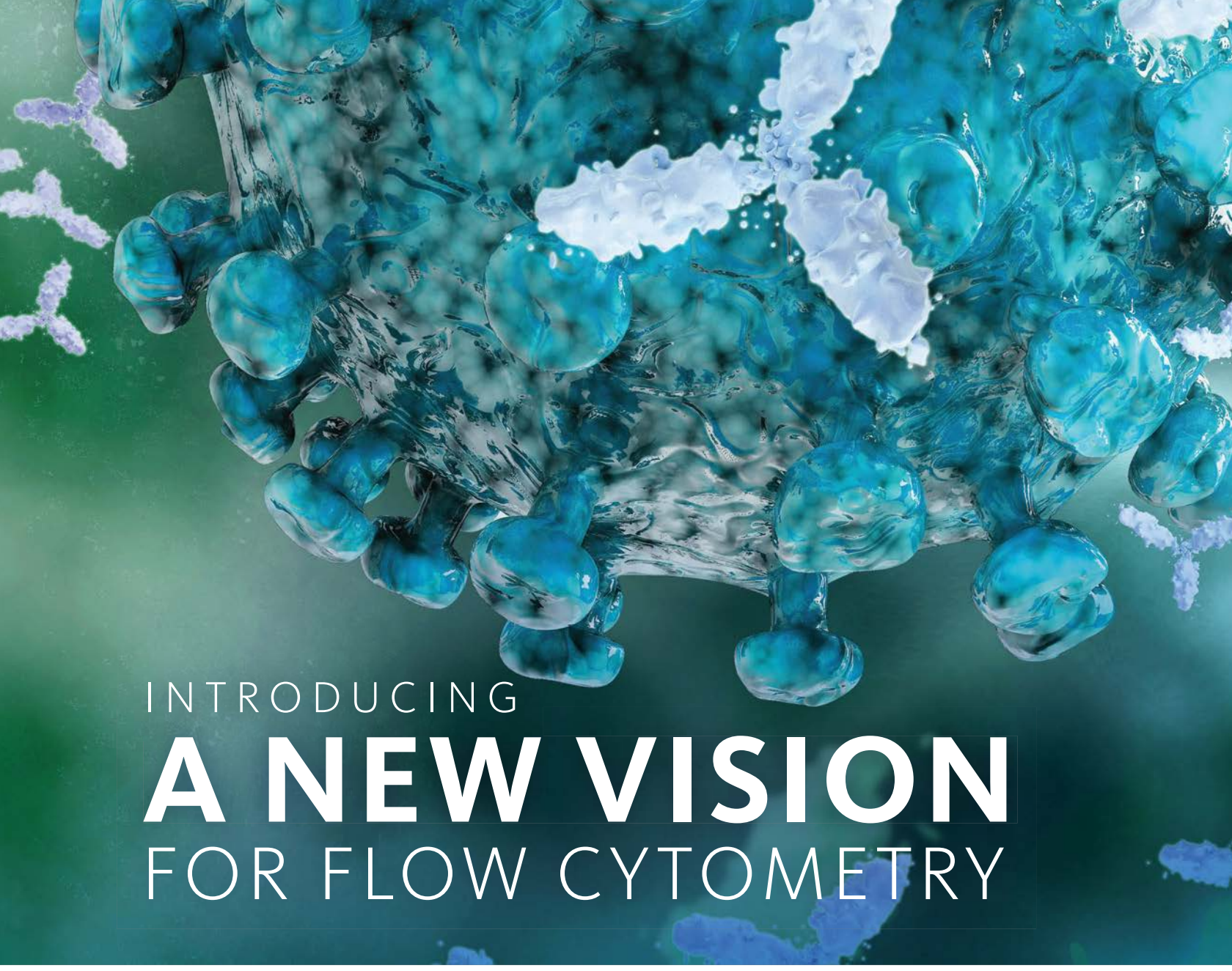
PAGE 8

PERFECTING GROWTH HORMONE MEASUREMENT

Turning Up the Heat on PCR

A Promising Kidney Biomarker

AACC Better health through laboratory medicine.



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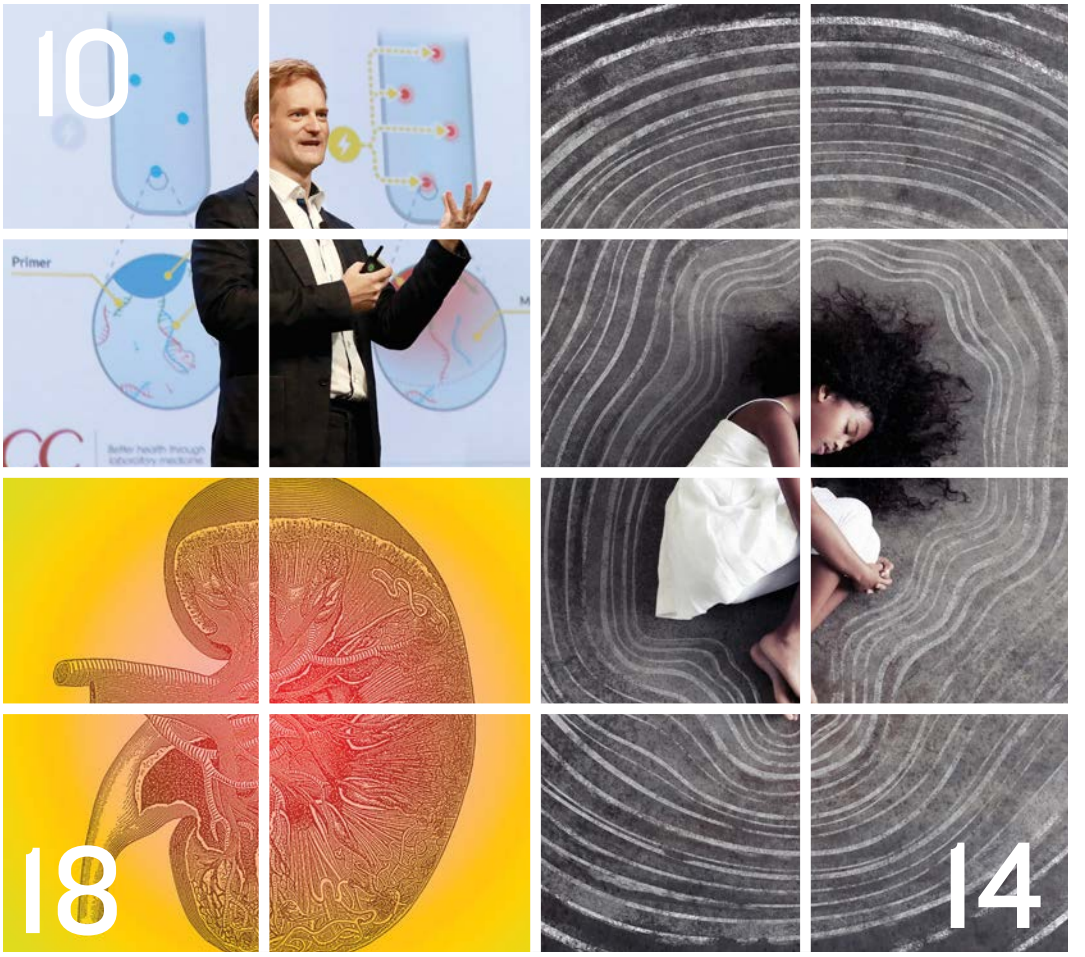

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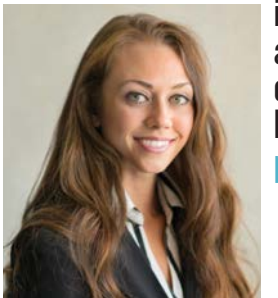

This is the first time CDC has received dedicated funding from Congress to improve the quality and reliability of diagnostic tests for hormones.
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Clinical Laboratory News (ISSN 0161-9640) is published monthly (11 times per year —Jan/Feb., March, April, May, June, July, Aug., Sept., Oct., Nov., and Dec.) by the American Association for Clinical Chemistry. 900 Seventh St., NW, Suite 400, Washington, DC 20001. Phone: +1 202.835.8756 or +1 800.892.1400 Fax: +1 202.833.4568.

Printing in the U.S.A. POSTMASTER: Send address changes to AACC, 900 Seventh St. NW, Suite 400, Washington, D.C. 20001.

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1 Palacio et al.: Meta-analysis of studies on biochemical marker tests for the diagnosis of premature rupture of membranes: comparison of performance indexes. BMC Pregnancy and Childbirth 2014 14:183

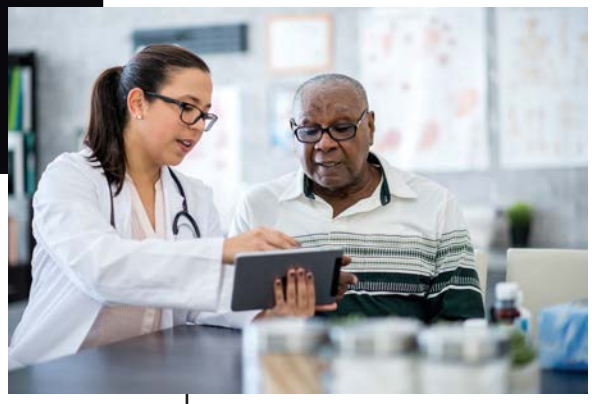
2 The test has been designed to minimize interference from bleeding, but in cases of heavy bleeding the blood locally may have a higher concentration of IGFBP-1 protein. In these cases, a positive result should be interpreted with caution. Actim PROM IFU.

Federal Insider

ACOs Find Success With Greater Incentives, Flexibility

A new breed of accountable care organizations (ACO) that allows groups of healthcare providers to share in both gains and losses from coordinating care under Medicare showed promising results in its first year, saving Medicare $62 million in 2016, about 1.7%. A Centers for Medicare and Medicaid Services (CMS) report on these next generation ACOs also found evidence of quality improvement. Beneficiaries had 1.3% fewer acute care hospital days per month, 1.5% fewer nonhospital visits per month, and 11.9% more annual wellness visits per year.

ACOs are groups of healthcare providers that agree to take responsibility for the total cost and quality of care for Medicare patients. In the new model, ACOs not only receive a portion of the savings they achieve versus benchmarks but also are responsible if they overspend.



"These results provide further evidence that ACOs succeed under two-sided risk," said CMS Administrator Seema Verma. "ACOs in the Next Generation Model are being held accountable with strong financial incentives and are provided with substantial flexibility and regulatory relief. They are delivering value and providing quality care to patients and taxpayers even in their first performance year."

One reason for the success of these ACOs may be a lighter touch on regulation, according to Verma. For example, traditional fee-for-service Medicare only allows telehealth in specially designated rural areas, but next generation ACOs can use telehealth anywhere. They also have greater flexibility under post-discharge home visit rules.

Verma plans to accelerate the pace at which providers can form ACOs and enter the two-sided risk model. The latest data show that, overall, 472 traditional and next-generation ACOs together cared for 9 million beneficiaries in 2017 for a total of $1.1 billion in savings compared to their benchmarks.

HHS PARTNERS WITH INDUSTRY FOR HOME FLU TESTS

The Department of Health and Human Services (HHS) will support development of two influenza A and B virus tests designed for over-the-counter sale. The agency's Biomedical Advanced Research and Development Authority (BARDA) will provide $14 million to Cue Health and $10 million to Diassess, with the option to extend additional funding of $30 million and $21.9 million, respectively, for developing home use tests that give results within 25 minutes.

"Empowering people to answer the basic question, 'Do I have the flu?' without leaving home could have a profound effect on controlling and treating influenza…," said BARDA director Rick Bright, PhD. "Putting that power in patients' hands could transform the speed and delivery of care. In a pandemic, that equates to lives saved and stronger national health security."

Both companies receiving grants will use mobile technology to enable patients who test positive to access telemedicine consultations and antiviral drug prescriptions from home. The companies are also working on a feature that will allow the devices to report de-identified flu data to local health departments in real time. Diassess expects its model to be disposable and battery-powered for use during public health emergencies. Cue Health is also developing tests for Zika and HIV.

UNINSURED RATE STABLE IN 2017

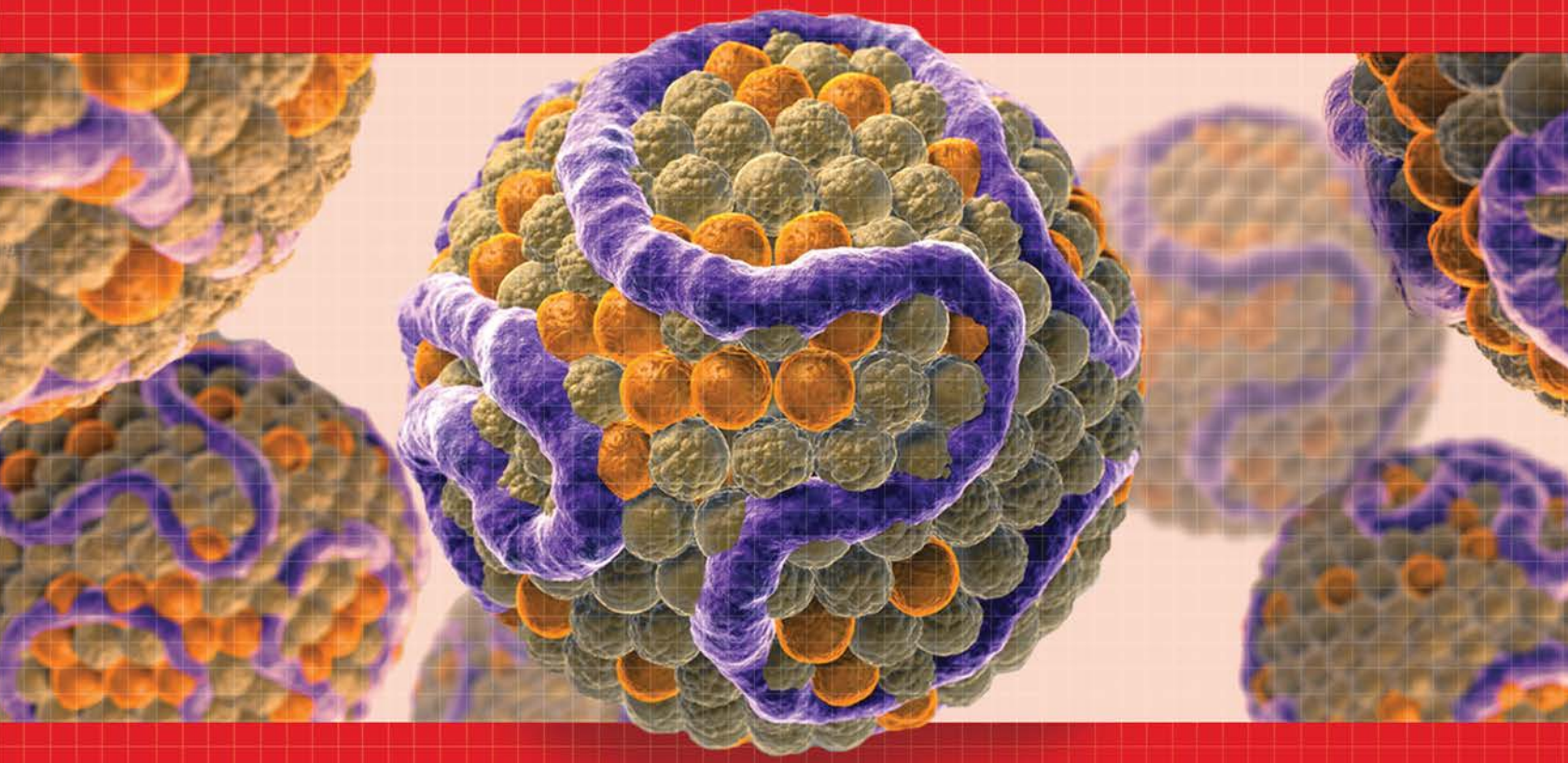
During a period of rising household income and under an administration that urged repeal of the Affordable Care Act, the uninsured rate in 2017 was not statistically different from 2016, according to a Census Bureau report. Nearly 9% of people in the U.S., or 28.5 million, did not have health insurance at any point during the year. During the same time, real median household income increased by 1.8%, up to $61,372.

The numbers of people without insurance varied by state: The uninsured rate actually increased in 14 states and declined in three. Louisiana showed the largest decrease—1.9%—after expanding Medicaid in 2017.

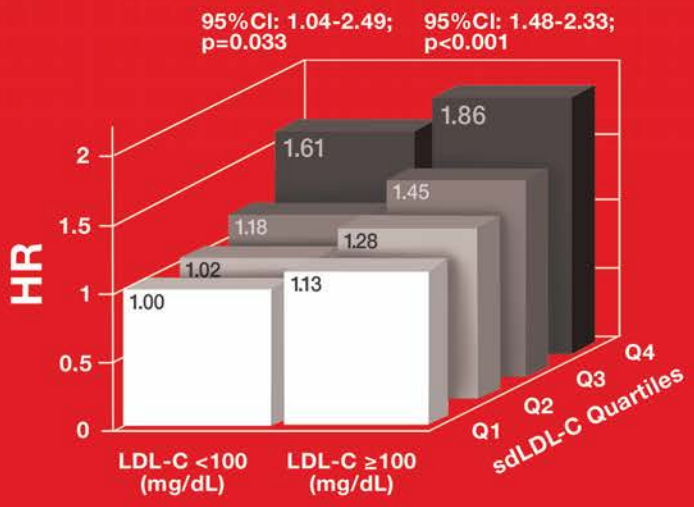
Private insurance coverage still dominates at 67%. Most private plans are employer-based, covering 56% of the population. Medicaid and Medicare are the next most common, at 19% and 17%, respectively.

Cardiovascular Disease Prediction by Small Dense LDL Cholesterol

Fully automated assay to quantify small dense LDL cholesterol cleared by US FDA



Small dense LDL can help identifying patients at a higher risk for cardiovascular disease and serve for a better management of the risk, especially for whom LDL cholesterol is moderately low.



Adjusted hazard ratios for incident coronary heart disease consisting of myocardial infarction, coronary heart disease death and revascularization by small dense LDL cholesterol (sdLDL-C) quartiles stratified by LDL-C risk categories. Adjusted for age, sex, and race, smoking, body mass index, hypertension, diabetes mellitus, diabetes mellitus medications, and log high-sensitivity C-reactive protein. CI indicates confidence interval (adapted from Hoogeveen et al. Arterioscler Thromb Vasc Biol. 2014;34:1069-1077 with approval).

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Bench Matters

Six Keys to Successfully Evaluating Method Performance

Stephanie G. Inman, MLS(ASCP)

I want to bring in a new assay for my analyzer. How should I verify it? Does my validation data look OK? These common questions reflect the uncertainty that crops up when it comes to evaluating new test method performance. Some labs rely on data provided by their vendors; others assign validation or verification responsibilities to team members who may or may not have sufficient knowledge about how to properly evaluate a test method.

Incomplete or poorly executed method evaluations can lead to inspection deficiencies, inadequate use of resources, and most significantly, to reporting erroneous patient results. Planning a detailed and comprehensive method evaluation study and accurately assessing the data is key to ensuring a new method is performing to standard. In my experience, the following points have proven useful in developing method evaluation plans and in assessing laboratory data derived from method evaluations.

1 **Determine whether a method validation or verification is required**. While these terms frequently are used interchangeably, there are important differences between the two. A validation refers to confirming a laboratory developed test or modified Food and Drug Administration (FDA)-approved method is producing accurate and reliable results in the context of its intended use. In contrast, a verification ensures an unmodified FDA-approved method is performing according to specifications outlined by the manufacturer.

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2 **Learn, research, and understand the new test method being implemented.** Many times, the uncertainty around method evaluations is not due to the validation or verification process, but rather to unfamiliarity with the test method. Staff involved in evaluating a new method should know its features, such as the reporting units, methodology, clinical utility, normal values ranges, important medical decision points, analytical measurement range, and dilution schemes. Understanding this information helps guide creation of an evaluation plan.

3 **Outline and plan the evaluation approach and acceptance criteria prior to performing a study.** While this may seem like an obvious step, it's easy to take the "let's do this study and see what happens" approach, especially when the method is new or unfamiliar. College of American Pathologists standards and Clinical and Laboratory Standards Institute guidelines offer solid foundations for organizing a method evaluation study. Considering these resources and the test method to be implemented should clarify which parameters need to be evaluated.

I recommend listing the studies required, materials needed, and results expected, as well as setting acceptance limits. All these measures will lead to organization and clarity as a lab moves through its evaluation process. Asking knowledgeable laboratory colleagues or the test's vendor to review a plan also can yield valuable insights and pinpoint any inadequacies.

4 **Use available resources.** Lean on the experience of other lab professionals, software tools, or published literature to guide the lab's evaluation of data.

If the new method is FDA-approved, refer to the manufacturer's stated performance specifications as a baseline for this method's performance. If the new method will be replacing a method, look for white papers that may indicate a known, expected bias. If the new method is an FDA-modified or laboratory developed test, reach out to other laboratories that employ a similar methodology to inquire about their validation experiences. Peer data, proficiency testing results, statistical analysis programs, and other reputable published literature also are valuable references.

5 **Evaluating method performance data is not always black and white.** Sometimes data fall outside the established statistical acceptance criteria defined in a lab's initial method evaluation plan. When this happens, don't immediately reject the study as unacceptable. Rather, consider the results from a clinical perspective to see if the difference in data is clinically significant. For example, when looking at a method comparison study, if two results don't correlate within the pre-established limits, consider if the two results would lead a physician to treat the patient differently or if the outcome would still be the same. Is result A for analyte X clinically different from result B? Overall, combining statistical analysis and clinical relevance when approaching data evaluation will give a holistic understanding of how a method is performing.

6 **Teach and coach other lab teammates.** Sharing knowledge of method performance evaluations with fellow laboratorians builds a team of qualified personnel who will be able to collaborate and contribute their expertise in future projects. No method evaluation study is the same, so building confidence in lab personnel's ability to think through plans and data evaluation is key for ensuring future success. The primary goal of a method evaluation plan is to confirm that a test method is producing accurate and reliable results for patient care. Developing teammates in their ability to perform method evaluation studies equips them to further serve their patients by providing quality care.

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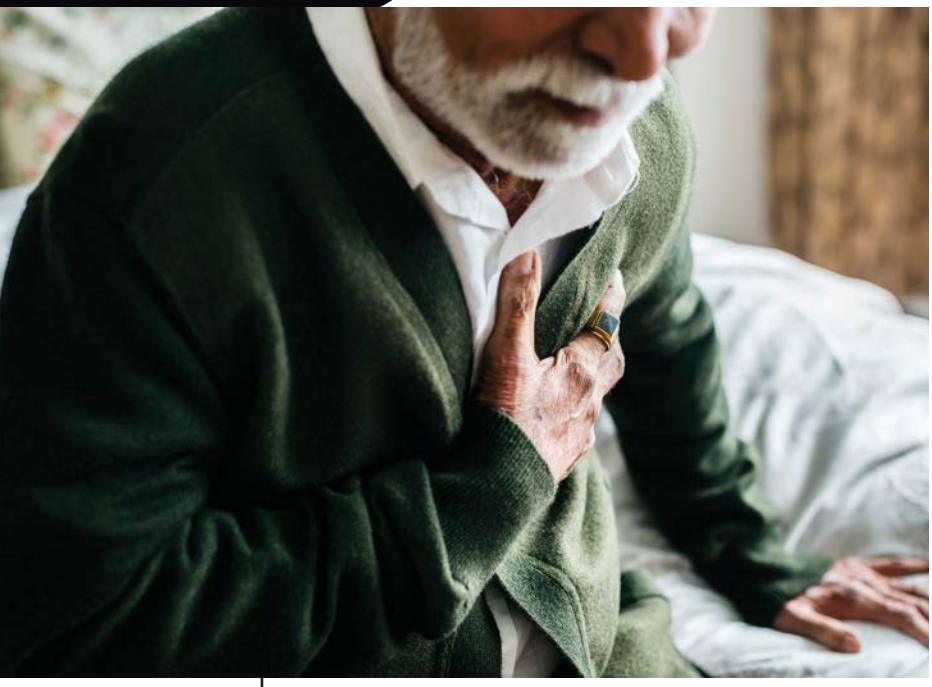
The Sample

Clinical Chemistry Score Bests Cardiac Troponin Results Alone in Stratifying Risk in Acute Coronary Syndrome

A laboratory score that incorporates high-sensitivity cardiac troponin (hs-cTn) and glucose results along with estimated glomerular filtration rate (eGFR) is more sensitive and specific than hs-cTn results alone in stratifying risk in patients who present to emergency departments with suspected acute coronary syndrome (ACS) (CMAJ 2018; 190:3974-84).

Adopting this clinical chemistry score (CCS) could improve lab reporting and analytics in the context of an ACS workup, according to the authors. Doing so "would standardize reporting of hs-cTn test results, how the tests are interpreted in the normal range, and represent an option less susceptible to both analytical and preanalytical errors," they wrote. "This could result in the safest laboratory approach for physicians to use at presentation in the emergency department."

Analytical variation and interferences in hs-cTn assays can lead physicians to misclassify patients' risk when using existing algorithms, according to the authors. This makes it imperative for improved lab services to assist doctors in evaluating patients with suspected ACS, they contend.



High glucose levels may identify patients who are more hemodynamically unstable, who have a larger infarct size, and who have higher 30-day mortality risk. Evidence also suggests that eGFR is an independent predictor of major adverse cardiac outcomes in patients with ACS, according to the authors.

The investigators validated the CCS performance as a predictor of myocardial infarction (MI) or death within 30 days in a post hoc analysis of 4,245 patients seen in emergency departments in Canada, Australia, Germany, and New Zealand. They assigned a total of 0 to 5 points for the overall CCS based on established cutoffs and either 0 or 1 point each for glucose levels and eGFR and from 0 to 3 points for hs-cTn results. They created separate CCSes incorporating hs-cTn I and hs-cTn T results. A CCS of 0 indicates a patient's lab results all are normal; a CCS of 5 indicates they all are abnormal.

Overall, 17.1% of participants died or had an MI within 30 days. Considering all four study populations, a CCS based on hs-cTn I with 0 points had a 100% sensitivity while a CCS based on hs-cTn T with 0 points had a 99.9% sensitivity and 1 false negative, with 8.9% of hs-cTn I and 10.5% of hs-cTn T populations classified as low risk for MI or death within 30 days. In contrast, hs-cTn I results alone with a cutoff <5 ng/L had a sensitivity of 96.6% while hs-cTn T results alone with a cutoff of <6 ng/L had a sensitivity of 98.2%.

A CCS with 5 points also performed better than hs-cTn results alone in

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identifying patients at high risk, with specificity of 96.6% and 94.0% for the hs-cTn I and hs-cTn T CCSes, respectively, versus 93.2% and 73.8% specificity for hs-cTn I and hs-cTn T results alone, respectively.

These findings suggest that a CCS of 0 "would classify close to 10% of the population in the emergency department who present with symptoms of [ACS] as being at low risk for unstable angina, MI, revascularization procedures and death," wrote the researchers, thereby reassuring physicians that such patients are at low risk after their first blood draw.

GENE EXPRESSION SIGNATURE DISTINGUISHES KAWASAKI DISEASE FROM OTHER INFECTIOUS DISEASES; COULD BECOME DIAGNOSTIC TEST

A 13-transcript gene expression signature distinguished patients with Kawasaki disease (KD) from those with bacterial, viral, or inflammatory disease and shows promise as a blood-based test that might aid in rapidly diagnosing KD (JAMA Pediatrics 2018; doi:10.1001/jamapediatrics.2018.2293). In a separate statement, the authors report being in discussions with biotech companies to develop a clinical test from the signature.

The researchers developed the signature in the hopes that it would help identify KD early in the disease process to facilitate prompt treatment and to prevent of one of the most serious sequelae of KD, coronary artery aneurism. KD diagnosis currently relies on the presence of four out of five clinical criteria, and symptoms of the disease are very similar to other infectious diseases.

Researchers in four countries conducted a case-control study involving 606 children, including 404 in a discovery and testing cohort and 202 in a validation cohort, with 78 and 102 KD patients, respectively. They identified 1,600 transcripts significantly expressed differentially in patients with KD versus those with other diseases and healthy controls. After subsequent modeling, the investigators identified 13 genes that when implemented as a disease risk score (DRS) distinguished patients with KD from other infectious and inflammatory conditions.

The DRS combines the fluorescence intensity of upregulated transcripts and subtracts the combined fluorescence intensity of down-regulated transcripts. In all, eight of the genes show increased expression in KD in comparison to other diseases, while five show decreased expression.

This 13-gene DRS had an area under the receiver operator characteristic (AUC), sensitivity, and specificity in the discovery test set and in the validation set of 96.2%, 81.7%, 92.1%, and 94.6%, 85.9%, and 89.1%, respectively.

To test how well the KD DRS corresponded with levels of diagnostic certainty the investigators also characterized patients in the validation set as having possible, highly probable, or definitive KD based on independent review of clinical data collected as part of the study. AUCs for the KD DRS tracked with these groups, rising from 70.0%. to 96.3% and 98.1%, respectively.

CREATIVE DIS

BY BILL MALONE

GNA Biosolutions, the winner of AACC's first Disruptive Technology Award, believes it can speed molecular testing by a factor of 10 for point-of-care diagnostics.

RUPTION

AACC launched its new Disruptive Technology Award in July at the 70th AACC Annual Scientific Meeting & Clinical Lab Expo in Chicago. The competition supports diagnostic developers at the forefront of science and technology in laboratory medicine and gives clinical laboratorians the opportunity to evaluate novel technologies and their potential impact on patient care.

This year, a panel of AACC members selected three finalists to present their technologies at the meeting from a pool of 42 applicants: Ativa Medical, GNA Biosolutions, and Two Pore Guys. During a session on July 30, judges scored the technologies on feasibility and overall performance. This year's winner, Munich, Germany-based GNA Biosolutions, also won the audience choice award. The company showcased its pulse-controlled amplification technology that enables ultrafast polymerase chain reaction (PCR).

The core idea behind GNA Biosolutions' technology does not have its origin in laboratory medicine, but in the research of a physicist. Joachim Stehr, PhD—who co-founded the company with Federico Bürsgens, PhD, and Lars Ullerich, PhD—first documented his idea of nanoparticle DNA analysis in his doctoral thesis. His idea was to speed up PCR, which underlies most molecular testing, by employing exquisitely small and efficient gold nanoparticles.

Traditionally, amplifying and detecting DNA using PCR amounts to cooking the DNA in a sample at precise temperatures over cycles of heating and cooling. Heat "melts" the DNA, unzipping its double strands. When the solution cools down, carefully selected primers latch onto a specific section of DNA that is targeted for replication and detection. Cycles of heating and cooling repeat dozens of times.

Due to the unique physics of nanoparticles, however, GNA Biosolutions believes it can radically change that process, managing director Ullerich told *CLN*. The key to making nanoparticles work is the company's proprietary pulse-controlled amplification system. Launched in November 2017, GNA Biosolutions' first commercial platform, Pharos V8, uses laser pulses to ignite the PCR reaction.

The interview has been shortened and edited for clarity.

HOW DOES PULSE CONTROLLED AMPLIFICATION DIFFER FROM TRADITIONAL PCR METHODS?

The basic problem with PCR is that you need to thermalize the whole reaction—obtaining different temperatures 30-40 times—and this heating up and cooling down of the entire reaction volume is the most time-consuming step.

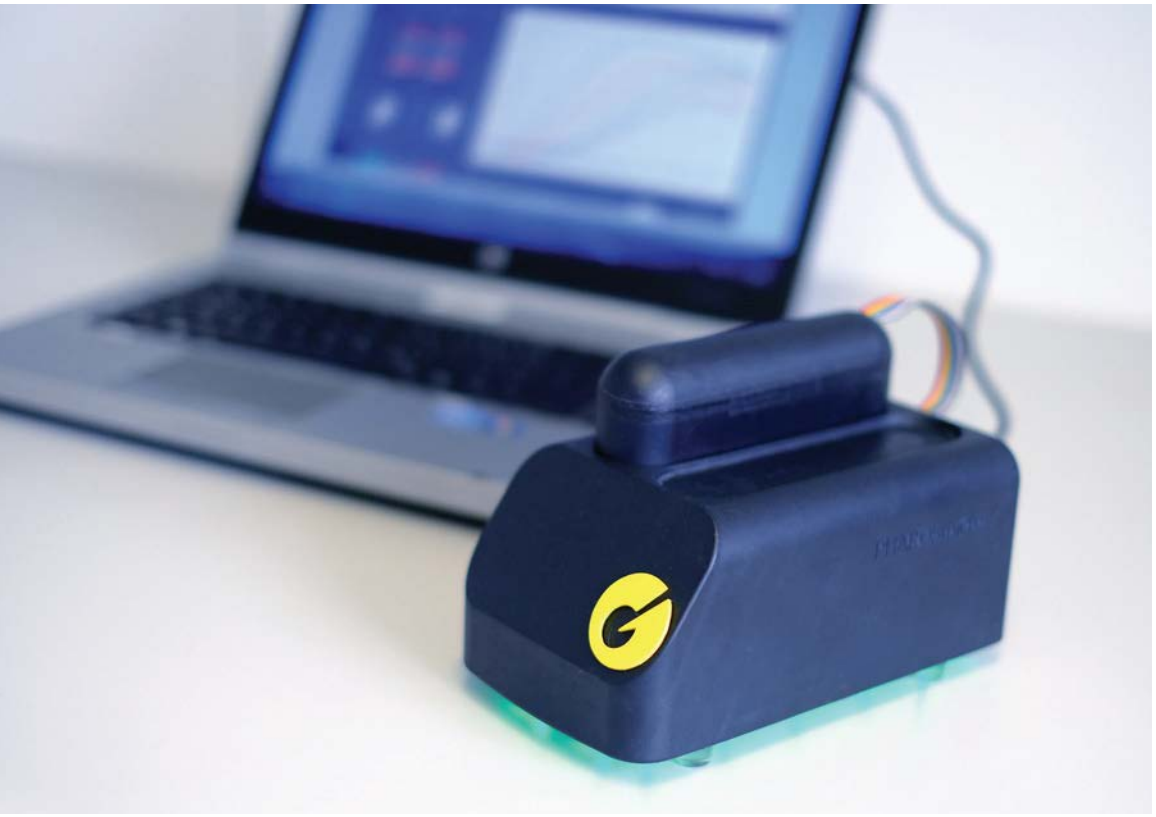
We use microcyclers—nanoscale thermocyclers—right inside the solution and heat them with an external energy source. They are so small that as soon as the energy source is turned off, they cool down instantaneously, because the liquid in the reaction volume itself serves as the cooling reservoir. This means our heating times are extremely short, and the microcyclers cool off automatically. This approach of using localized heating elements in the solution is at our core. In the Pharos V8 instrument we do this with laser-heated nanoparticles. In our new prototype, we use electrically heated microcyclers inside the solution.

Using localized microcyclers in the solution also makes the instrument essentially volume independent—it can process very small or very large volumes in the same time frame, with amplification and detection often taking fewer than 10 minutes.

WHAT ABOUT SAMPLE PREPARATION?

Sample preparation is another bottleneck in molecular diagnostics. A traditional method would use columns with resins and several wash and elution steps. This eluate would then need to go into another reaction process.

In our case we use the microcyclers for target capture, amplification, and detection in the same reaction well to simplify the process. This allows the instrument to purify nucleic acids out of crudely lysed sample directly, even from whole blood. And the ultrasound



lysis step is very quick and integrated into the device.

HOW IS THE PHAROS V8 INSTRUMENT BEING USED IN CLINICAL LABORATORIES?

Pharos V8 is mainly for speeding up lab-developed tests. Clinical labs can port their own probe-based tests onto the platform. The same principle applies to life science applications in which researchers want to speed up PCR.

We have not disclosed most of our instrument placements, but many are focused on infectious diseases. One collaboration we've made public is our work with the Lazzaro Spallanzani National Institute for Infectious Diseases in Rome, where we co-developed Ebola and tuberculosis assays.

Now we're focusing on our next-generation system, still based on pulse-controlled amplification, but miniaturized for point-of-care testing. Instead of lasers, the new platform uses an electrical current that goes through the solution and produces heat on the surface of microcyclers.

HOW CAN ADVANCED TECHNOLOGY LIKE YOURS BE COST-EFFECTIVE?

First, you always have to look at the real world: Real clinical samples are very important to include in your experiments as soon as possible, and then you can look at ease of use and manufacturing. Of course, it's important to be able to scale manufacturing of chips and devices. However, in our case, our chemistry is rather standard, and microcyclers don't add significantly to the cost.

Partly this is by design—our chips have a much simpler workflow than current cartridges on the market. Most cartridges that perform molecular diagnostics are still too slow, complex, and costly for the point-of-care, and they typically have 30-35 individual parts to combine. We can use about five parts for the cartridge. With sample prep taking place intrinsically on the microcyclers, we can keep the instrument simple, and there's no sophisticated heating block like other systems.

WHERE DO YOU SEE THIS TECHNOLOGY BEING USED—MAINLY AT THE POINT-OF-CARE, OR IN CORE LABORATORIES AS WELL?

In principle, both. We want to bring molecular testing into new environments and closer to patients through speed that fits the point-of-care workflow, ease of use, and cost. But the principles of pulse-controlled amplification are also scalable, so we see applications for centralized laboratories for medium-to-high throughput applications. This simple heating mechanism can be scaled up to larger plates, for example, something we're looking at with potential partners, even while our own focus is on point-of-care devices.

For the point-of-care, we feel it's extremely important to be as fast as possible, because at the point-of-care every minute counts. Many companies out there say that first result is within a certain short time frame, but often it would take much longer for a full analysis and for samples that would not contain a high burden target load.

For example, PCR testing for an acute flu infection already has been made quite rapid. The reason is that there is not a lot of sample preparation and there's a high titer. But for other clinically significant sample types like blood—probably still the most important sample type—often other systems aren't nearly so fast, especially when it comes to important bacteria with low target concentration, such as tuberculosis.

Ultimately, our goal is a Food and Drug Administration-approved and CLIA-waived system, and our assay pipeline includes tuberculosis and antibiotic-resistant bacteria.

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[1]based on review of competitor operator manuals and websites up to September 2018

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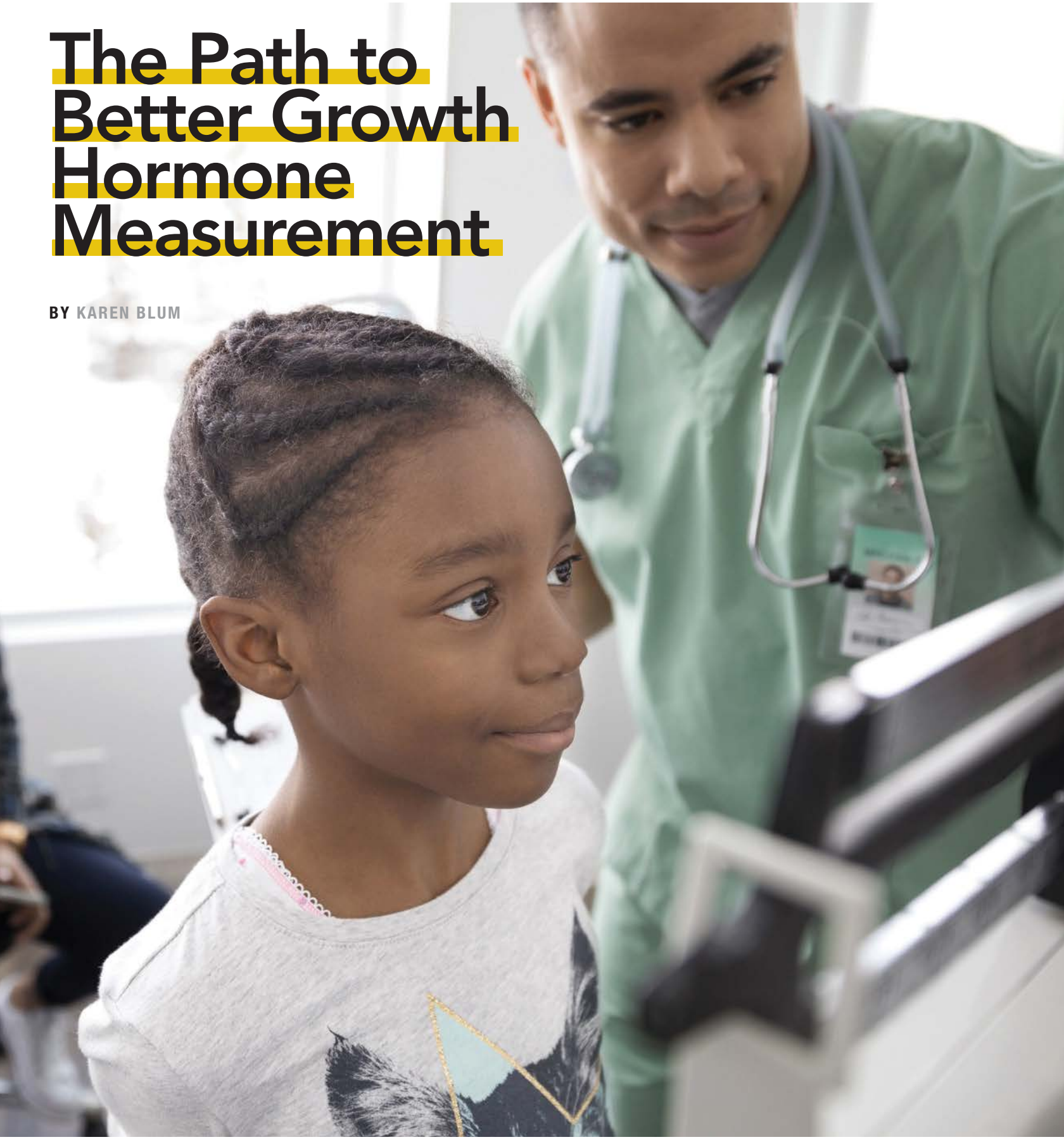
The Path to Better Growth Hormone Measurement

BY KAREN BLUM



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Endocrinologists looking to quantify growth hormone in their patients frequently rely on laboratory tests for insulin-like growth factor-1 (IGF-I) and IGF-binding protein-3 (IGFBP-3). But getting accurate readings is tricky for a variety of reasons, including biological and both intra- and inter-assay variations. While efforts to push a universal standard for growth hormone and IGF-I immunoassays have made some progress, there is still room to improve, said laboratory experts. Labs also have a role to play in returning as robust results as possible and in better informing clinicians about the limitations of their methods and about interpreting test results.

IGF-I, a protein stimulated by growth hormone that plays an important role in growth during childhood, is primarily produced by the liver. It's a useful marker for growth hormone deficiency or surplus because it is released fairly consistently, unlike growth hormone itself, which can fluctuate throughout the day, said Ravinder Singh, PhD, DABCC, director of the Mayo Clinic endocrine laboratory, in Rochester, Minnesota. Measuring serum IGF-I and IGFBP-3 concentrations helps assess short stature or gigantism and helps predict growth response in patients taking growth hormone therapy. Clinicians also monitor IGF-I levels to assess patients' adherence to therapy and to ensure that doses remain in the therapeutic range.

But measuring IGF-I accurately has its challenges, said Martin Bidlingmaier, MD, head of the endocrine laboratory at the University of Munich, in Germany. For one, IGF-I binds not only to IGFBP-3 but also to acid labile subunit. One must separate out the IGF-I, he said, by adding an acid and then a factor like IGF-II to bind to the other proteins so as to measure free IGF-I. Measurement has to be done quickly, he added, as IGF-I will re-aggregate with its binding proteins within 20-30 minutes.

In addition, said Singh, the reference range for IGF-I has been evolving, now getting as specific as providing norms for patients at almost every year of age to reflect how dramatically IGF-I varies with age. Different assay manufacturers also may use different calibration materials, Singh added, and antibodies used for the assays may not be consistent, making it quite challenging to compare results from one assay to another. These nuances may not cause problems for one patient whose testing is performed consistently at one lab, but when patients move and their tests are run by different labs, the results could be vastly different.

In another twist, manufacturers should verify the reagents sent to clinical laboratories, but these agents may not be consistent from lot to lot. This happened at Mayo Clinic a few years back, when the lab was using a commercial IGF-I assay, said Alicia Algeciras-Schimnich, PhD, DABCC, chair of the medical center's division of clinical biochemistry and immunology. She and her colleagues were noticing elevated IGF-I results in some patients that were considered false positives once they reviewed patients' clinical data (Endocr Pract 2014;20:421-5). "The clinical picture was not consistent with growth hormone excess," she said. "That created a challenge for us to try to figure out what was going on."

Ultimately, they determined the problem to be related to inconsistent reagent lots. "It was an assay performance issue, not a patient or sample collection issue," she said. Mayo Clinic subsequently switched to a lab-developed mass spectrometry assay to try to achieve better consistency over time (See Box).

These variances can go unnoticed by physicians, not all of whom are schooled in laboratory techniques, said David Clemmons, MD, Sarah Graham Kenan professor of medicine at the University of North Carolina at Chapel Hill. "They just get a number back, and if there's interference or if there's a lack of reproducibility, they really don't know it," he said. Inaccurate results could lead them to make errors in treatment, such as prescribing unnecessary therapies or improper doses.

CONSENSUS ON ASSAY PERFORMANCE

Clemmons, along with Bidlingmaier and Algeciras-Schimnich, was part of a 2010 meeting of clinicians and clinical laboratory professionals convened by the Growth Hormone Research Society, the International Society for IGF Research, the International Federation of Clinical Chemistry and Lab Medicine, and the Pituitary Society to define criteria and strategies for harmonizing growth hormone and IGF-I assays. The group's consensus statement recommended that manufacturers all adopt the same standard, and that all assays need appropriate, specific reference intervals (Clin Chem 2011;57:555-9).

Results are still a work in progress, said Bidlingmaier, although the proposal that all IGF-I assay manufacturers adopt a uniform, standard preparation has largely been achieved. Most assays are now calibrated against the most recent World Health Organization international reference preparation, 02/254. This in part led to better agreement among some assays, he noted.

In addition, Bidlingmaier and others, in 2014, published reference intervals for both IGF-I and IGFBP-3 based on a population of about 15,000 subjects for the IDS iSYS assay (J Clin Endocrinol Metab 99:1712-21 and 1675-86, respectively). "For the clinician, the key issue with IGF-I assays is to get appropriate reference intervals, or normative data to make a useful interpretation of the numbers you get. That's a point where different assays have different quality to offer," he observed.

PUBLICATION REQUIREMENTS

In other updates, the Endocrine Society announced that it would no longer accept papers for publication in its journals unless growth hormone results were expressed in micrograms, said Catharine Sturgeon, PhD, FRCP, a clinical scientist at the Royal Infirmary of Edinburgh, in Scotland, and director of the U.K. National External Quality Assessment Service proficiency testing center. "That made a major difference because people had to state how their method had been calibrated, and to use those units, which meant that the manufacturers had to take notice. This changed things considerably in terms of bringing results closer together."

This move has been important, she said, because when dealing with relatively small patient populations, "it's highly desirable to be able to

compare results across countries and studies." Sturgeon also was a co-author of the consensus statement on growth hormone and IGF-I assays.

DETAILED REFERENCE INTERVALS

As standardization efforts continue, clinical labs should take several steps to ensure the accuracy and solid interpretation of their IGF-I and IGFBP-3 test results. Bidlingmaier suggested providing clinicians with a very detailed, transparently established reference interval to help guide interpretation of test results. Some laboratory handbooks have reference intervals for IGF-I "which are absolutely insufficient in terms of the population investigated," he noted—maybe testing just a few subjects with no appropriate age classification.

"You need a huge reference population to make these reference intervals reliable," Bidlingmaier elaborated. "Many laboratories underestimate the importance of this point." Labs should not simply rely on information provided in the manufacturer's kit insert, he said. Ideally, there should be a publication providing detailed information on what population was investigated, including subjects' ages, ethnicities, and genders.

In addition, laboratories should monitor long-term performance of their assays. "All assays come with quality control samples, but these in many cases are provided by the manufacturer so are not true serum samples," Bidlingmaier said, and therefore do not ideally mimic clinical samples. Some companies provide quality control samples, but they have IGF-I spiked into an artificial matrix that does not contain all of the binding proteins, he added. Beyond these commercial controls, labs should measure patient serum samples daily: "Prepare little aliquots from a large pool, which you put into the freezer, and every day you measure the same sample again and follow the results. This is the only way to get a better understanding of the performance of your method in real world samples," said Bidlingmaier.

Laboratories also should participate in external quality assessment programs to compare their IGF-I results to those from other laboratories, ensure they calibrate their method against the most current reference standards, and evaluate the applicability of manufacturer-provided reference intervals to their patient populations. In addition, labs should inform physicians about the assay being used and be ready to confer with doctors about assay performance or other issues anytime a patient's clinical presentation doesn't jibe with test results.

"Reference laboratories are pretty well aware of these issues—it's not like they're mysterious," Clemmons said. "But the extent to which they apply the principles on a daily basis can fluctuate. You have to keep readdressing the issue to make sure that there is reproducibility."

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Is Mass Spectrometry the Way to Go?

Mass spectrometry (MS) offers some advantages over immunoassays in detecting insulin-like growth factor-1 (IGF-I) but may not be the best choice for all labs, according to experts. Mayo Clinic in Rochester, Minnesota, offers a high-resolution MS assay for IGF-I optimized to detect different IGF-I isoforms including clinically relevant, rare mutants, which can help in confirming the diagnosis of growth hormone deficiency, said Alicia Algeciras-Schimnich, PhD, DABCC, chair of Mayo's division of clinical biochemistry and immunology. But not all MS assays are set-up to detect these variants, she said. In addition, "The mass specs will have the same standardization and quality challenges as immunoassays in terms of consistency over time, so performance will still need to be monitored as closely as when monitoring immunoassay performance."

On the plus side, MS methods notably are less impacted by the interference problems affecting routine immunoassays and give labs responsibility for and control over the reagents used instead of needing to rely on manufacturers for calibrators and controls, according to Ravinder Singh, PhD, DABCC, director of the Mayo Clinic endocrine laboratory.

Not all clinical laboratory professionals are sold on these benefits, however. "As of today, the advantages of mass spectrometry assays are very theoretical, because it has not been proven yet that there is a clear advantage," contended Martin Bidlingmaier, MD, head of the endocrine laboratory at the University of Munich in Germany. There are publications suggesting good, perfectly validated measurements with MS and others indicating the agreement among different labs is no better than the agreement among labs using immunoassays, he said.

Analytics aside, the volume of IGF-I also would factor into MS versus immunoassay decisions. For smaller laboratories with a limited amount of testing, it wouldn't necessarily make sense to invest in the equipment, Algeciras-Schimnich noted: "You probably will get the same quality results in the majority of cases with immunoassays."

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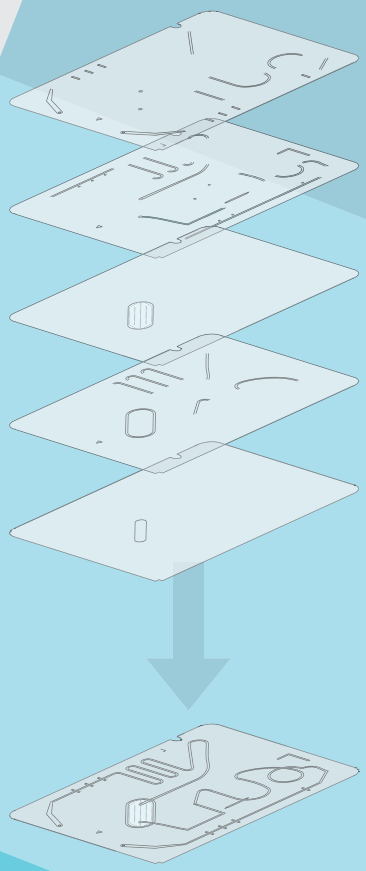

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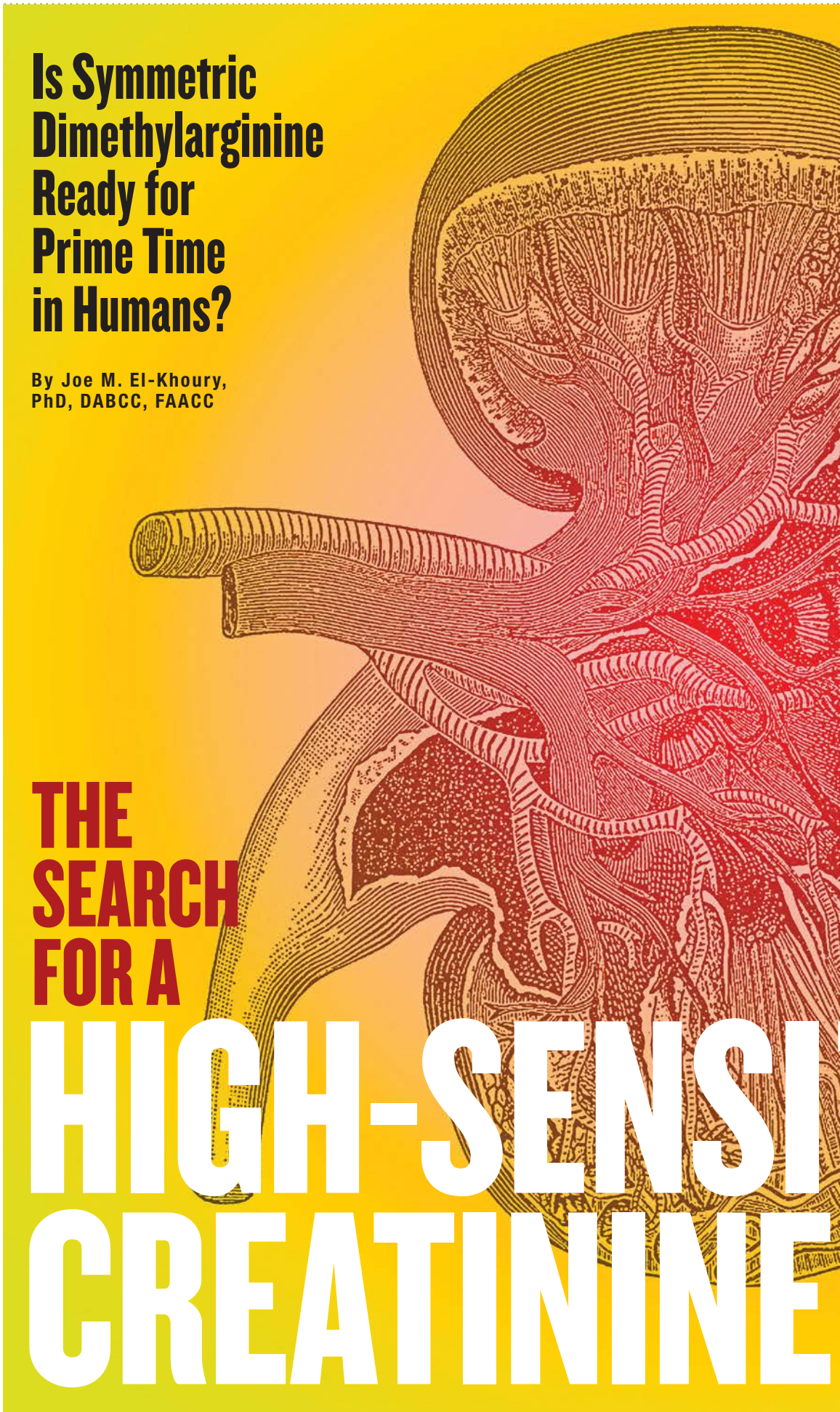
Is Symmetric Dimethylarginine Ready for Prime Time in Humans?

By Joe M. El-Khoury, PhD, DABCC, FAACC



THE SEARCH FOR A HIGH-SENSI CREATININE

Chronic kidney disease (CKD) is the ninth leading cause of death in the U.S. with an estimated 14.2% of the U.S. population presenting evidence of CKD stages 1-4 (1). This disease affects African Americans at a rate three times higher than Caucasians and has been termed the "silent killer" because it shows no symptoms in early stages, and many physicians and patients remain unaware of the diversity of its clinical characteristics (2).

To address these issues globally, the international organization Kidney Disease: Improving Global Outcomes (KDIGO) issued evidence-based clinical practice guidelines in 2013 with clear criteria for diagnosing CKD (3). KDIGO defines CKD as abnormalities of kidney structure or function present for more than 3 months. Abnormalities include one of two factors: either a marker of kidney damage, such as urine sediment abnormalities or albuminuria, or decreased glomerular filtration rate (GFR) (< 60 ml/min/1.73 m^2).

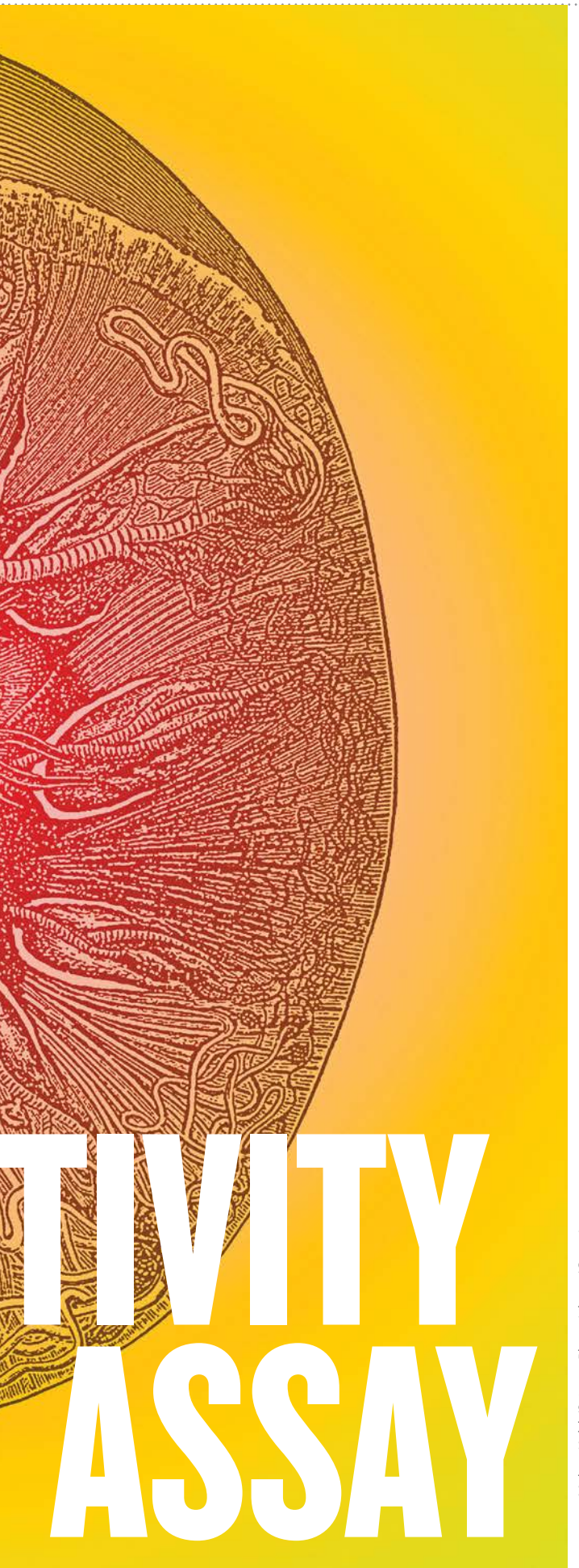
GLOMERULAR FILTRATION RATE: ESSENTIAL AND ELUSIVE

GFR, which represents the total amount of blood filtered through the glomerulus in the kidney, is the best overall index of kidney function. KDIGO has established six categories for GFR (Table 1) based on the severity of kidney dysfunction (3).

GFR can only be determined by measuring the clearance of a substance from blood into urine (4). However, for the clearance of this substance to truly reflect GFR, the substance must meet the following characteristics:

- Freely filtered at the glomerulus;
- Produced at a constant rate, so stable blood concentrations are maintained;
- Neither secreted nor reabsorbed by the renal tubules;
- No extra-renal elimination pathways; and
- Physiologically inert.

To date, no single known biomarker produced by the human body meets all these characteristics. As a result, laboratories use clearance of exogenous markers such as iothalamate and iohexol as a reference method for determining GFR, while using serum



TIVITY ASSAY

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measurement of endogenous markers such as creatinine and cystatin C for estimating GFR (eGFR).

EGFR EQUATIONS AND THEIR LIMITATIONS

The expense and invasiveness of assessing kidney function using exogenous markers makes doing so impractical for screening purposes. Consequently, clinical laboratories rely on serum creatinine to screen for kidney disease. Creatinine is the waste product of interconversion between phosphocreatine and creatine in muscle cells. Thus, the amount of creatinine produced in an individual every day is fairly constant and correlates with muscle mass. However, muscle mass varies widely among individuals, and creatinine varies significantly by age, sex, and race.

Several equations have been developed to account for these variations, such as Modification of Diet in Renal Disease (MDRD) and more recently the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). But while these equations improve accuracy, they do not account for other non-renal factors that affect creatinine, such as diet, certain medications, and amputations (4). In patients with these factors, as well as in those with abnormally low or high muscle mass, cystatin C is the recommended marker for eGFR.

Cystatin C has been shown to be superior to creatinine as a marker of kidney function and for eGFR (5). However, cystatin C is also influenced by non-renal factors such as inflammation, thyroid function, and obesity (4), and is a much more expensive test than creatinine. For these reasons it has limited use in clinical practice, though recent guidelines recommend it to confirm CKD among individuals with eGFR 45-59 ml/min/1.73 m^2.

SDMA BIOMARKER CHARACTERISTICS

Symmetric dimethylarginine (SDMA) is an emerging endogenous biomarker of kidney function that is already widely used in veterinary medicine. Asymmetric dimethylarginine (ADMA) and SDMA both are produced consistently by hydrolysis of histones with post-translational methylation of arginine residues. In addition, SDMA is almost exclusively eliminated by the kidneys after filtration, making it an ideal candidate for a GFR marker.

ADMA and SDMA have been known to biochemists for decades. ADMA emerged as a marker of endothelial dysfunction, while SDMA had been left in the shadows as a structural isomer of ADMA with no clinical utility. It took many years for SDMA to attract attention, until the early 2000s when in back-to-back studies it surprised researchers as an independent cardiovascular disease (CVD) risk factor along with ADMA. Furthermore, a meta-analysis of 18 studies published in 2006 showed a highly significant correlation between SDMA and kidney function (6). These studies also reported no effect from non-renal factors known to affect creatinine and/or cystatin C, such as muscle mass, diet, inflammation, diabetes, and estrogen therapy. Importantly, in the absence of kidney disease, SDMA concentrations were not affected by hepatic disease, CVD, diabetes, or an acute inflammatory response.

SDMA has other advantages as a biomarker, including its low intra-individual biological variability (5.8%) in comparison with cystatin C (8.6%), and that unlike creatinine, no racial differences have been observed in studies examining SDMA levels in Caucasians versus African American men. On the other hand, SDMA levels have been shown to be slightly increased based on age and sex, so it is likely that a GFR estimating equation using SDMA would need to take into account at least these two variables.

SDMA AND KIDNEY FUNCTION

A significant number of studies have reported strong correlations between SDMA and measures of kidney function in humans (7). However, only a handful compared the performance of SDMA to measured GFR using gold-standard or well-characterized exogenous biomarkers such as inulin, iothalamate, or chromium-EDTA (Table 2). These studies reported correlations ranging from 0.78 to 0.90 and included healthy as well as CKD and type 1 diabetes populations.

In 2016, our group published the first report comparing the performance of SDMA, creatinine, and cystatin C to measured GFR (8). Although the sample size was small (n=40), SDMA

showed similar correlation with GFR as reported in larger studies (r=0.84). This was better than creatinine (r=0.70) but similar to cystatin C (r=0.86). Notably, we also included healthy and diseased populations in the comparison so that we were able to evaluate the performance of these markers across the spectrum of GFR values (13 to 151 mL/min/1.73 m^2). Together, these studies demonstrate that SDMA is a strong marker of kidney function that highly correlates with GFR in adults.

Studies showing correlation of SDMA with measured GFR in pediatric populations are lacking, but several have examined correlations with eGFR. In one that included 35 patients with CKD and 42 healthy controls, SDMA had a higher diagnostic efficiency than cystatin C for detecting CKD and for identifying early stages of CKD (stages G1 and G2) (9).

Another important characteristic of SDMA is its early rise in the pathological process of kidney disease. In a recent study examining changes in GFR markers after living-related kidney donation, SDMA increased within 6 hours after unilateral nephrectomy (i.e. 50% loss of kidney function) (10). While additional data in humans is lacking, SDMA has been shown to allow earlier detection of CKD in cats and dogs in comparison with creatinine.

T1 GFR categories based on KDIGO 2012

Category	Description	GFR (mL/min/1.73 m^2)
G1	Normal or increased	Greater than or equal to 90
G2	Mildly decreased	60-89
G3a	Mildly to moderately decreased	45-59
G3b	Moderately to severely decreased	30-44
G4	Severely decreased	15-29
G5	Kidney failure	Less than 15

GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes

T2 Summary of Correlation of SDMA levels with measured GFR in humans

Study (Year)	Population	n	GFR Marker	Correlation with SDMA
Kielsten et al. (2002)	CKD	24	Inulin	0.78
Tarnow et al. (2004)	Type 1 Diabetes	394	Chromium EDTA	0.90
Fliser et al. (2005)	CKD	227	Iothalamate	0.84
El-Khoury et al. (2016)	Healthy and CKD	40	Iothalamate	0.84

SDMA, Symmetric dimethylarginine; GFR, glomerular filtration rate; CKD, chronic kidney disease

ANALYTICAL CONSIDERATIONS

Measurement of SDMA has been largely restricted to translational research laboratories with liquid chromatography-tandem mass spectrometry (LC-MS/MS) instruments. While the adoption of LC-MS/MS by clinical laboratories has increased in recent years, the technology remains complex and requires a significant level of expertise for test development and operation. In addition, LC-MS/MS assays are not fully automated and require significant sample preparation and time before a result can be produced, increasing its turnaround time (TAT) in comparison with automated assays for creatinine and cystatin C. This lack of an automated assay has hampered SDMA's widespread adoption in research and in clinical practice.

We recently evaluated the performance of a pre-commercial, research-use-only automated immunoassay for SDMA on two different platforms and compared its performance to LC-MS/MS. The new automated method showed strong correlation with LC-MS/MS on both platforms (unpublished data). The availability of an automated SDMA immunoassay with fast TAT raises the hope that this biomarker may be used in clinical practice in the future.

FUTURE PERSPECTIVES

The commercial availability of an automated assay for SDMA is a high priority for the field as stakeholders seek to address with precise and reliable laboratory testing the growing burden of CKD and other chronic diseases. An automated assay will also speed adoption of SDMA measurement in translational and clinical laboratories and accelerate researchers' ability to generate the data needed to fully characterize the biomarker for clinical use.

On the clinical side, it is important to investigate the non-renal factors that affect SDMA levels that may confound interpretation of results. Clinicians will also need an eGFR equation that establishes the relationship between SDMA and GFR and accounts for some of these confounding variables.

For now, it seems that the most promising application of SDMA is in

the pediatric population, where it has already demonstrated superiority to cystatin C. However, further research along this line of investigation also is needed.

Finally, we should learn from the experiences of our colleagues in veterinary medicine, where this biomarker has been in routine clinical use since 2015. Their experience is especially relevant considering that normal SDMA levels are relatively consistent among humans, cats, and dogs. We have a lot in common with our furry friends, and we can use this knowledge to our advantage when it comes to measuring SDMA to assess kidney function.

**Dr. El-Khoury has received research support, as well as honorarium/expenses, from IDEXX Laboratories.*

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AACC INNOVATORS PUSH THE ENVELOPE IN CHICAGO

More than 20,000 medical professionals and other healthcare leaders gathered from July 29–August 2 in Chicago at the 70th AACC Annual Scientific Meeting & Clinical Lab Expo, showcasing advancements in clinical laboratory technology, services, and research that are improving patient care.

The conference program featured some 200 scientific sessions and included five plenary talks presented by scientific luminaries on subjects ranging from precision cancer therapeutics to the World Health Organization's new Essential Diagnostics List. Brian Druker, MD, recipient of AACC's 2018 Wallace H. Coulter Lectureship Award, delivered the opening keynote on his research that led to targeted treatment for chronic myeloid leukemia.

The 70th AACC Clinical Lab Expo featured 819 exhibitors, the highest number in AACC's history. The meeting has continued to see dramatic growth in the level of industry participation, as exhibitors can reach both high-level laboratory managers and thousands of distributors from throughout the world. A digital product showcase, three sold-out exhibit hall theaters, and a booth dedicated to disruptive technologies provided a backdrop for the hundreds of new products launched and promoted at the flagship gathering of global in vitro diagnostics leaders.

In Chicago, an eight-member editorial board of AACC members followed the science for *CLN Daily*, the official publication of the AACC Annual Scientific Meeting & Clinical Lab Expo, which was produced and distributed on-site. Read the full stories featured in the following snapshots at www.aacc.org.

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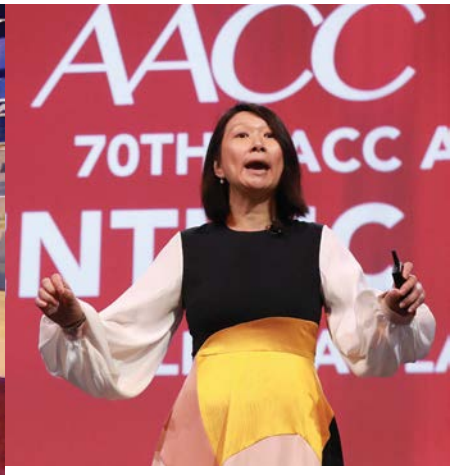

PUSHING THE PRENATAL ENVELOPE

By Tina Lockwood, PhD

Since 2011, prenatal screening for chromosome abnormalities has undergone a paradigm shift as test positive predictive values skyrocketed from a dismal 4% to more than 45%. The evolution of prenatal screening is due to short fragments of cell-free fetal DNA that circulate in maternal blood. Attendees of the plenary presentation by Rossa Chiu, MBBS, PhD, heard about the game-changing advances in prenatal testing, much of which has been developed by Chiu and her colleagues.

Preanalytical variability is a familiar challenge for all disciplines of laboratory medicine. When Chiu started her graduate work, cell-free DNA as an analyte had been questioned in the literature due to its low abundance and apparent intra-individual variability. Chiu described her experiments that ultimately standardized blood sample processing for isolation of cell-free DNA, a method now used in all cell-free DNA clinical applications.

Chiu imagines a new era of prenatal care in which fetuses will be assessed for an expanded range of conditions beyond chromosome abnormalities. Her research team has successfully detected both recessive and dominant inherited conditions as well as de novo conditions. In a nod to bedside medicine, she also described her work exploring the use of handheld sequencing devices for detecting fetal cell-free DNA from maternal plasma.

DECIPHERING THYROGLOBULIN AND THYROGLOBULIN AUTOANTIBODY ASSAYS

By Sami Albeiroti, PhD

Thyroid cancer is the most commonly diagnosed malignancy of the endocrine system, affecting three times more women than men. Detectable levels of thyroglobulin (Tg) after thyroidectomy may suggest incomplete tumor removal or cancer recurrence.

Measurement of Tg, to put it simply, is complex. This complexity arises from the variability among assays and, most importantly, the fact that up to 30% of thyroid cancer patients have anti-Tg autoantibodies (TgAb) that can interfere with Tg immunoassays, mostly causing false negative results. Consequently, TgAb testing has become an indispensable companion of Tg testing.

Experts tackled the performance of these assays and offered insights on how laboratorians should approach their complexity. Alicia Algeciras-Schimnich, PhD, explained misconceptions about assay performance and the benefits and disadvantages of available methods. Mass spectrometry (MS)-based methods have helped labs overcome many of the challenges of Tg testing, as they are not susceptible to TgAb interference. However, MS's limit of quantitation needs to improve, she said.

Joely Straseski, PhD, emphasized the need to understand which test is most appropriate for specific clinical situations and offered strategies for interpreting confusing test results. She also argued that the way laboratories often define a positive TgAb is controversial, as it varies by assay as well as the population being tested.

SHERLOCK HOLMES' MODERN MAGNIFIER

By Joe El-Khoury, PhD

More than 30 years ago, Cincinnati Children's Hospital Medical Center implemented an international screening program for genetic causes of cholestatic liver disease that led to the identification of six new defects in bile acid synthesis. These conditions are fatal if not treated, causing idiopathic neonatal cholestatic syndromes and accounting for 2%–5% of pediatric liver diseases.

Plenary speaker Kenneth Setchell, PhD, and his team discovered bile acid synthetic defects as a cause of progressive cholestatic liver disease, a success he attributes exclusively to the application of mass spectrometry (MS) in the 1980s. He outlined his journey with MS from discovery of the disease to treatment.

Presenting a series of pediatric clinical cases, Setchell walked the audience through his fascinating

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molecular investigation of the causes of cholestasis using MS. Setchell's colleagues cautioned him that administering bile acids to a patient with liver disease was dangerous. But armed with molecular understanding of the pathophysiology of the disease and insights from MS, he persisted.

His persistence paid off in March 2015 when the Food and Drug Administration approved Cholbam, a cholic acid formulation marketed by the company Setchell co-founded, to treat rare bile acid synthesis disorders.

CHANGING REIMBURSEMENT MODELS FORCE LABS TO DEVELOP NEW STRATEGIES

By Nicole Tolan, PhD

Healthcare has shifted from a fee-for-service to a capitated reimbursement model that is now extending to clinical diagnostic testing. However, many labs struggle to provide the clinical and economic evidence for how laboratory medicine supports this value-based endeavor.

This challenge was the focus of the Chair's Invited Session. Kathleen Swanson, MS, RPh, Michael Crossey, MD, PhD, and Richard VanNess, MS, of TriCore Reference Laboratories discussed how laboratories can provide targeted interventions in disease management programs for use in clinical workflows.

The speakers described how population health management relies on aggregating patient information such as longitudinal laboratory data, as well as innovative data analytics, patient-specific targeted interventions, and clinical decision support. Health systems are using these tools to improve patient outcomes and reduce the total cost of care.

In another session related to cost-effective care, Octavia Peck-Palmer, PhD, and Eugenio Zabaleta, PhD, explored how to make patient-centered care both efficient and standardized. They explored how laboratorians must not only mine the literature of evidence-based medicine, but also proactively create evidence to support best practices.

Both Peck-Palmer and Zabaleta also emphasized the role of clinical laboratory professionals as accountable team members in improving test utilization, specifically through disease-specific protocols and evidence-based test order sets.

ACHIEVING BETTER DIALOGUE AMONG LAB LEADERS

By Dustin Bunch, PhD

Communication is a long-standing issue in every field. This becomes apparent in clinical laboratories when medical directors and administrators not only have different reporting structures but also distinct primary goals. These differences play out through issues such as hospital network standardization, instrument procurement, test stewardship, and daily operational concerns. The consequences of misunderstandings in these areas span the gamut from patient redraws to life-threatening errors.

AACC's Society for Young Clinical Laboratorians hosted a workshop to take on some of the communication challenges in labs, with speakers representing both academic and multi-hospital systems.

Joshua Nielson, a lab operations director, focused on collaboration among lab medical directors and administrators. A truly functional laboratory operation will only be achieved with open communication channels, he emphasized. Steve Manzella, PhD, identified major reasons for miscommunication in a highly matrixed institution, which included misunderstanding of roles and responsibilities, ambiguity of authority, and lack of a guardian. Alison Woodworth, PhD, examined the world outside the laboratory silo. Laboratorians are essential members of patient care teams, she stressed, and need to engage with clinical teams to determine their laboratory testing needs. Finally, Elise Yu, PhD, covered approaches to folding a new hospital into a healthcare system, including consolidation, standardization, and preparing medical directors to manage conflicting priorities.

WHEN TEST RESULTS DON'T MAKE SENSE

By Zahra Shajani-Yi, PhD

Sometimes laboratory results are puzzling: Results don't match a patient's clinical picture, or even more perplexing, the results of complementary

analytes are contradictory. In times such as these, what's a clinician to do? Call the friendly local clinical laboratorian, of course.

In a scientific session, "What Endocrinologists Will Ask You," experts helped equip laboratorians to answer three of the most common laboratory queries facing endocrinologists. Mark Gurnell, MBBS, PhD, spoke about the difficulties in interpreting thyroid function tests when the results are discordant. He outlined potential confounders such as pregnancy, non-thyroidal illness, or medications such as thyroxine, amiodarone, heparin, or glucocorticoids.

Nikola Baumann, PhD, spoke about how biotin sometimes interferes with lab measurements. It is essential for clinical laboratorians to know not only how assays in their labs work, but also how to explain potential interferences to clinicians. Based on a survey of nearly 200 patients, Baumann and her colleagues discovered that only 8% of outpatients were aware that they were taking biotin supplements.

The third speaker, David Sacks, MB ChB, FRCPath, explained how factors independent of glucose concentration changes can alter HbA1c. Hemoglobin variants, elevations of hemoglobin F, and renal failure all can cause analytical interferences. When a lab suspects one of these, testing by an alternative method often provides an accurate result.

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Regulatory Roundup

FDA Clears Inova's Test to Help Diagnose Myopathy

Inova Diagnostics has received Food and Drug Administration clearance for Quanta Flash HMGCR, a test that aids in the diagnosis of idiopathic inflammatory myopathy (IIM). IIM is a group of conditions that affect the skeletal muscles, resulting in progressive muscle weakness and in some cases leading to tissue necrosis and disability. In some instances, IIM develops in patients taking statins to lower blood cholesterol. Inova's test detects autoantibodies to the enzyme 3-hydroxy-3 methylglutaryl-coenzyme A reductase (HMGCR). These antibodies are a biomarker for IIM and also associated with statin exposure. The test is designed to run on the Bio-Flash instrument, a random access chemiluminescent system. By detecting HMGCR antibodies, the assay is designed to help differentiate between patients on statins with self-limited myopathy who will recover after statin discontinuation and those with progressive disease who are at risk of severe morbidity and often require aggressive immunosuppressive therapy.

FDA ISSUES ALERT ABOUT RISKS ASSOCIATED WITH RUPTURE OF MEMBRANES TESTS

The Food and Drug Administration (FDA) has issued a letter to healthcare providers about the serious adverse events related to the improper use of tests intended as an aid in detecting if a pregnant woman's water has broken—also known as a rupture of the membranes (ROM). The letter reminds providers that the labeling for these tests specifies that they should not be used on their own to independently diagnose a ROM, and that FDA has only cleared these tests for use in conjunction with other clinical assessments. The agency decided to send this letter after an ongoing assessment of medical device reports revealed adverse events related to the use of ROM tests, including 13 fetal deaths and multiple reports of health complications in pregnant women. This information indicates that healthcare providers may be relying solely on ROM tests when making critical patient management decisions, which could increase the risk of fetal harm or death.

FDA has also separately notified the public of a voluntary recall for one brand of these tests, Qiagen's AmniSure ROM test strips, which were distributed between October 2017 and March 2018. These devices do not exhibit a control line, making it potentially difficult for healthcare providers to interpret results. This recall is unrelated to the improper use of the tests, however, and FDA is not aware of device malfunctions associated with ROM tests made by other manufacturers.

FDA APPROVES ROCHE COMPANION DIAGNOSTIC FOR LUNG CANCER THERAPY

Roche has received Food and Drug Administration (FDA) approval for the cobas EGFR Mutation Test v2 to be used as a companion diagnostic test for the lung cancer treatment Iressa. Iressa (gefitinib) is a targeted monotherapy for patients with advanced or metastatic non-small cell lung cancer (NSCLC) that is positive for epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations. The cobas EGFR Mutation Test v2 uses real-time polymerase chain reaction (PCR) to qualitatively detect 42 defined mutations of the *EGFR* gene in exons 18-21—including L858R, exon 19 deletions, and T790 mutations—in order to identify patients who are most likely to respond to treatment with Iressa. It is the first FDA-approved EGFR test to include both tissue and liquid biopsy (plasma) as specimen types for testing. The test is performed on the cobas 4800 system, which offers PCR amplification and detection coupled with software that automates result interpretation and reporting.

GRIFOLS GETS FDA NOD FOR ZIKA VIRUS ASSAY

The Food and Drug Administration (FDA) has approved Grifols' Procleix Zika Virus assay for the detection of the virus in individual or pooled plasma specimens from human donors, including from volunteer donors of whole blood and blood components for transfusion. Grifols' assay is also approved for testing plasma or serum specimens in order to screen other living (heart-beating) or cadaveric (non-heart beating) organ donors, as well as human cells, tissues, and cellular and tissue-based products. The assay is performed on the Procleix Panther system automated platform using nucleic acid technology, and is designed to enable blood banks and donor centers to enhance the safety of their blood supplies. It has been in use since June 2016 under an FDA Investigational New Drug protocol to screen donated blood collected in the U.S. In 2016, the Procleix Zika Virus assay was also CE-marked for use in European countries.

ILLUMINA RECEIVES APPROVAL FROM CHINA FOR BENCHTOP NGS SYSTEM

The China Food and Drug Administration (CFDA) has approved Illumina's MiSeqDx Sequencing system, making this Illumina's first CFDA-cleared, next-generation sequencing system in China. A benchtop sequencer designed specifically for clinical laboratories, the MiSeqDx system uses Illumina's sequencing by synthesis chemistry and includes integrated software that enables run setup, sample tracking, user management, audit trails, and data interpretation. The system is designed for use with a menu of in vitro diagnostic (IVD) assays and also as an open platform for the development of custom IVD tests. MiSeqDx features an automated workflow that starts by extracting genomic DNA from peripheral whole blood specimens or formalin-fixed paraffin embedded tissues. These DNA samples are then used to generate indexed libraries, which are sequenced with a ready-to-use, prefilled, MiSeqDx reagent cartridge.

In addition to China, the MiSeqDx Sequencing system now has regulatory approval in the U.S., Canada, Argentina, European countries recognizing the CE mark, Australia, South Korea, Thailand, and the Philippines.

CHINA FDA OKS NOVOGENE LUNG CANCER CO-DIAGNOSTIC

Tianjin Novogene Bioinformatics Technology Company, a fully-owned subsidiary of Novogene, has received China Food and Drug Administration (CFDA) approval for its NovoFocus NSCLC CDx test. The NovoFocus uses next-generation sequencing (NGS) to simultaneously analyze tumor samples for multiple genomic mutations associated with the efficacy of several CFDA-approved targeted therapies for non-small cell lung cancer (NSCLC). The NovoFocus was developed on the Thermo Fisher Ion Proton sequencing platform, while the reagent kits for sample processing and library construction, as well as the data analysis and result reporting software system, were developed by Novogene. Following this CFDA approval, healthcare professionals can use results from the test's sequencing and analysis of three genes, *EGFR*, *ALK*, and *ROS1*, to identify NSCLC patients who might be eligible for treatment with Iressa (gefitinib), Tagrisso (osimertinib), and Xalkori (crizotinib), respectively. The test also provides mutation analyses for three other oncogenes, *KRAS*, *BRAF*, and *PIK3CA*, which can be used with other test results and a patient's disease characteristics to guide clinical decisions.

Industry Playbook

Tufts and Partners to Evaluate Targeted Genomic Sequencing Panel for Newborns

Tufts Medical Center researchers and several collaborators have received a 5-year grant award for more than $8 million from the National Center for Advancing Translational Sciences of the National Institutes of Health to study integrating targeted genomic sequencing into neonatal diagnosis and care. The six-site study will evaluate the accuracy and efficacy of a targeted genomic sequencing panel that analyzes 1,722 genetic disorders known to affect newborns and that Tufts is developing in conjunction with Quest Diagnostics. In addition to Tufts, the other study sites include Rady Children's Institute for Genomic Medicine, Mt. Sinai Hospital, University of North Carolina at Chapel Hill, Cincinnati Children's Hospital, and the University of Pittsburgh. The study will recruit 400 newborns with a wide variety of possible genetic disorders unable to be diagnosed using standard testing. Each infant will undergo whole genome sequencing in addition to testing with the targeted panel. The researchers will then compare the two approaches for accuracy and efficacy in identifying genetic disorders, and will determine whether the targeted panel can be safely integrated into newborn care.

The study also will conduct statistical and health economic analyses to determine if, and how much, targeted genomic testing for newborns would save the healthcare system. Since targeted screening is less costly than whole genome sequencing, the collaborators believe targeted testing could lead to substantial savings in addition to improving the standard of care.

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GENEDRIVE, FIND TO ASSESS HCV KIT FOR LIMITED-RESOURCE SETTINGS

Genedrive and the Foundation for Innovation of New Diagnostics (FIND) have teamed to evaluate the performance of the Genedrive HCV ID kit. The kit, a qualitative hepatitis C virus (HCV) diagnostic assay that is performed on Genedrive's portable molecular diagnostics platform, delivers results in 90 minutes. Under the terms of this agreement, FIND was expected to lead evaluation studies of Genedrive's test in Cameroon and the country of Georgia from September 2018 through May 2019. These studies are intended to assess the diagnostic accuracy of Genedrive HCV ID across diverse genotypes, as well as the test's usability in the limited-resource settings for which it is designed. The studies will also feed into FIND's broader efforts as the lead partner on a multi-year, multi-country HCV

project intended to support the development of simple point-of-care HCV diagnostic tools that can be made widely available.

NATERA, FOX CHASE CANCER CENTER TO STUDY CTDNA ASSAY FOR KIDNEY CANCER

Natera and Fox Chase Cancer Center have partnered to assess Natera's Signatera customized circulating tumor DNA (ctDNA) assay for monitoring recurrence of kidney cancer. The study will analyze biological specimens collected and banked from 49 patients diagnosed with kidney cancer, including one group whose cancer recurred and another that did not experience recurrence after 3 years or more. The study will use Signatera—currently a research-use only assay—as well as next-generation sequencing technology to determine whether Signatera distinguishes between the recurring and non-recurring kidney cancer cases. "There is a paucity of data for [ctDNA] in kidney cancer," said Philip Abbosh, MD, PhD, an assistant professor at the Fox Chase Cancer Center and study lead. "Determining the relationship between kidney cancer genetic profiles and prognosis, including recurrence, using the Signatera assay has great potential to improve patient care by detecting cancer recurrence earlier, assisting adjuvant therapy decision-making, determining treatment effects, and assessing the need for intervention during follow-up."

TECAN TO BUY NUGEN TECHNOLOGIES

The Switzerland-based Tecan Group has entered an agreement to acquire NuGen Technologies for $54.5 million with the goal of expanding Tecan's offerings to include next-generation sequencing (NGS) reagents. Under the terms of the acquisition, NuGen will become part of Tecan's Life Sciences Business. NuGen provides NGS and microarray sample preparation solutions for a broad range of specimen types including RNA and DNA from whole tissues, formalin-fixed paraffin-embedded tissue samples, and single cells from blood samples. By combining NuGen's products with its own automated workstations, Tecan aims to offer complete solutions for NGS library preparation that include dedicated workstations, accompanying consumables, and differentiated NGS reagents. "NuGen's innovative NGS kits and genomic sample preparation solutions are an excellent complement to our industry-leading automated workstations for genomic applications," said David Martyr, PhD, CEO of Tecan. "Through this acquisition, we are accelerating our broad genomics strategy and further increasing our recurring revenues."

DIAGENODE ACQUIRES EPIGENETICS SERVICE PROVIDER

Diagenode has bought Nxt-Dx in the hopes that this acquisition will broaden the company's role in epigenetic biomarker discovery. Based in Belgium, Nxt-Dx provides a broad range of epigenetics services, including targeted DNA methylation assays that use pyrosequencing or next-generation sequencing and Illumina's Infinium Methylation Epic array. These technologies are designed to enable more targeted screening of DNA methylation biomarkers. In addition, Nxt-Dx offers chromatin and messenger RNA wet-lab and analysis services. "The services offered by Nxt-Dx perfectly complement Diagenode's current chromatin, RNA, and DNA methylation assay services and will allow researchers to focus both on discovery and validation of epigenetic signatures," said Didier Allaer, CEO of Diagenode. "Additionally, the targeted DNA methylation analyses that Nxt-Dx offers now close the gap between epigenetics and [in vitro diagnostic] assay development."

SOTERA HEALTH BUYS GIBRALTAR LABORATORIES

Sotera Health has acquired New Jersey-based Gibraltar Laboratories, thereby expanding the U.S.-based analytical testing capabilities of Sotera Health's Nelson Labs business. Gibraltar Laboratories provides microbiology and analytical chemistry testing, as well as sterility assurance, for medical device and pharmaceutical manufacturers. Its facilities are Food and Drug Administration-registered and ISO 17025-accredited. Sotera expects this acquisition to enhance Nelson Labs' offerings, which include microbiological testing, analytical testing, and expert advisory services to assist customers in developing and maintaining sterilization solutions in medical devices, as well as in tissue/implantable products and the pharmaceutical and biologics fields. "Gibraltar's offerings and the strategic location of its facilities will be a great benefit to our mutual customers," said Jeff Nelson, president of Nelson Labs. "The Gibraltar team … has an excellent reputation for designing specialized studies that help manufacturers prove the safety, efficacy, and regulatory compliance of their products."

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Ask The Expert

How the CDC Clinical Standardization Programs Are Improving Hormone Tests

EXPERT
Krista Poynter

Why is standardization of laboratory tests important?

A: Correct diagnosis, treatment, and prevention of diseases depend on accurate and reliable laboratory tests. Standardization, also known as harmonization, ensures that laboratory tests meet these requirements; if a test is standardized, this means that a thorough, independent assessment has demonstrated that its analytical performance meets defined analytical performance goals and clinical needs. With standardized laboratory tests, patients should receive the same diagnosis and treatment independent of where or how the measurements are made. In addition, it is more time and cost efficient for labs that use standardized tests to also use reference ranges and clinical decision levels defined by a standardized test.

What is the Centers for Disease Control and Prevention (CDC) doing to standardize laboratory tests?

The CDC Clinical Standardization Programs (CSP) ensure that the accuracy, precision, and other analytical performance parameters of a laboratory test are improved, verified, and maintained. To achieve this, CDC CSP maintain metrological reference laboratories, operate programs to standardize and harmonize assays, and monitor measurement performance in patient care and research. CDC CSP also work with partners and stakeholders, such as the Partnership for the Accurate Testing of Hormones (PATH), to define analytical performance criteria and reference ranges and generate biomarker data in the U.S. population.

Currently, CDC CSP reference laboratories provide reference measurements for eight analytes including total testosterone and estradiol. CDC CSP also operate standardization programs, including the Hormone Standardization Program (HoSt), the Vitamin D Standardization-Certification Program, and the Lipids Standardization Program, with more than 300 assay manufacturers and laboratories with laboratory-developed and commercial tests participating. CDC CSP are working with these participants to improve the accuracy and reliability of laboratory tests and achieve standardization for consistent and effective patient care.

What progress has CDC made with standardizing total testosterone and estradiol tests?

Since HoSt began in 2010, CDC has had more than 350 participants in 15 countries. Participants have shown measureable improvements for both total testosterone (TT) and estradiol (E2). Specifically, the among-laboratory bias has decreased from 16.5% in 2007 to 2.8% in 2017 for TT and from 54.8% in 2012 to 13.9% in 2017 for E2. Not only has bias improved, but data from proficiency testing programs also show that standardized testosterone assays are more accurate and consistent compared to non-standardized assays.

Recently, CDC CSP also collaborated with the Endocrine Society and PATH to develop reference ranges for testosterone in non-obese men ages 19-39 years old. These reference ranges are now part of an Endocrine Society clinical practice guideline and according to this guideline can be used by laboratory tests standardized to CDC's criteria.

What are the next steps now that CDC has received additional funding from Congress for harmonization in 2018?

This is the first time CDC has received dedicated funding from Congress to improve the quality and reliability of diagnostic tests for hormones. With these funds, CDC CSP plan to increase in size and scope through the addition of new programs, such as the Accuracy-based Monitoring Program for routine laboratories, and new biomarkers such as parathyroid hormones, free thyroxine, and free testosterone. CDC CSP will continue to work with stakeholders and participants to reduce calibration bias and individual sample bias in order to enhance patient care and public health.

The author would like to thank Hubert W. Vesper, PhD, for his support with this article. CDC CSP would like to thank AACC, PATH, and the Endocrine Society for their support and assistance. *The findings and conclusions in this article have not been formally disseminated by CDC and should not be construed to represent any agency determination or policy. Use of trade names and commercial sources is for identification only and does not constitute endorsement by the U.S. Department of Health and Human Services or CDC.*

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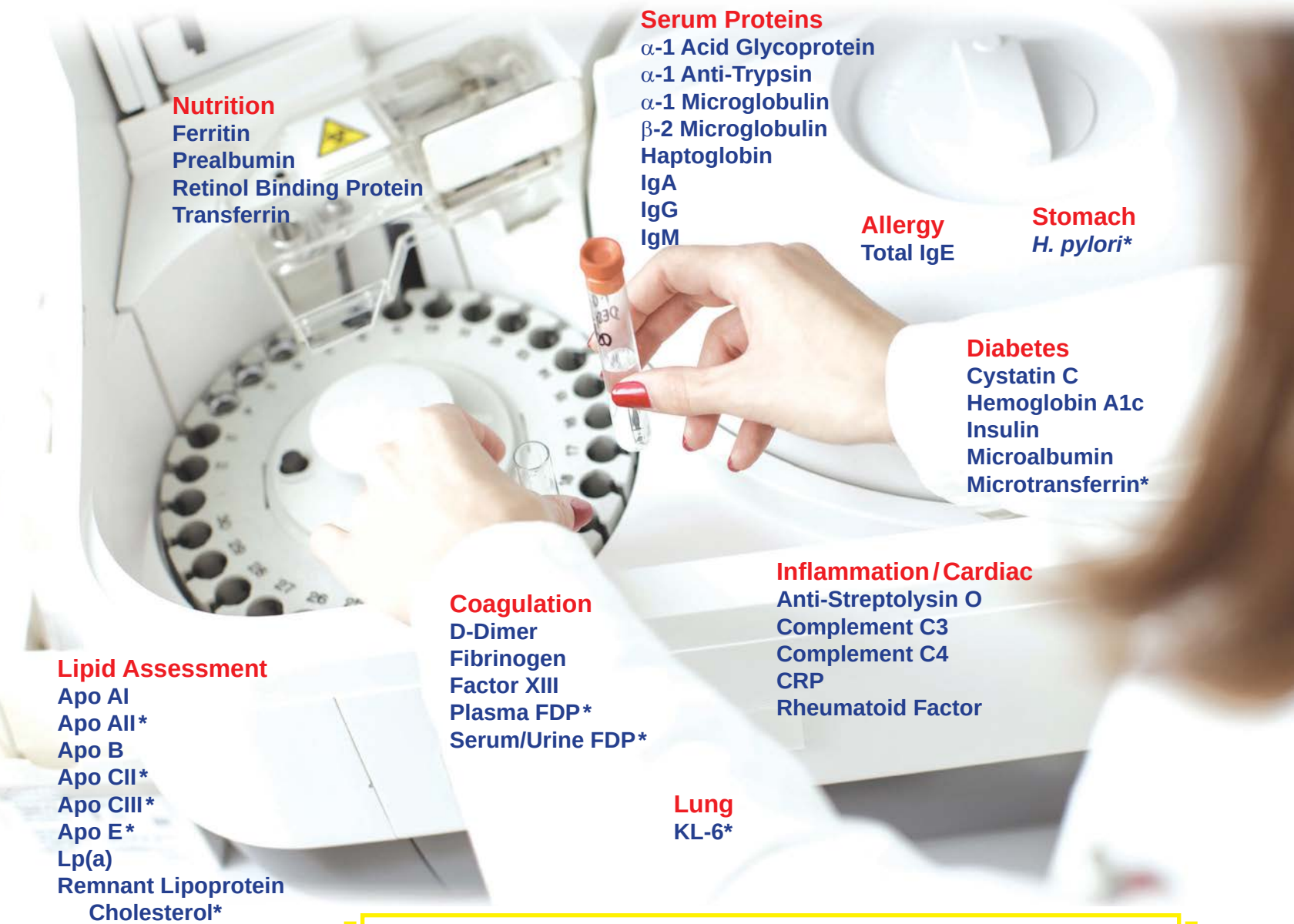

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