November 2022

CLN Clinical Laboratory News

An AACC Publication | Volume 48, Number 9

AUTOMATED CVD RISK SCORE

97.5%

Specificity for identifying statin-eligible patients

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- Implementing High-Sensitivity Troponin
- Comparing Assays
- Lipid Reporting Primer

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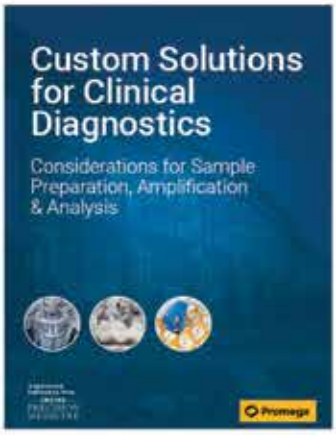

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Clinical Laboratory News is published monthly (10 times per year—Jan./Feb., March, April, May, June, July/Aug., Sept., Oct., Nov., and Dec.) by the American Association for Clinical Chemistry. 900 Seventh St., NW, Suite 400, Washington, DC 20001. Phone: +1 202.835.8756 or +1 800.892.1400 Fax: +1 202.877.5093. Contents copyright © 2022 by the American Association for Clinical Chemistry, Inc., except as noted. Printing in the U.S.A. POSTMASTER: Send address changes to AACC, 900 Seventh St. NW, Suite 400, Washington, DC 20001.

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Features

Departments

The most important thing the lab can do is to maintain an open dialogue with clinicians.
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Federal Insider

FDA Must Improve EUA Process, Federal Investigators Say

The Food and Drug Administration's (FDA) use of emergency use authorizations (EUAs) in the early part of the COVID-19 pandemic came at a cost to quality, but the agency's experience during the pandemic offers lessons the government needs to learn from, according to a report by the Department of Health and Human Services (HHS) Office of Inspector General (OIG).

OIG analyzed data about SARS-CoV-2 EUAs in the first 5 months of the pandemic and found that while FDA's policies helped tests get to market quickly, these policies also resulted in numerous problematic tests on the market, requiring further action by FDA. For example, an FDA study of 125 EUAs found that more than half had design or validation problems.

Additional issues arose when FDA began allowing tests on the market without EUAs in the spring of 2020, with serology tests posing a particular problem, OIG said. For example, by April 2020, the agency saw a "flood of poorly performing and inappropriately marketed serology tests." OIG also criticized FDA for lacking "clear and direct" communication with the lab community.

To avoid future problems, OIG issued six core recommendations: assess and revise guidance for test EUA submissions; develop a suite of EUA templates for future emergencies involving novel pathogens; expand the FDA Center for Devices and Radiological Health's existing device-tracking platform to facilitate EUA submission and monitoring; expand and improve resources for test developers on the EUA process; establish formal communication channels between FDA and the lab community for use in emergencies; and finally, work with federal partners to implement lessons learned about a national testing strategy that goes beyond the EUA process.

NATIONAL BIODEFENSE STRATEGY HIGHLIGHTS DIAGNOSTICS

The U.S. Department of Health and Human Services (HHS) announced its approach to implementing the administration's 2022 National Biodefense Strategy. President Biden has requested $82 billion from Congress over 5 years for pandemic preparedness and biodefense.

One area of focus is early warning and awareness of potential pandemics. HHS will invest in expanded ability to conduct rapid genomic sequencing and analysis and support the development of global systems to share information, data, and samples internationally and across industry sectors.

Specifically, HHS wants the government to be able to deploy at least one "pathogen-agnostic" test within 12 hours for thousands of samples on the first day and tens of thousands of samples per day within 1 week, and sufficient pathogen-specific tests within 30 days of a significant biological incident being determined.

Additionally, the plan calls for HHS to enable the development, validation, and production of authorized pathogen-specific, rapid point-of-care tests within 90 days of a significant incident determination.

CMS TO CREATE NATIONAL HEALTHCARE DIRECTORY

The Centers for Medicare and Medicaid Services (CMS) is seeking public input on creating a national directory with information on healthcare providers and services with the goal of spurring electronic health data exchange and resources for patients. The directory would help facilitate care coordination and public health data reporting as well, according to CMS.

The agency noted that patients sometimes struggle to find up-to-date information about providers in their network. Meanwhile, providers face redundant and burdensome reporting requirements to multiple databases. As a result, existing directories often contain inaccurate information, rarely support interoperable data exchange or public health reporting, and are costly to the healthcare industry.

CMS wants the directory to serve as a "centralized data hub" for all healthcare directory and contact information with validated data in a publicly accessible index, developed through streamlined information submission from providers.

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Although postoperative acute kidney injury (AKI) is a serious complication after cardiac surgery, preventive measures are limited. Despite the known association of preoperative low magnesium levels with cardiac surgery–related atrial fibrillation, the association between preoperative magnesium concentration and postoperative AKI has not been fully elucidated.

In this webinar, Dr. Hee Byung Koh, Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, South Korea will describe the association between preoperative serum ionized magnesium level and the development of AKI after cardiac surgery. He will discuss the need for close monitoring of ionized magnesium levels, both preoperatively and intraoperatively, and the benefits of active magnesium supplementation.

By the end of the presentation, the viewer will:

- Recognize the benefits of closely monitoring ionized magnesium levels before cardiac surgery
- Understand the prevalence of postoperative AKI in patients with lower serum magnesium levels
- Learn how hypomagnesemia is a modifiable risk factor for cardiac surgery related AKI
- Learn how point of care testing can aid in monitoring ionized magnesium levels and other critical analytes

Primary Presenter
Hee Byung Koh, MD, PhD
Severance Hospital, Dept. of Internal Medicine, Institute of Kidney Disease Research, Yonsei University College of Medicine
Seoul, South Korea

Ionized Magnesium Testing and AKI Screening

In this presentation, Dr. Naveen Bangia will review point of care methods for monitoring ionized magnesium as well as BUN, Creatinine, eGFR and estimated plasma volume for kidney injury.

Presenter
Naveen Bengia, PhD
North American Director of Medical and Scientific Affairs
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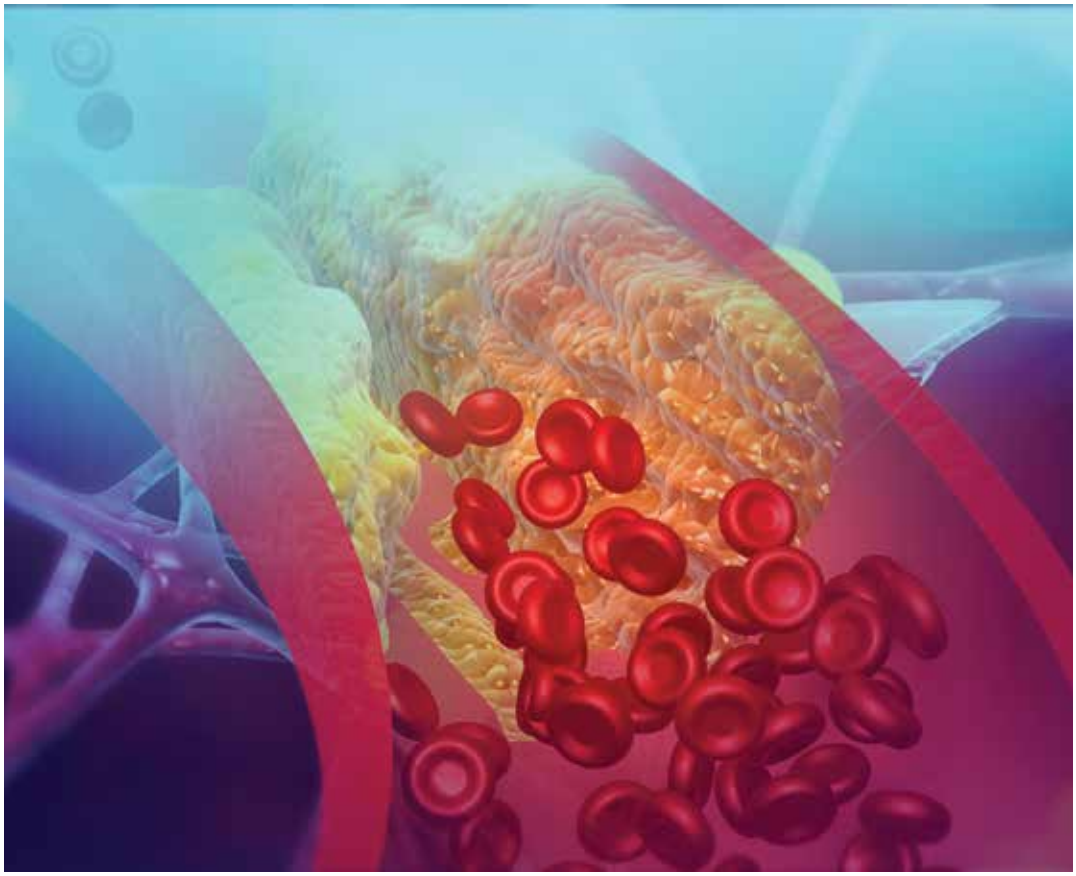
Bench Matters

The Skinny on Lipid Reporting



By Sarah R. Delaney, PhD, DABCC

By Daniel R. Beriault, PhD, FCACB

Lipid testing is a cornerstone in atherosclerosis and cardiovascular disease (ASCVD) risk assessment. While there are several comprehensive clinical guidelines that focus on the primary prevention of ASCVD, guidance for the clinical lab remains limited. This causes significant variability in the way lipid testing is reported.

Here, we provide a general overview of recommendations from various clinical practice guidelines and briefly discuss considerations for lipid reporting in the clinical laboratory. More comprehensive evidence-based guidance on reporting, flagging, and interpretation is covered in the recently published Canadian Society of Clinical Chemists Harmonized Reference Interval Working Group (CSCC hRI-WG) recommendations.

What Should A Standard Lipid Profile Consist Of?

A standard lipid profile can provide the essential information needed to screen for dyslipidemia and establish CVD risk. A lipid panel should consist of total cholesterol, high density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), non-HDL-C, and triglycerides. This, along with relevant clinical and demographic information, allows for the estimation of ASCVD risk using a variety of endorsed tools, such as the Framingham Risk Score or the Pooled Cohort Equation. These tools are used by providers and patients to estimate the risk of a cardiovascular event in the next 10 years. LDL-C and non-HDL-C are used as treatment targets in patients being monitored over time. LDL-C is the primary treatment target; however, non-HDL-C is recommended as an alternative when triglycerides are elevated.

Apolipoprotein B (apo B) is another important test in ASCVD screening. These markers should be offered only as individual orderable tests and not a part of the standard panel. ApoB is recommended as an alternative treatment target and risk-enhancing biomarker by multiple guidelines. However, apoB is not currently endorsed as a routine screening measure because LDL-C and non-HDL-C are readily accessible on the standard report. Direct measurement of ApoB is particularly useful in situations where the calculated

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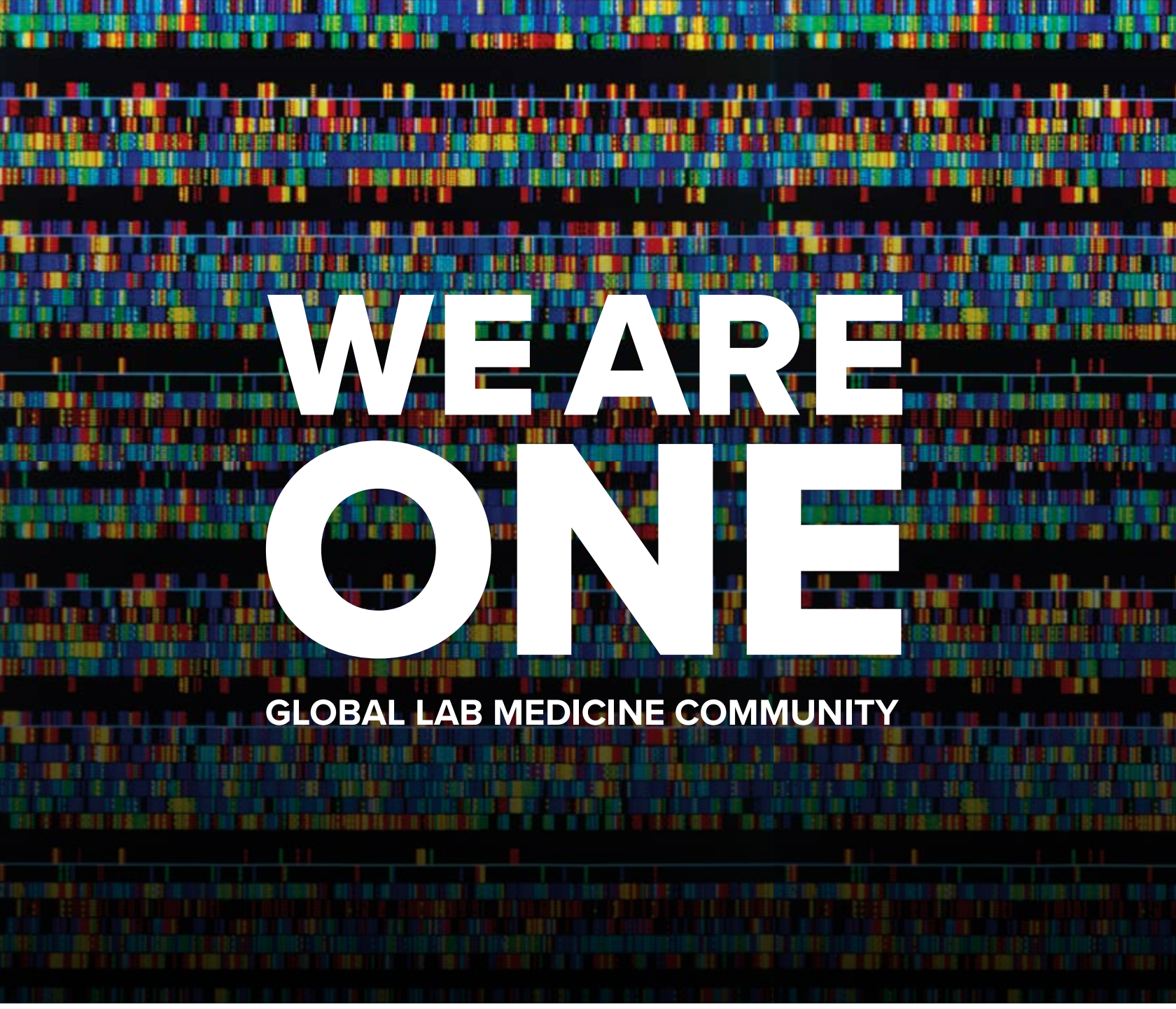

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Image: Human DNA Sequence for the Human Genome Project. James King-Holmes/Science Photo Library

LDL-C or non-HDL-C result may not be accurate (e.g., genetic conditions of dyslipidemia).

The Emergence of Lp(a) in Clinical Guidelines

Recently, U.S., Canadian, and European cardiovascular societies have recommended Lp(a) testing to help identify patients at higher risk for ASCVD. As Lp(a) concentration is highly dependent on variations in the LPA gene, measurement is recommended only once in a person's lifetime. Values ≥50 mg/dL (≥100 nmol/L) are associated with an increased risk of myocardial infarction and aortic valve stenosis; thus, it is recommended that these patients undergo earlier and more intensive health behavior modification and management.

What these clinical guidelines neglect is the significant heterogeneity in commercial Lp(a) assays. The apo(a) protein on Lp(a) exhibits significant variation in its size from person to person. The use of immunoassays with polyclonal antibodies against apo(a) will overlook the variation in apo(a) size and result in inaccurate Lp(a) results. Therefore, laboratories should select Lp(a) assays that are insensitive to apo(a) isoform size with calibrators traceable to the WHO/IFCC reference material. The most appropriate units of measurement for Lp(a) are nmol/L, as mass units (mg/dL) will be affected by the size of apo(a).

LDL-C Estimation: Farewell to Friedewald?

For decades, the Friedewald equation has been used to calculate LDL-C using results from components of the standard lipid panel. This equation is sufficiently accurate for normolipidemic patients; however, due to the nature of the formula (LDL-C = total cholesterol – HDL-C – (triglycerides/5)), hypertriglyceridemia can lead to the significant underestimation of LDL-C and can even produce negative (invalid) results. Due to the lack of direction from existing guidelines, a nonsensical result often gets reported and left to the interpretation of clinicians.

Novel estimation methods (e.g., Martin/Hopkins and Sampson/NIH equations) have been developed to improve LDL-C calculation, particularly in samples with triglycerides >400 mg/dL (4.5 mmol/L) or with low LDL-C. The 2019 American Heart Association/American College of Cardiology guidelines recommended the equation developed by Martin et al. (see suggested reading) as the preferred method for patients with low LDL-C.

More recently, the NIH developed a novel equation (Figure 1) to calculate LDL-C in patients with triglycerides up to 800 mg/dL (9.0 mmol/L) with improved accuracy and without the pitfalls of the Friedewald equation. Others have validated this estimation method and have recommended reporting limits of >20 mg/dL (>0.5 mmol/L) for LDL-C and <800 mg/dL (9.0 mmol/L) for triglycerides (Table 1). An advantage of the NIH equation is that it can easily be implemented using the lipid parameters from the standard lipid panel. The equation below and is free to use.

To Flag Or Not to Flag? That Is the Question

In lipid testing, flagging a result is not as simple as setting a clinical cutoff, as target concentrations change based on clinical scenario. Lipid testing can be utilized for initial screening or for monitoring patients after the initiation of lipid-lowering therapy. However, due to the complexity of decision algorithms, it is challenging for a clinical laboratory to provide flags for each scenario.

There is agreement on which levels indicate when lipid-lowering treatment should be initiated—without any additional risk assessment. The evidence suggests that it is best to flag results lower than this cutoff to invite clinicians to assess if any additional risk factors might increase the likelihood of CVD. Further clarification on flagging limits and interpretive comments are included in the CSCC hRI-WG harmonized lipid reporting guidelines.

Food For Thought: Nonfasting Lipid Testing

The utility of nonfasting lipid testing continues to be promoted by many clinical practice guidelines. In short,

F1 NIH equations in mg/dL and mmol/L

In mg/dL

$$LDL-C = \frac{Cholesterol}{0.948} - \frac{HDL-C}{0.971} - \left(\frac{Triglycerides}{8.56} + \frac{Triglycerides \times Non-HDL-C}{2140} - \frac{Triglycerides^2}{16100}\right) - 9.44$$

In mmol/L

$$LDL-C = \frac{Cholesterol}{0.948} - \frac{HDL-C}{0.971} - \left(\frac{Triglycerides}{3.74} + \frac{Triglycerides \times Non-HDL-C}{24.16} - \frac{Triglycerides^2}{79.36}\right) - 0.244$$

T1 Recommended reporting limits for Friedewald and NIH equations

	Friedewald	NIH
Triglycerides	<400 mg/dL (<4.5 mmol/L)	<800 mg/dL (<9.0 mmol/L)
LDL-C	Not established*	>20 mg/dL (>0.5 mmol/L)

* Do not report negative results

for patients it is more convenient, encourages compliance, and yields accurate predictions for ASCVD risk, with the added advantage for the laboratory of reducing bottlenecks for sample collection and testing.

Although there is no consensus on triglyceride concentration that would require repeat testing in a fasted state, clinical scenarios warranting fasting lipid assessment include mainly patients with hypertriglyceridemia. Offering both fasting and nonfasting options (with the number of fasting hours recorded) is recommended for the most comprehensive ASCVD risk assessment.

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Suggested Reading

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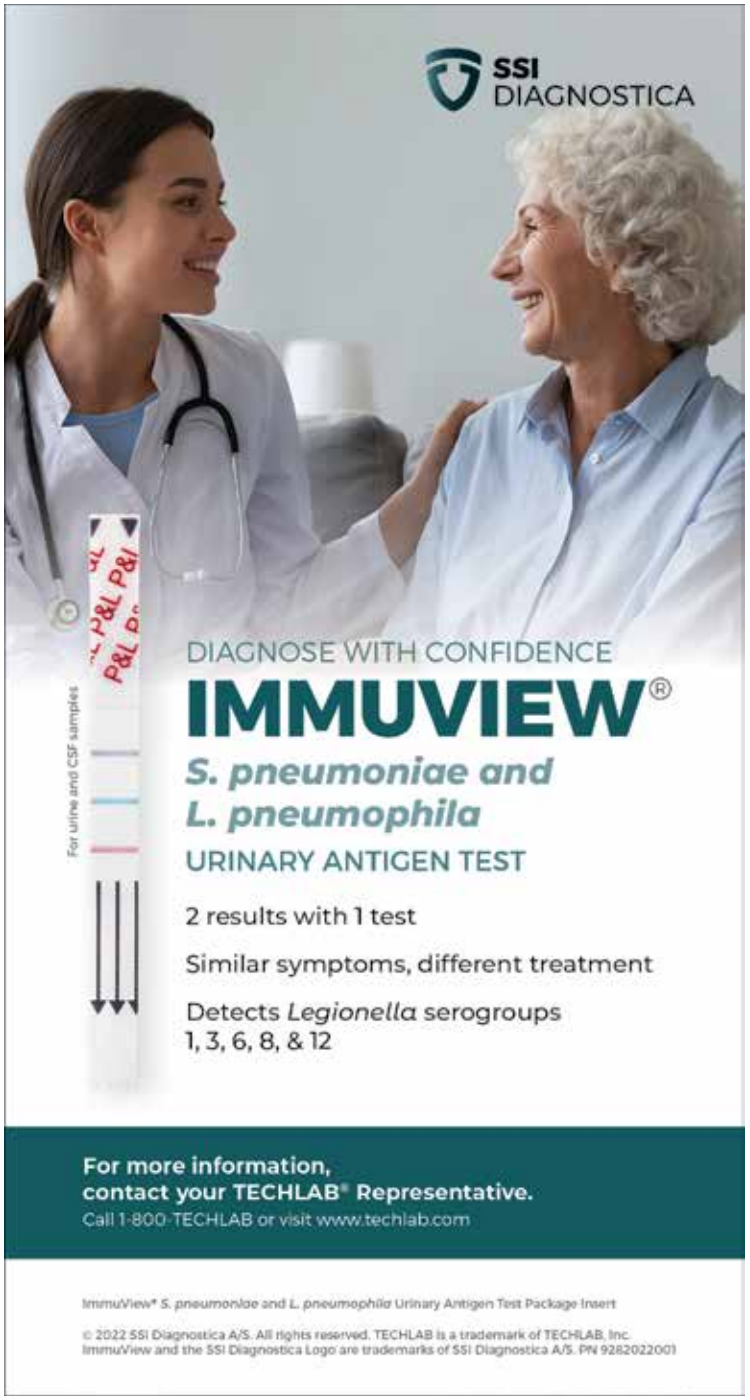

The Sample

New Risk Score Helps Show Who Needs Statins

A newly developed risk score for patients who have fasting lipid panel testing can help healthcare providers identify those eligible for statins (Clinical Chemistry 2022; doi: doi.org/10.1093/clinchem/hvac120).

Guidelines recommend atherosclerotic cardiovascular disease (ASCVD) calculations via pooled cohort equations (PCE) for calculating a 10-year ASCVD risk and statin eligibility for most patients ages 40 to 75. However, only about a third of eligible patients receive appropriate treatment, and roughly half of patients prescribed statins inappropriately discontinue them. In response, researchers developed an alternative risk equation that allows for the automated calculation of ASCVD risk by clinical laboratories that process fasting standard lipid panels.

The researchers developed estimated ASCVD (eASCVD) risk score equations using concentrations of total cholesterol, high-density lipoprotein cholesterol, triglycerides, and age as variables for nonhispanic white men, Black men, nonhispanic white women, and Black women. The researchers derived eASCVD scores using regression analysis to yield similar risk estimates as the standard ASCVD risk equations for 6,027 nondiabetic National Health and Nutrition Examination Survey subjects who were not on lipid-lowering therapy.

At a cutpoint of 7.5% for the whole population over 10 years, the eASCVD risk score had an overall sensitivity of 69.1% and a specificity of 97.5% for identifying statin-eligible patients with at least intermediate risk, based on the standard risk score.

Using the sum of other available risk factors, including systolic blood pressure more than130 mmHg and use of blood pressure medication and cigarettes, the eASCVD score's overall sensitivity was 93.7%, and its specificity was 92.3%. The eASCVD score showed 90% concordance with the standard risk score in predicting cardiovascular events among 14,742 Atherosclerosis Risk in Communities (ARIC) study subjects.

Calculating eASCVD score involves no extra expense, the authors. It can help identify patients for whom a more careful consideration of nonlipid risk factors is warranted. When used with the PCE, the eASCVD risk score can help healthcare providers who do not specialize in lipid management increase compliance with statin therapy guidelines, the researchers noted.

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ALBUMINURIA LEVELS USEFUL FOR MANAGING NEWLY DIAGNOSED KIDNEY DISEASE

Recent research shows that albuminuria levels are inversely associated with a favorable chronic kidney disease (CKD) course, also known as regression (JAMA Netw Open 2022; doi: 10.1001/jamanetworkopen. 2022.25821).

Chronic kidney disease (CKD) patients are risk-stratified for adverse events based on estimated glomerular filtration rate (eGFR) and albuminuria level, but CKD often has a favorable course regardless of eGFR. The researchers aimed to determine whether lower albuminuria is associated with CKD.

The researchers assessed the 5-year probability of CKD regression across albuminuria categories accounting for the competing risks of CKD progression and death in people with newly diagnosed CKD and the association between albuminuria level and CKD regression. They analyzed administrative and laboratory data for adults with incident moderate to severe CKD in Alberta, Canada, using sustained eGFR of 15–44 mL/min/1.73 m2 for more 90 days as a definition for moderate to severe disease.

They also created categories by albumin to creatinine ratios (ACRs). Group A1 had ACR of more 3 mg/mmol), group A2 had ACR of 3–29 mg/mmol, group A3<60 had ACR of 30–59 mg/mmol), and group A3≥60 had ACR of 60 mg/mmol or higher.

In 58,004 subjects with moderate to severe CKD, albuminuria level was directly associated with CKD progression and death, and inversely associated with sustained improvement of eGFR for 90 days or longer. Five-year probabilities of CKD regression were higher in people with lower urine albumin-creatinine ratios in a stepwise fashion.

Sixty-one percent of subjects fell into group A1, 27% were in A2, 3% in A3<60, and 10% in A3≥60 albuminuria. Five-year probability of regression was highest for group A1 at 22.6%, followed by A2 at 16.5%, and A3<60 at 11.6%. Five-year probability of regression was lowest in A3≥60 at 5.3%.

Using A1 albuminuria as the reference group, the hazard of regression was highest for A2 (0.75; 95% CI, 0.72-0.79) and A3<60 (HR, 0.47; 95% CI, 0.40-0.54), and lowest for A3≥60 (HR, 0.27; 95% CI, 0.24-0.30).

These findings suggest that albuminuria can play a key prognostic role and inform CKD management, the researchers wrote.

BIOMARKERS PREDICT TBI OUTCOMES

Measuring two blood biomarkers the day of a traumatic brain injury (TBI) can predict which patients are likely to die or become severely disabled. These measurements aid clinicians' treatment decisions. (Lancet Neuol 2022; doi: 10.1016/S1474-4422(22)00256-3).

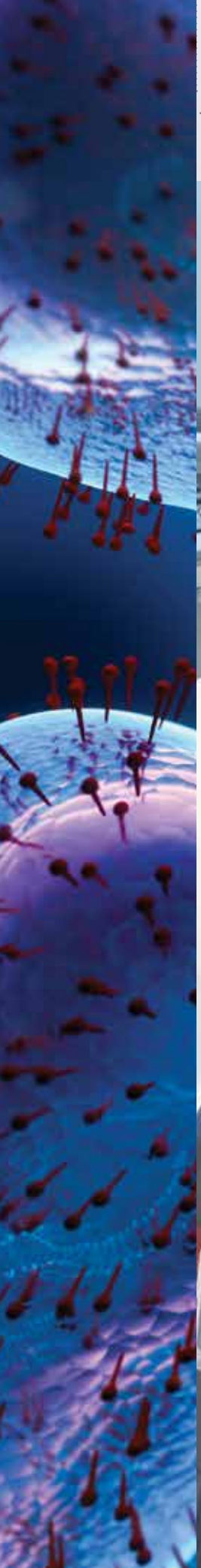
Known for their diagnostic value, day-of-injury glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase L1 (UCH-L1) plasma concentrations also have good to excellent prognostic value for predicting death and unfavorable outcome, but not incomplete recovery at 6 months. The researchers found that these biomarkers contribute the most prognostic information for participants presenting with Glasgow Coma Scale (GCS) scores of 3–12.

To quantify biomarkers' prognostic accuracy and investigate whether they contribute new prognostic information to existing clinical models, the researchers studied 1,696 patients aged 17–90 years. Patients had day-of-injury plasma samples for measurement of GFAP and UCH-L1 and completed 6-month assessments for outcome due to traumatic brain injury with the Glasgow Outcome Scale–Extended (GOSE-TBI). The researchers analyzed biomarkers as continuous variables and in quintiles.

Of the 1,696 participants with complete information, 7.1% died, 13.9% had an unfavorable outcome, 66.9% had incomplete recovery, and 33.1% recovered fully. GFAP had an area under the curve (AUC) of 0.87 (95% CI 0.83–0.91) for predicting death at 6 months in all patients, 0.86 (0.83–0.89) for unfavorable outcome, and 0.62 (0.59–0.64) AUC for incomplete recovery was 0.62 (0.59–0.64).

UCH-L1 had AUC of 0.89 (95% CI 0.86–0.92) for predicting death, 0.86 (0.84–0.89) for unfavorable outcomes, and 0.61 (0.59–0.64) for incomplete recovery at 6 months.

Participants with GCS scores of 3–12 had higher AUCs than for those with GCS score of 13–15. Among participants with GCS score of 3–12, adding GFAP and UCH-L1 (alone or combined) to three existing TBI models significantly increased their AUCs for predicting death to from 0.90–0.94 and for unfavorable outcomes to AUC range 0.83–0.89. However, among the 1,297 participants with GCS score of 13–15, adding GFAP and UCH-L1 to an observational cohort study model only modestly increased the AUC for predicting incomplete recovery.

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Pathology and Lab Medicine

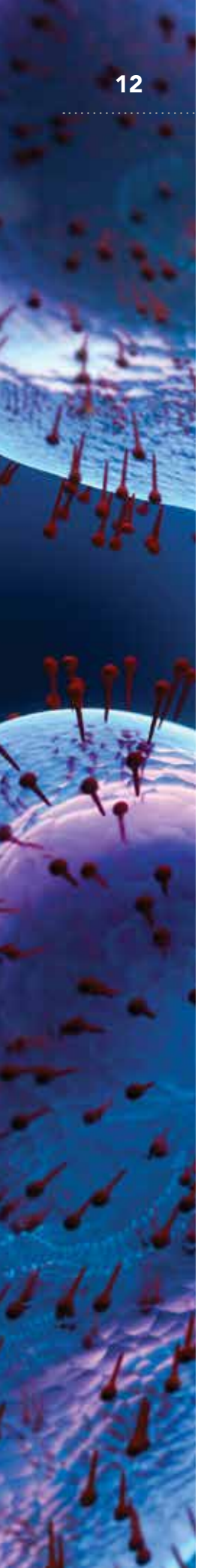
IS MONKEYPOX HERE TO STAY?

Even though officials see progress in the public health response, the virus continues to pose challenges for clinical laboratories.

BY KAREN BLUM

As things seemed to be calming down following the peak of the COVID-19 outbreak, clinical laboratories should have gotten a bit of a reprieve. Instead, they found themselves facing a new challenge this year: monkeypox. The current outbreak of monkeypox, declared a public health emergency in August by the U.S. Department of Health and Human Services (HHS), caused an initial scramble for laboratory directors and personnel, most of whom never expected to be responding to another emerging viral disease so soon.

After a few hiccups early on, there now appears to be plenty of capacity for testing, approved laboratory procedures for working with specimens, and even an emergency use authorization (EUA) in place from the Food and Drug Administration (FDA) to allow for quick approval of additional laboratory testing options. Still, some lingering issues remain regarding sample collection quality, as well as questions about who will cover the cost of tests, if testing can



expand beyond lesion material, and how the virus may evolve over time.

Learning from the COVID-19 pandemic, government agencies worked quickly to expand testing capabilities from public health laboratories to additional commercial labs, and they allowed the use of additional platforms and equipment to move things along. The expansion was three to four times what was seen during COVID-19, said Demetre Daskalakis, MD, MPH, deputy coordinator for the White House National Monkeypox Response. It has helped that the demand for testing hasn't approached that of COVID-19, either.

Like COVID-19, it's unlikely monkeypox will be eradicated, said Matthew Binnicker, PhD, director of clinical virology at Mayo Clinic in Rochester, Minnesota, and vice chair of practice in the Department of Laboratory Medicine and Pathology. "Labs likely will be testing for monkeypox in the future, and it may be something that we test for alongside other causes of dermal and genital diseases like herpes or syphilis," he said.

LABORATORY RESPONSE NETWORK SPRINGS TO ACTION

Public health laboratories found themselves on the frontlines of the monkeypox response. Soon after the first case was reported in Boston in May, the Centers for Disease Control and Prevention (CDC) began weekly communication with its Laboratory Response Network (LRN), a collection of some 120 sites (mostly state and local public health laboratories) called on to respond to public health emergencies, said Christina Hutson, PhD, branch chief of the Poxvirus and Rabies Branch at CDC and lead of the CDC Monkeypox Laboratory and Testing Task Force. About 73 of these labs use a FDA-approved assay designed by CDC to test for non-variola orthopoxviruses.

Prior to the outbreak, Hutson said, state epidemiologists would counsel clinicians to determine if pox testing was warranted, and they requested that LRN laboratories send samples to CDC for additional molecular testing and potential sequencing to characterize the monkeypox clade and lineages circulating. As cases increased, the process quickly evolved so that anyone presenting with lesions was encouraged for testing, and labs were given the option to send just 10% of their samples for further evaluation, she said.

"Labs likely will be testing for monkeypox in the future, and it may be something that we test for alongside other causes of dermal and genital diseases." —Matthew Binnicker

"We were in a very different place from COVID-19, because this is a virus we've studied for many years, although this outbreak had differences, so we are still learning," Hutson said. "We already had some tools available, including an FDA-cleared test, ready to go. What we saw, though, was although testing capacity was sufficient, it was testing access that needed improvement." This challenge was exacerbated by people unfamilair with the process of going to a public health laboratory or feeling like that was inconvenient or too cumbersome.

PIVOT TO EXPANDING ACCESS TO TESTING

CDC and other agencies took steps to help increase testing capacity. In June, CDC received approval from FDA to expand their test from only manual extraction, to add an automated extraction platform and another PCR platform to increase laboratory capacity and flexibility in what equipment could be used, Hutson said. CDC, FDA, and the HHS also expanded monkeypox testing to five commercial laboratories including Aegis Science, Labcorp, Mayo Clinic Laboratories, Quest Diagnostics, and Sonic Healthcare. They also supported non-LRN labs in developing their own tests by publishing primers and probes for CDC PCR tests.

"What we are seeing is a lot of academic medical centers come online with their own laboratory-developed testing," said Jennifer Mahn, MPA, director of clinical and sexual health for the National Coalition of STD Directors. "If they're CLIA certified or under an IRB for research, they can do [monkeypox] testing with probes or primers available from some of the firms, and control reagents or state lab positives if the public health lab is willing to give those."

CDC has a website dedicated to laboratory testing data for monkeypox, and data indicates that testing capacity for now far exceeds testing demand. As of September 28, 110,920 specimens have been tested, with 28.2% cumulative positivity rate. The available capacity is 93.8%.

"Initial concerns about the availability of laboratory tests were very much colored by the concerns that arose at the beginning of COVID-19," said Ewa King, PhD, chief program officer at the Association of Public Health Laboratories. "We see that it was somewhat unjustified because the capacity is plentiful." The PCR test started as a manual extraction, but very quickly the CDC got FDA approval to amend the 510(k) for the CDC PCR test to add one automated extraction platform as well as additional enforcement discretions to allow the use of other automated extraction platforms to push this into more of a high-throughput test category, she said.

There still have been a few issues laboratories are facing, said Binnicker, whose lab has been testing about 100 monkeypox samples a day since July. While large commercial labs have partnered with CDC and HHS to expand testing, "most hospital and small clinical labs don't have access to monkeypox tests. So that's causing a delay in the turnaround time for

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The Monkeypox Virus's Future Remains Unclear

What will happen with the current outbreak depends on both public health response and the evolving virus itself. "We've been studying this virus for years within endemic areas," said Christina Hutson, PhD, branch chief of the Pox Virus and Rabies Branch at CDC and lead of the Laboratory and Testing Task Force. "The current outbreak is not historically what we've seen as far as spread from human to human, or where the lesions are occurring. A lot of people don't seem to have the prodrome prior to lesion onset that is typical with what we classically have seen."

Benjamin Pinsky, MD, PhD, director of the Clinical Virology Laboratory at Stanford Health Care and a professor of pathology and medicine at Stanford University School of Medicine, agreed. "The presentation is not the classic presentation that you see in the textbooks. And it's been impacting a certain demographic, primarily gay, bisexual, and other men who have sex with men, due to close contact," he said.

After a bit of a slow start, there's been more availability of vaccines and more emphasis on getting vaccines to high-risk populations, Pinsky noted. Test volumes are dropping, and the positivity rate is declining; however, "the question we don't know is whether this will reemerge in other populations in the United States, or whether it has gotten into an animal reservoir such that it will be endemic."

Research shows the virus has mutated more than 50 times since a 2018 outbreak, and there have been reports of a deletion in the tumor necrosis factor receptor gene in three cases from California. This could mean that laboratory-developed tests designed using the CDC-published primers and probes that specifically target monkeypox may not detect the virus. So far CDC's Laboratory Response Network laboratories are not having this issue because they are using the nonvariola orthopoxvirus test.

"We're usually hesitant to pull out any crystal balls about where the cases are going to go, simply because it depends on so many factors," said Ewa King, PhD, chief program officer at the Association of Public Health Laboratories. "We spend our time worrying about the laboratory tests, whether there's enough of them and whether they perform well. And that seems to be largely taken care of."

results for some patients if samples have to be sent to one of the [commercial or LRN] labs."

That could change in the foreseeable future, as FDA in September released guidance for EUA requests for additional monkeypox diagnostic tests. The agency also provided voluntary templates that test developers can use when validating a test or submitting EUA requests. There also may be more options for rapid tests over the next 12 months, Binnicker said.

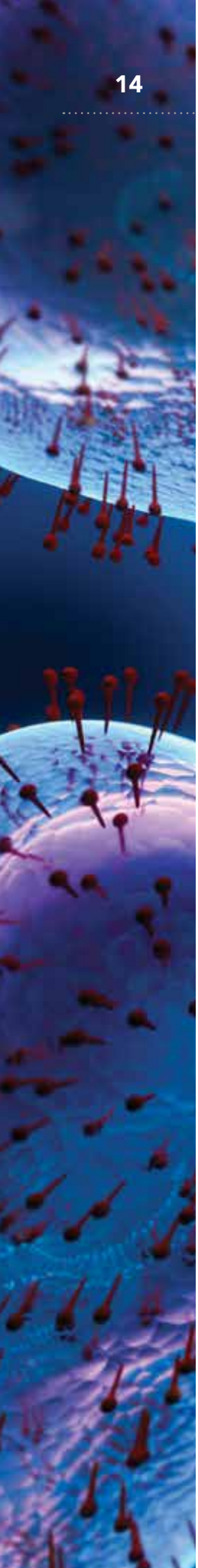
"We generally see this as a good development to have some process for registration and FDA review, when appropriate, of newly produced or modified tests," King said. "This can make tests available in locations where they have not been available yet, and at the same time, make sure that these tests perform well … and assure that laboratory-developed tests are of sufficient quality to be really helpful in the response."

EDUCATION AND SAFETY FOR LAB PERSONNEL

Education and safety for lab personnel working with samples also quickly evolved with the outbreak. For labs performing viral culture, monkeypox presents a safety risk to laboratory staff, Binnicker said: "We've actually had to discontinue viral culture of dermal and genital samples, because we don't want to inadvertently grow monkeypox and expose our staff."

Binnicker said that prior to 2022 he was familiar with monkeypox, but had not seen a case of the viral infection. "I don't think there is a strong understanding of monkeypox by most laboratory professionals or general physicians. This is something that we have not tested for or had to deal with prior to July of this year." Binnicker soon found himself giving presentations about the basics of monkeypox to his department and keeping them updated on testing protocols, including how to keep lab staff safe.

At Mayo Clinic, it's standard for staff to work with samples inside a biosafety cabinet, Binnicker said. Working inside of a laminar flow hood keeps the airflow in a certain direction and minimizes the chance of exposure. Laboratory personnel



also wear a gown, gloves, and a face shield to prevent exposure in the rare event of a spill or splash. "I think if lab staff take the right precautions, and use standard good laboratory practice, that the chance of being infected in the laboratory is very low," he said.

As an added precaution, some clinical and public health laboratories had their staff get vaccinated against monkeypox, said Chris Mangal, MPH, director of public health preparedness and response for the Association of Public Health Laboratories. They also followed protocols to use a lysis buffer and/or heat to inactivate the virus prior to working with it, allowing workers to test samples at a lower-level biosafety environment while minimizing risk of exposure.

Laboratory and medical personnel also needed to learn more about the virus and collection methods. Some staff at Labcorp and Quest were refusing to draw blood from patients who might have monkeypox, according to news reports published in August, while those companies worked on new policies.

Sample quality, too, has been an ongoing issue, said Benjamin Pinsky, MD, PhD, director of the Clinical Virology Laboratory at Stanford Health Care and a professor of pathology and medicine at Stanford University School of Medicine. His laboratory has seen "a very high rate of samples that are inadequately collected," indicating that people are not collecting the samples "as vigorously as necessary."

Physicians collecting samples "can't just rub the swab gently over the top of the rash or lesion," Binnicker explained. "There needs to be a good, vigorous collection" both to ensure there are enough cells that contain virus but also to ensure the internal control passes. CDC posted a document for clinicians describing adequate specimen collection of lesion material.

MORE QUESTIONS ARISE

Because the FDA-approved CDC test is only for samples taken from lesions, it's important that laboratories consider other specimen types, Pinsky said. "Patients don't always present with lesions. This is well-described in the literature," he said. "There are patients that present with a sore throat, or with anorectal pain or things like that. Being able to test other specimen types may be able to identify patients earlier in their prodromal phase."

Additional studies have been published looking at throat swabs, nasal swabs, and rectal swabs from patients with monkeypox.

A saliva-based test has been developed but has not reached widespread usage. Some reports from Europe have demonstrated that blood also can contain high levels of virus, Pinsky noted. Additional studies have been published looking at throat swabs, nasal swabs, and rectal swabs from patients with monkeypox. Virus can be detected in these other sample types but it's not as common for them to be positive as the swab from the rash or lesion, Binnicker said. There is interest by CDC and others studying those who have been exposed to monkeypox to see if a saliva sample can identify patients before they start to develop symptoms.

"We know that lesions are an accurate specimen type for monkeypox detection. Additional studies to look at other specimen types prior to lesion onset are worthwhile, but we must balance early detection with possible false negatives if the specimen does not consistently give accurate results for monkeypox detection," Hutson said.

And these concerns also don't yet have clear answers:

Costs of testing. Just as a federal mechanism made COVID-19 testing free, it would be nice to have something like that for monkeypox, Mahn said. "These are not insignificant costs for these PCR tests," King said, and it's unclear what will happen with patients who are uninsured. For now, public health laboratories are covering tests for those patients.

Changing geographics. While reports indicate that cases of monkeypox are declining, that may be just in larger metropolitan areas, said Mahn, whose organization has heard about increasing cases in metropolitan-adjacent neighborhoods and in monolingual, Spanish-speaking communities. There could be an opportunity for larger academic medical centers with testing capabilities to partner with under-resourced areas to support monkeypox testing, she said.

Regulations. "It's not necessarily the volume of laboratories that are testing, but the quality of those tests," Mangal said. "FDA's EUA process is a good thing in that it allows for regulatory oversight and provides more information on the performance characteristics of tests that are being developed or are out there on the market." Even with all these issues at play, it's important to remember that laboratories will work as part of integrated care teams, King said.

"There are still people who feel like [monkeypox testing] needs to be available in every hospital laboratory, or at least the major academic centers, and I think the EUA will help with that," she said. "But I always say it's not enough to have tests to detect the cases. It's the prevention piece—the vaccination availability, efficacy of vaccination, and finding these cases quickly enough to prevent further infections—that really make a difference in terms of this epidemic spreading further or being contained."

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Implementing HIGH-SENSITIVITY CARDIAC TROPONIN

Experts lay out their best advice for ensuring laboratories, clinicians, and patients experience a smooth transition.

Troponins are a family of structural proteins found in muscle fibers that damaged muscle releases into the bloodstream. Troponin I and T are specific to heart muscle, and therefore, measurement of an elevated troponin I or T supports the diagnosis of cardiac muscle disease or injury.

Troponin I or T measurements for acute myocardial infarction (MI) diagnosis were introduced into practice in 1995 and became the preferred laboratory test (versus traditional cardiac enzymes) in 2000 (*1*,*2*). Troponin levels greater than the 99th percentile of the reference population (upper reference limit, or URL) indicate myocardial injury (*3*). In acute myocardial injury, troponin I or T levels show a rising and/or falling pattern; in chronic myocardial injury, troponin I or T levels remain elevated above the 99th percentile URL (*3*).

It is imperative to understand the performance characteristics of a specific assay being used for patient care (*4*). Current professional society recommendations have defined standards for allowable imprecision at the 99th percentile URL, measured by coefficient of variation, as <10% (*5*). However, initial troponin assays were limited by the ability to precisely measure concentrations at very low levels.

BY BRANDON R. ALLEN, MD, FACEP, STACY G. BEAL, MD, AND DAVID E. WINCHESTER, MD, FACC, FACP, FASNC, AND MARTIN P. THAN, MBBS, FACEM

AN ASSAY PREVIOUSLY CONSIDERED IN A LARGELY BINARY FASHION IS TRANSITIONING TO ONE WHERE THE RESULTS MUST BE INTERPRETED WITH GREATER NUANCE.

Technological advances in the development of troponin assays have allowed for increased precision at levels lower than the 99th percentile, in the area previously considered to be "normal range." The assays have become so precise that they can achieve <10% coefficient of variation approaching their lowest concentration of detection. Hence, newer definitions of "high- sensitivity troponin" (hs-cTn) require <10% imprecision at or below the 99th percentile URL and the ability to detect troponin in 50% of healthy individuals (*4*).

TRANSITIONING TO A CONTINUOUS VARIABLE

The dramatically improved precision creates an uncommon paradigm change in clinical medicine where an assay previously considered in a largely binary fashion is transitioning to one where the results must be interpreted with greater nuance. This is arguably a natural advancement in test use. Troponin is, after all, a continuous variable. The 99th percentile threshold used as a key determinant of myocardial infarction (MI) and injury is relatively arbitrary, varies between populations, and even changes according to the statistical technique used to account for outliers (*6*).

If implemented well, the improvements in precision offer an opportunity to reduce the number of missed MIs and perhaps also reduce the number of patients admitted to the hospital. If implemented poorly, the new assays could result in increased hospitalizations or increased demand on cardiovascular services, including consultations and diagnostic tests.

HOW TO PLAN IMPLEMENTATION OF HIGH-SENSITIVITY TROPONIN ASSAYS

If a hospital decides to transition to a hs-cTn assay, what comes next? For some clinicians, this can provoke anxiety. However, if done well, it can change how you provide care within your health system.

There are six keys in preparing for hs-cTn assay implementation: 1) identify best practices of other institutions, 2) identify key stakeholders and meet regularly to plan the transition, 3) communicate the change to the all clinical staff who contribute to the management of patients with suspected chest pain (and also those who might deal with abnormal hs-cTn assays), 4) make the change, 5) expect uncertainty post-implementation and adjust accordingly, and finally, 6) assess your outcomes (*8*). Januzzi, et al., have provided a detailed framework and checklist of how to systematically approach the transition from the lab, emergency department (ED), or hospital perspective (*9*).

Proper preparation can take up to a year or more based on your lab's validation, cut point determinants, and integration into the electronic health record (EHR) while the ED and hospital are working on consensus for the timing of serial testing and the utilization of an accelerated diagnostic protocol. Providers and staff need extensive education to understand the differences from their contemporary assay and the 4th universal definition of MI prior to implementation (*10, 11*).

TIMING OF TESTING AND THE ACCELERATED DECISION-MAKING PATHWAY

It is worth noting that the threshold used to indicate a positive troponin test result was once approximately ten times higher than the 99th percentile thresholds used now. As a result, it was not unreasonably felt that it could take some time from symptom onset for measurable troponin concentrations to meet such a threshold. It was commonplace for tests to be repeated after 12 hours or the following morning after admission.

One of the key benefits of high-sensitivity troponin is the ability to measure both very low concentrations and changes to low concentrations with high precision and confidence. The timeframe between symptom onset and reliable detection of very low concentrations of troponin (or concentration changes) can now be much shorter. This has led to clinical pathways that incorporate troponin measurement at 0 and 6 hours then 0 and 3 hours, using the 99th percentile as a decision threshold. Subsequently, pathways have been written using 0- and 2-hour blood sampling, but more recently, pathways have incorporated other thresholds in addition to (and sometimes instead of) the 99th percentile for decision-making have also been developed.

The expression "accelerated decision-making or diagnostic

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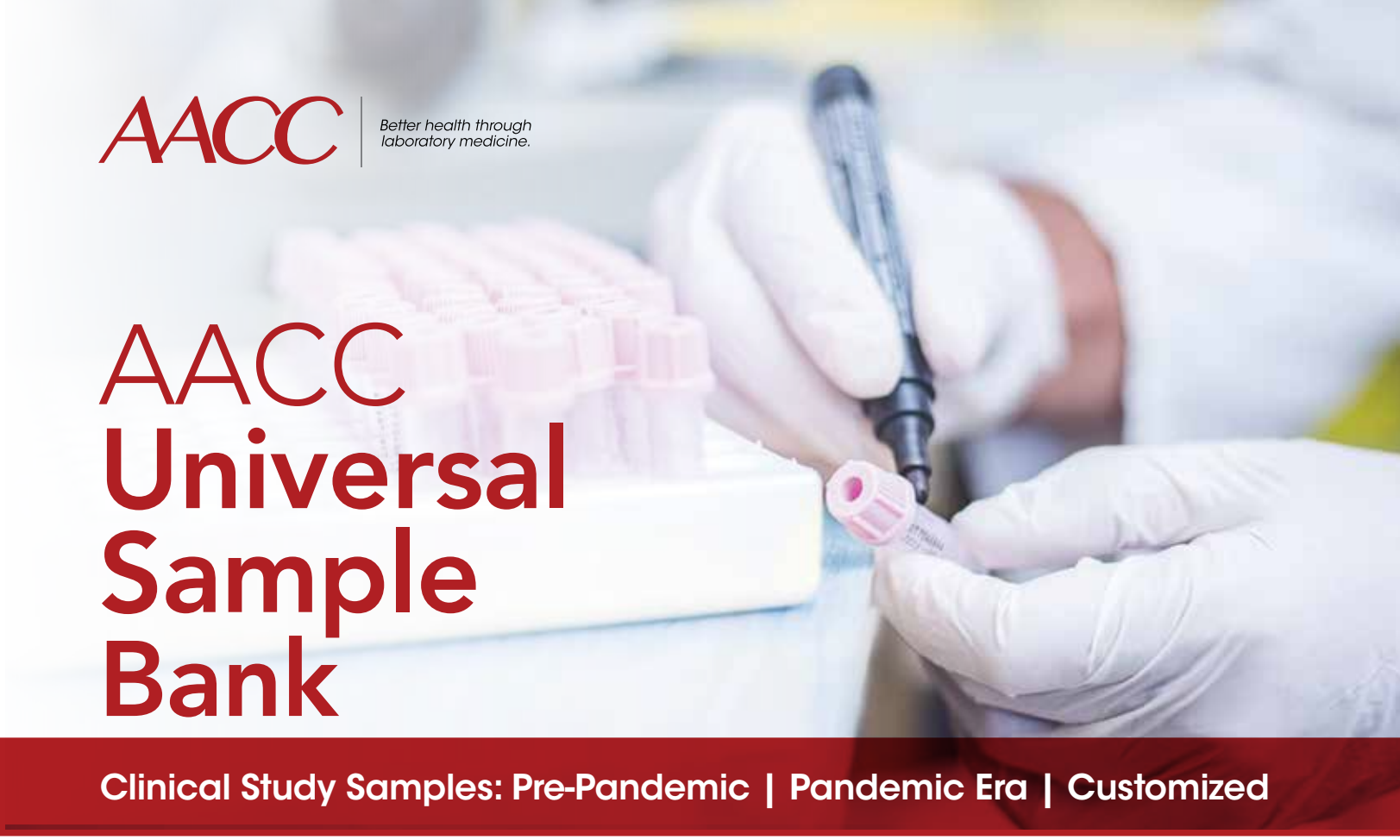

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pathway" (ADP) is often used to describe decisionmaking strategies that combine troponin with ECG findings and risk assessment (usually in a structured format). Examples of such ADPs incorporate risk assessment aids such as the HEART score, TIMI score, EDACS (Emergency Department Assessment of Chest Pain Score) and MACS (Manchester Acute Coronary Syndromes).

Newer strategies that are troponin-based, such as the European Society of Cardiology Guidelines and High-STEACS (High-Sensitive in the Evaluation of Patients with Acute Coronary Syndrome), demonstrate the use of single test and dynamic change (delta) decision-making without a focus on the use of a risk score.

For a high-sensitivity assay there will be a very low troponin concentration threshold (often near the level of detection or limit of quantification) that can be used for rule out of MI after a single troponin concentration measurement (provided the patient is not a very early presenter following symptom onset—a timeframe of 2 or 3 hours is often used). Suggested delta change thresholds for each troponin assay can be found in the latest iteration of the ESC Guidelines (*6*).

The overall impact of using single tests and early delta change for decision-making means that a marked proportion of patients (20–40%) can be discharged from the ED following a first test result. A further 30–50% can be discharged after the result from a second troponin drawn 1 or 2 hours after the first, meaning that it is possible to discharge approximately 60% of patients from the ED within a short timeframe.

This is a dramatic shortening from the historical timeframes required for safe rule out of MI from the past, and such pathways have an important impact on ED and hospital crowding.

DELTA ANALYSIS

Delta values represent the difference between two values. In this context, deltas represent the change over time, with large changes representing increased likelihood of acute myocardial damage. A patient with elevated troponins that do not change over time is likely to have chronic myocardial damage or decreased excretion of the protein through the kidney.

In a procedure that includes three troponin levels, a total of three deltas are possible: the first value versus the second, the second versus the third, and the first value versus the third. Institutions must decide if they will report all three or the "max delta," which may change after the third troponin level is determined.

Additionally, institutions must decide if they will utilize and report the delta as a whole number difference (the absolute value of one value minus another value) or as a percentage difference between values. Generally, troponin deltas are viewed as whole positive numbers (absolute values) as either a rise or fall in troponin overtime is indicative of an acute event.

Finally, delta values should be verified as part of a reference range in an institution's patient population. In our system, deltas were calculated by the electronic health record when a value obtained at any time point was greater than the limit of detection (LOD) of 6 pg/mL and less than 99 pg/mL. The delta was reported as a "max delta" so that whichever delta was highest between 0 and 1 hours, 0 and 3 hours, or 1 and 3 hours would be reported. Deltas were always reported as positive, whole numbers. In other words, if the troponin changed in a falling pattern, the delta was still reported as a positive number (*12*). Following our initial testing strategy, our system has moved to a 0- and 2-hour pathway with a single troponin option for those who have had symptoms for greater than 3 hours and the value is below the LOD.

CARDIOLOGY'S PERSPECTIVE ON GO-LIVE AND ASSESSMENTS

As cardiac biomarkers like troponin have continued to improve in sensitivity clinicians, are less and less likely to miss a clinically important acute cardiac event. This improvement is undoubtedly beneficial for patients with acute coronary syndromes (ACS), especially for those who might benefit from an invasive management approach. On the other hand, when looking at the whole population of patients with abnormal levels of circulating troponin, it becomes more challenging to interpret results in order to determine which patients will benefit from additional cardiac testing and/or invasive procedures.

Multiple large-scale cohort studies have helped us understand the scope of this challenge. The CHARIOT study gathered samples from a consecutive cohort

DELTA VALUES SHOULD BE VERIFIED AS PART OF A REFERENCE RANGE IN AN INSTITUTION'S PATIENT POPULATION.

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undergoing blood tests for any reason and found that 5.4% (n=1,080 of 20,000) had hs-cTn concentrations above the 99th percentile. Once elevated hs-cTn is detected, an in-patient team (often cardiology) is responsible for distinguishing Type 1 MI from from Type 2 MI. This task is not as straightforward as one might suspect: The proportion of patients with Type 2 MI varies wildly from <5% to >70%, owing to differences in population but also differences in how the Universal Definition of MI is applied. Among those with a suspected ACS, Type 1 and 2 MI may represent the minority of those with elevated hs-cTn, as little as one third in some cohorts. Despite relatively specific diagnostic criteria and recommendations on how to interpret patterns of rise/fall of hs-cTn, some clinicians find the definitions arbitrary, and the criteria depend highly on interpretation of historical symptom details provided by the patient.

With so many patients who have elevated hs-cTn, some clinicians are concerned about switching to the hs-cTn assay because of the potential for overwhelming demand on resources already stretched too thin. Projections from a variety of sources suggest the U.S. healthcare system will continue to suffer from a shortfall in cardiologists and adequately trained advanced practice providers. Thankfully, most available data seems to show that, for the inpatient setting, the demand for cardiac testing and consultations does not dramatically increase with transition to hs-cTn and may reduce admissions and length of stay (*13*, *14*).

The other remaining question that looms over cardiologists

about hs-cTn is ongoing management. Data are lacking on which patients may benefit from additional structural, perfusion, and coronary anatomic assessment. Although studies like the ISCHEMIA trial are reassuring that stable ischemia heart disease may be managed medically, no similarly impactful large-scale studies have evaluated hs-cTn elevations due to chronic or acute MI.

Patients with Type 2 MI who are referred to a cardiologist are more likely to have factors associated with mortality, and the patients are much more likely to undergo cardiac testing. But any improvement in outcomes is unclear at this point. Optimal management should be a high priority for the cardiology community, as multiple lines of evidence have demonstrated that outcomes are worse for Type-2 MI patients compared to Type-1 MI.

CONCLUSION

The evolution of the assessment of ACS has led to improved precision and management of these patients with hs-cTn as the primary biomarker. There are many topics and challenges to consider when your hospital or health system is transitioning to a high sensitivity troponin assay. Thankfully, a framework has been developed in the literature to support decisions leading to improved safety and efficacy while also enhancing the management of patients with defined acute myocardial injury or infarction.

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DATA ARE LACKING ON WHICH PATIENTS MAY BENEFIT FROM ADDITIONAL STRUCTURAL, PERFUSION, AND CORONARY ANATOMIC ASSESSMENT.

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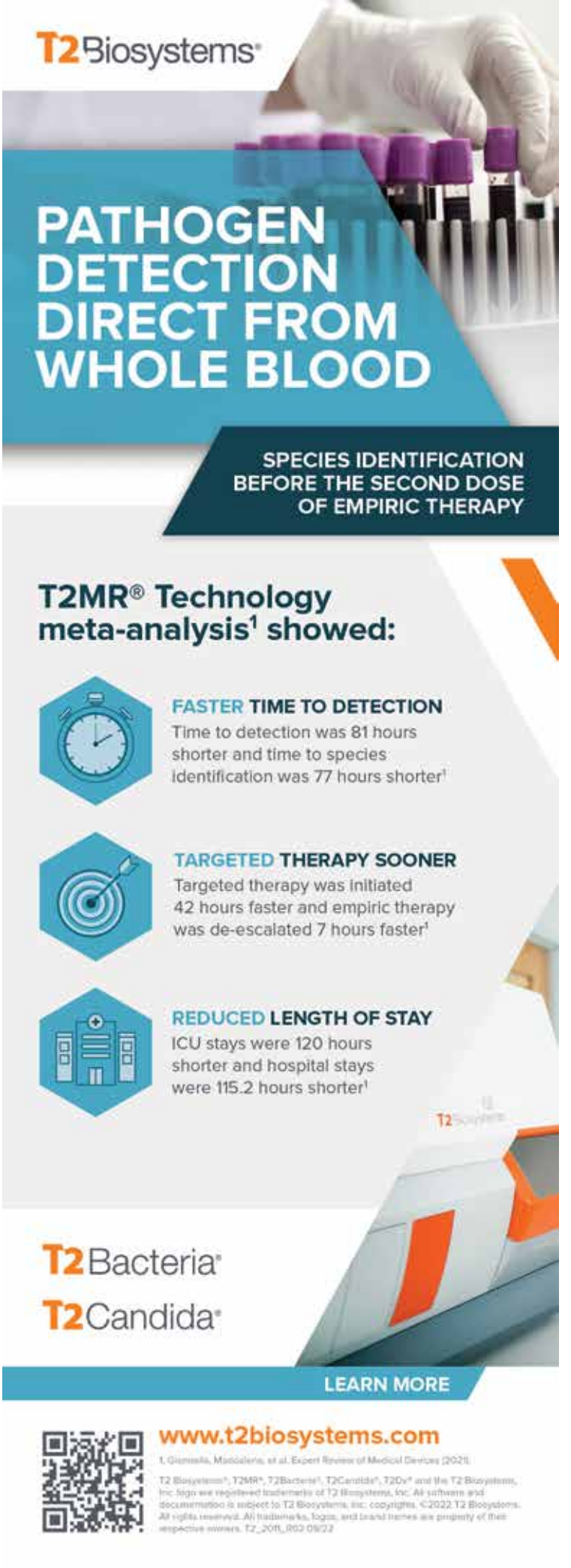

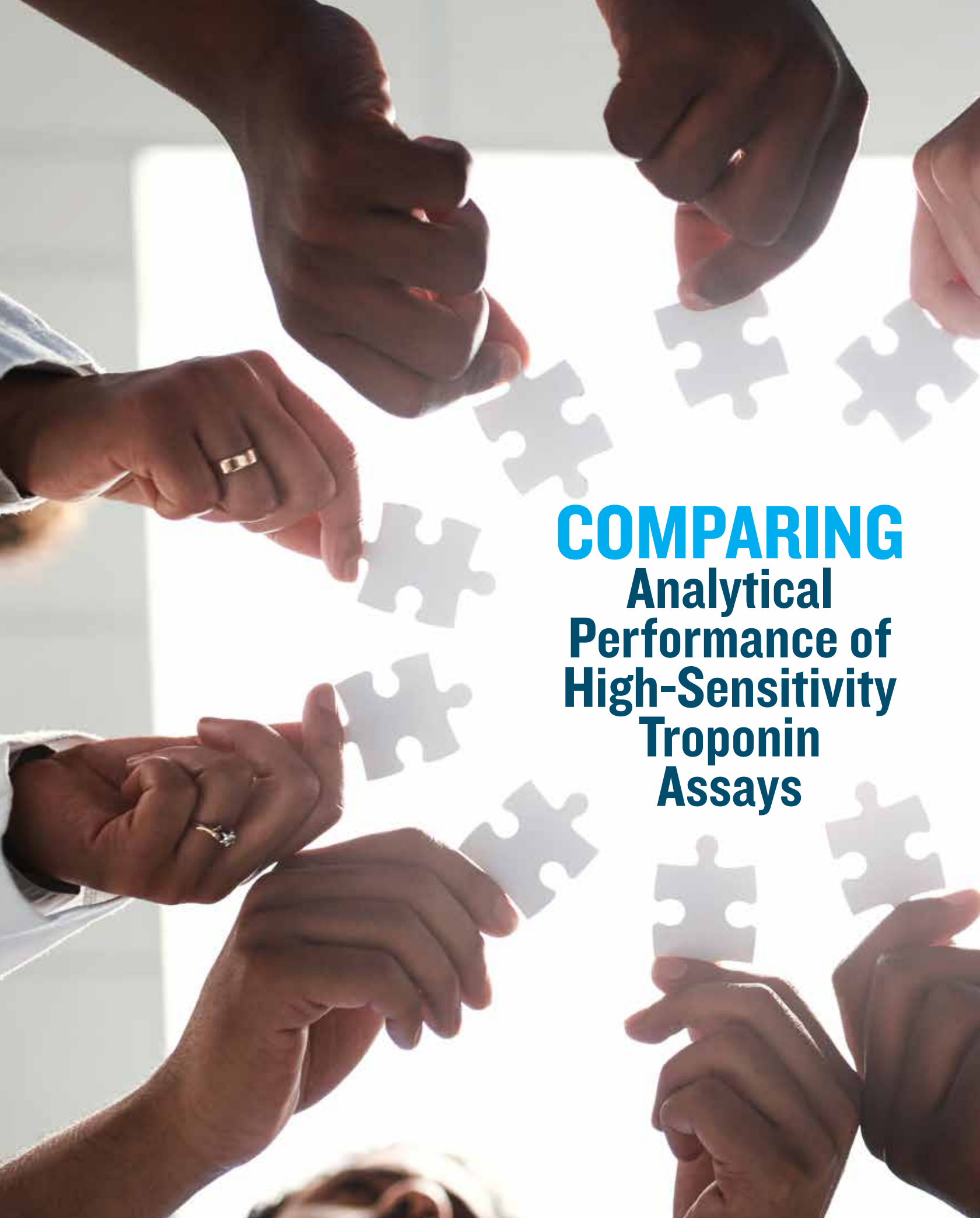

COMPARING
Analytical Performance of High-Sensitivity Troponin Assays

With a growing number of options approved in the U.S., clinical laboratories have more choices in how to integrate high-sensitivity assays into workflows and take new steps to improve patient care.

Cardiac troponin (cTn) is the key biomarker in the Universal Definition of Myocardial Infarction (UDMI) and integral to the diagnosis of myocardial infarction (MI) and myocardial injury (*1*). Utilization of high-sensitivity cTn (hs-cTn) assays allow for rapid triage and early diagnosis or exclusion of MI, in particular non-ST elevation MI (NSTEMI), in the Emergency Department (ED). Several hs-cTnI and hs-cTnT assays have gained approval by the Food and Drug Administration (FDA) and increasingly have been adopted and incorporated into novel algorithms and early rule-out strategies.

This article provides an overview of the analytical and clinical performance of some of the currently FDA-approved hs-cTn assays, discusses integration of hs-cTn with risk scores, and provides perspective on the future of hs-cTn assays.

DEFINITIONS, ANALYTICAL CRITERIA, AND RISK SCORES

Acute myocardial injury requires at least one troponin concentration above the 99th percentile, taken in conjunction with dynamic changes, and can occur due to multiple pathological causes. Diagnosis of acute myocardial infarction occurs if myocardial ischemia is simultaneously present based on clinical or imaging findings.

BY KANG XIONG-HANG, PHD, AND AMY K. SAENGER, PHD, DABCC, FAACC

Chronic myocardial injury is characterized by increased serial hs-cTn concentrations that do not change acutely, frequently caused by long-term cardiac exposure to multiple metabolic risk factors. Chronic elevations in hs-cTn signal a poor long-term prognosis, along with increased risk for cardiovascular diseases, heart failure, and overall mortality. Large observational studies have demonstrated an association between long-term prognosis and hs-cTn concentrations even as low as the limit of blank (LoB) to the 99th percentile upper reference limit (URL).

High-sensitivity cardiac troponin assays must meet analytical criteria established by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Committee on Clinical Applications of Cardiac Bio-markers (C-CB) and the American Association for Clinical Chemistry (AACC) Academy, which focus on imprecision at the 99th percentile URL and the ability to measure hs-cTn in ≥50% of males and ≥50% of females above the limit of detection (LoD) within a normal healthy cohort. The recommendations for defining the reference population, along with the number of individuals required to gain statistical significance, have been recently updated by the IFCC C-CB (*2*).

Risk scores can be utilized to identify 20–50% of patients evaluated for possible AMI who are at low risk for major adverse cardiovascular events (MACE) and may be candidates for early discharge. Commonly used risk scores include the Thrombolysis in Myocardial Infarction (TIMI); Emergency Department Assessment of Chest Pain Score (EDACS); Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker (ADAPT); and the History, Electrocardiogram, Age, Risk Factors and Troponins (HEART) scores. A modified HEART score has been proposed that uses the 0/ 1-hour algorithm with high-sensitivity cardiac troponin-I assay (hs-cTnI) to identify a cohort of very low-risk chest pain patients. A simplified EDACS (sEDACS) score has also been described that uses fewer variables than in the original EDACS score (Figure 1).

ANALYTICAL PERFORMANCE CHARACTERISTICS OF HS-CTN ASSAYS

The IFCC C-CB maintains up-to-date information about the analytical characteristics of hs-cTnI and hs-cTnT assays from different manufacturers which are globally utilized (*3*). Further details on analytical specificity issues related to hemolysis and biotin interferences in hs-cTn assays also are published on the IFCC C-CB website. Commercially available hs-cTn assays available in the United States include those from Abbott, Beckman Coulter, Roche, and Siemens; notably, these same assays differ from ones used worldwide in that results below the limit of quantitation (LoQ) are blinded to the laboratory due to FDA restrictions.

ABBOTT HS-CTNI ASSAYS

Abbott hs-cTnI assays are approved on the ARCHITECT i1000SR, ARCHITECT i2000 and Alinity i instruments. The UTROPIA (Use of Abbott High Sensitivity Troponin I Assay in Acute Coronary Syndromes) study was a U.S.-based clinical trial that evaluated the diagnostic performance of the hs-cTnI assay on the Architect analyzer using sex-specific 99th percentiles of 16 ng/L and 34 ng/L for females and males, respectively (*4*).

For patients with a normal ECG and serial hs-cTnI concentrations ≤ the 99th percentile at 0 and 3 hours, the sensitivity was 100% for ruling out acute MI. For MI rule-in, the clinical specificity was 86.9% at presentation and 85.7% with serial testing, and 89.3% when a delta hs-cTnI > 5 ng/L was used. When evaluating outcomes, even individuals with measurable (from the LoD to the 99th percentile URLs) hs-cTnI within the reference interval had more than a 3-fold higher risk of MACE, including death, MI, unstable angina, revascularization, or congestive HF at 180 days compared to individuals with an undetectable hs-cTnI less than the LoD of 3 ng/L (*5*). Only 0.5% of patients with a baseline hs-cTnI less than the LoD had MACE at 30 days, compared to 3.0% of patients with a measurable hs-cTnI. No differences in the rate of MACE between males and females were observed. Studies in this cohort reflect the importance of interpretation of hs-cTnI concentrations as a continuous variable, as a continuum of risk.

F1 Simplified Emergency Department Assessment of Chest Pain

	CLINICAL RISK SCORE				
	TIMI	EDACS	sEDACS	HEART	ADAPT
TROPONIN	≥99th percentile: +1			≥3x upper limit: +2 1-3x upper limit: +1	≥99th percentile at either 0 or 2 hours: +1
HISTORY	Aspirin use within 7 days: +1 Known coronary disease: +1 At least 3 risk factors: +1	Coronary disease or ≥3 risk factors: +4	Coronary disease or ≥3 risk factors if ≤50 years: +1	≥2 risk factors: +2 1 risk factor: +1	Aspirin use within 7 days: +1 ≥3 risk factors: +1 Coronary disease, known stenosis ≥50%: +1
PHYSICAL	Age ≥65: +1 Severe angina within 24 hours: +1	Age: +2 to 20 points Male sex: +6 Symptoms: Diaphoresis, +3 Radiation to arm/shoulder: +5 Worse on palpitation: -6 Pleuritic: -4	Age: +0 to 6 points Male sex: +1 Symptoms: Radiation to arm/shoulder: +1	Age: 45 - <65: +1; ≥65: +2 Typical: +2 Atypical: +1	Age ≥65: +1 Severe angina within 24 hours: +1
ECG	ST changes ≥0.5 mm: +1			ST depression: +2 T-wave inversion: +1	Ischemic changes on initial ECG: +1 ST changes ≥0.5 mm: +1
LOW RISK CRITERIA	0 or 1	Less than 16	0 – 3	Less than 3	0

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Abbott recently received approval for hs-cTnI on the Alinity i immunoassay platform, and studies in US cohorts are expected to be forthcoming. The package insert clinical data was generated across 23 EDs from 6,174 patients presenting with symptoms consistent with acute coronary syndrome. Using sex-specific 99th percentiles (females: 14 ng/L; males: 35 ng/L), the sensitivity and negative predictive value (NPV) 0–6 hours post-presentation for females was 85.29–98.46% (NPV: 98.80–99.85%) and for males the clinical sensitivity ranged from 72.20–92.06% (NPV: 97.05–99.19%) (*6*).

BECKMAN COULTER HS-CTNI ASSAYS

The Beckman Coulter hs-cTnI assay received FDA-approval in 2018 for testing on the Access 2 and UniCel DxI instruments. A U.S. study evaluated the utility of the baseline hs-cTnI alone to rule out acute MI (*7*). While use of sex-specific cutoffs for males (20 ng/L) and females (15 ng/L) resulted in a sensitivity of 77.8% (NPV: 97.3%) and 89.5% (99.1%), respectively, even greater performance could be achieved using the LoD (<4 ng/L) for MI rule-out. Patients with a baseline hs-cTnI below the LoD had a NPV of 100.0%, sensitivity of 100% and no MACE at 30 days, effectively ruling out 40.9% of all patients presenting to the ED suspected of having acute MI.

One Australian study evaluated the diagnostic accuracy of the Beckman hs-cTnI assay in conjunction with different accelerated diagnostic pathways including EDACS, ADAPT, and HEART scores (*8*). The ADAPT, EDACS, and HEART pathways demonstrated high clinical sensitivity for acute MI (96.9% for ADAPT and 97.9% for EDACS and HEART), but lower sensitivity for acute coronary syndrome (≤95.0% for all). All risk scores enabled half of ED patients to be rapidly referred for objective testing and classified a significant number of patients as low risk without MACE (64.3%, 62.5%, and 49.8% for ADAPT, EDACS, and HEART, respectively).

These assays differ from ones used worldwide in that results below the limit of quantitation are blinded to the lab due to FDA restrictions.

ROCHE HS-CTNT ASSAYS

The Roche Elecsys Troponin T Gen 5 STAT is approved on the cobas e411, e601, e602, and e801 analyzers. The determined cutoffs were overall 19 ng/L, females 14 ng/L, and males 22 ng/L (*9*). The Rapid Evaluation of Acute Myocardial Infarction in the United States (REACTION-US) study evaluated the diagnostic performance based on results below the LoQ (6 ng/L) and a baseline/30-minute algorithm (baseline of less than 8 ng/L and 30-minute delta of less than 3 ng/L) (*10*). From that study, patients ruled out using the LoQ and baseline/30-minute algorithms both have an NPV of 100% and sensitivity of 100%.

Furthermore, a multisite prospective study conducted at eight U.S. sites reported improvement in NPV from 98.3% to 99% for MACE at 30 days when baseline hs-cTnT below the LoQ of 6 ng/L was used alone vs. the LoQ used in conjunction with a HEART score (*11*). This study reflects the importance of considering other risk factors in evaluating acute MI.

SIEMENS HS-CTNI ASSAYS

The High-Sensitivity Cardiac Troponin I in the United States (HIGH-US) study evaluated the clinical performance of the Siemens Atellica IM hs-cTnI assay using sex-specific 99th URLs derived from the AACC Universal Sample Bank

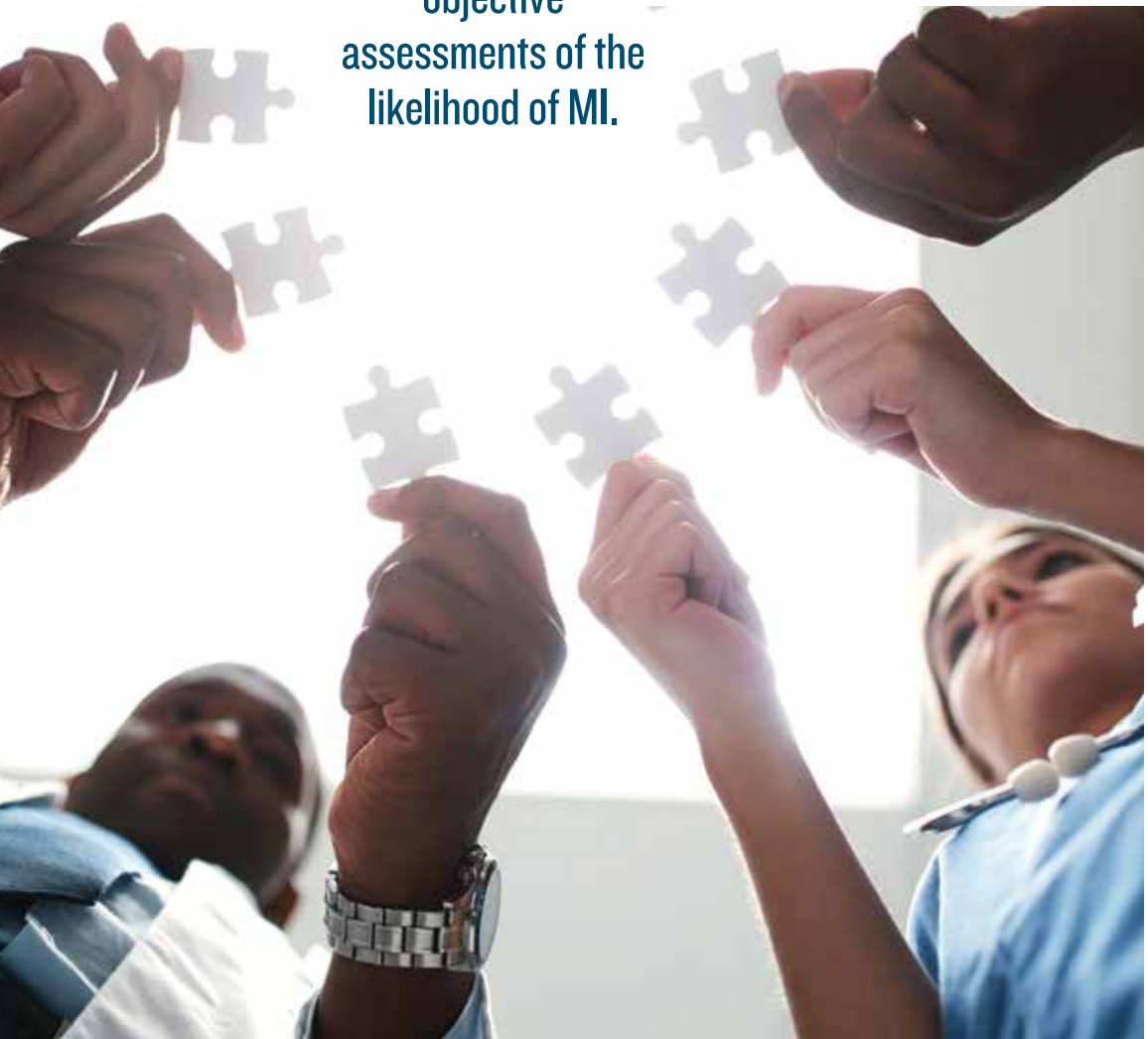
(males: 53 ng/L; females: 34 ng/L). Approximately 3 hours after presentation the clinical sensitivity and specificity was >90% for all patients, with an NPV of ≥98% (*12*).

Furthermore, an optimized threshold of <5 ng/L safely identified 47% of all patients as low risk at presentation, resulting in a sensitivity of 98.8% and NPV of 99.7% for acute MI and a sensitivity of 98.6% and NPV of 99.6% for 30-day risk of acute MI or death (*13*). This study also validated specific cut points from ESC guideline recommended accelerated diagnostic protocols in this diverse US population and demonstrated a 0/1-hour or 0/2- to 3-hour algorithm could be used with acceptable performance and outcomes.

When the TIMI, HEART, and sEDACS scores were used in this cohort and supplemented with the Siemens Atellica hs-cTnI assay, the TIMI score was superior for identifying patients at risk for AMI or death within 30 days (100%). However, the sEDACS and HEART scores identified significantly more patients as low risk compared with the TIMI score (34.5%, 36.6%, and 12.1%, respectively) which allows for faster discharge from the ED without further testing (*14*).

The Dimension VISTA High Sensitivity TnI, EXL High-Sensitivity TnI and Advia Centaur are also Siemens hs-cTnI assays with similar clinical performance to the Atellica. However, due to lack of standardization and harmonization of hs-cTnI assays even within one manufacturer, all assays have different 99th percentiles, analytical parameters, and clinical performance.

Studies have demonstrated the potential utility of machine learning algorithms to provide individualized and objective assessments of the likelihood of MI.



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OPPORTUNITIES IN MACHINE LEARNING AND POINT OF CARE

Several studies have demonstrated the potential utility of machine learning algorithms to provide individualized and objective assessments of the likelihood of MI to rapidly identify low- and high-risk patients for triage in the ED (*15*). The differences in hs-cTnI dependent on age and sex, along with variability in sampling times, can make rapid evaluation of acute MI challenging.

One study evaluated a machine learning algorithm (myocardial-ischemic-injury-index [MI3]) that incorporates age, sex, and hs-cTnI concentrations at baseline and 30 minutes in 529 patients evaluated for possible acute MI. The MI3 generates an index value from 0 to 100 reflecting the likelihood of acute MI, dividing patients into 3 categories by MI3 score: low-risk (≤3.13), intermediate-risk (>3.13–51.0), and high-risk (>51.0).

The study followed patients at 30–45 days for major adverse cardiac events (MACEs). The sensitivity for acute MI was 100% with a MI3 value ≤3.13 and 353 (67%) ruled-out after 30 minutes. At 30–45 days, there were 2 (0.6%) MACEs (2 non-cardiac deaths) in the low-risk group, in the intermediate-risk group 4 (3.0%) MACEs (3 acute MIs, 1 cardiac death), and in the high-risk group 4 (9.1%) MACEs (4 acute

MIs, 2 cardiac deaths). Results of this study are promising to identify low-risk cohorts who then may be discharged earlier.

Another exciting growth area is in hs-cTn point-of-care (POC) assays. Implementing of POC testing offers the ability to expend hs-cTn across different healthcare settings and decrease the time between specimen collection and testing, ultimately expediting clinical care decisions (*16*).

Current requirements for hs-cTn POC assays include comparable analytical performance to the central laboratory hs-cTnI assay and that test results must be the rate-limiting step in the diagnostic pathway (*17*). Recent studies show promising data using the Siemens Atellica VTLi whole blood hs-cTnI assay, which satisfy the analytical criteria and with a clinical sensitivity of ≥99% for acute MI and ≥99.5% NPV (*18-19*). With recent advancements in hs-cTn POC technology, the future potential opportunities to integrate testing into clinical care pathways is hopefully near.

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Regulatory Roundup

Early Cervical Cancer Test Approved in China

The cervical cancer screening test GynTect is now available to physicians and patients in China. Developed by the German company oncgnostics, it is the first methylation assay for triage of human papillomavirus (HPV)-positive cases that the Chinese National Medical Products Administration has approved. GynTect received this approval after a large-scale, multiyear study involving approximately 10,000 participants that demonstrated the test's efficacy.

GynTect clarifies early on whether a patient with an abnormal finding on cervical cancer screening has a predisposition for or already has cervical carcinoma and needs prompt treatment. The screening test detects epigenetic changes and requires a sample from a cervical smear—the same sample type typically obtained for thin-layer cytology or HPV testing.

China has approved GynTect for use in women 30 years and older who are infected with high-risk, cancer-causing HPV types. Studies have shown that approximately 17% of women, or about 70 million female patients in China, are infected with one of these types of high-risk HPV and need screening. However, only a few women with an HPV infection will develop cervical cancer. These are the cases that the Gyntech test is designed to detect.

GynTect is distributed in China by GyneoDx under exclusive license. In addition to China and numerous European Union countries, GynTect is also marketed in Brazil and Mexico.

THERMO FISHER SCIENTIFIC GETS CE MARK FOR CANCER SEQUENCING TEST AND ANALYSIS SOFTWARE

Thermo Fisher Scientific has received the CE mark for a next-generation test, genomic reporting software, and sequencer to speed tumor molecular profiling. Altogether, the Oncomine Dx Express test, Oncomine Reporter Dx, and Ion Torrent Genexus Dx Integrated Sequencer offer an automated end-to-end workflow. Operated from a single software interface, the process requires less than 20 minutes of under time and delivers results in less than 24 hours.

The Oncomine Dx Express test is qualitative and detects deletions, insertions, substitutions, and copy number gain present in 42 genes, as well as fusions or splicing variants in 18 genes from DNA and RNA in formalin-fixed paraffin-embedded tumor tissue samples of solid malignant neoplasms. Additionally, the assay detects deletions, insertions, substitutions in 42 genes, and fusions or splicing variants in seven genes from cell-free DNA extracted from plasma samples of non-small cell lung cancer.

HELIX DIAGNOSTICS' MULTIPLEXED SARS-COV-2 ASSAY EARNS FDA EUA

The Food and Drug Administration has granted emergency use authorization (EUA) to Helix Diagnostics' SARS nCoV-19 multiplexed assay. The test is authorized for qualitative detection of SARS-CoV-2 RNA in human anterior nasal swab samples collected from individuals who have symptoms of COVID-19. The test can also be used with individuals without symptoms when the individuals are tested at least once per week using test

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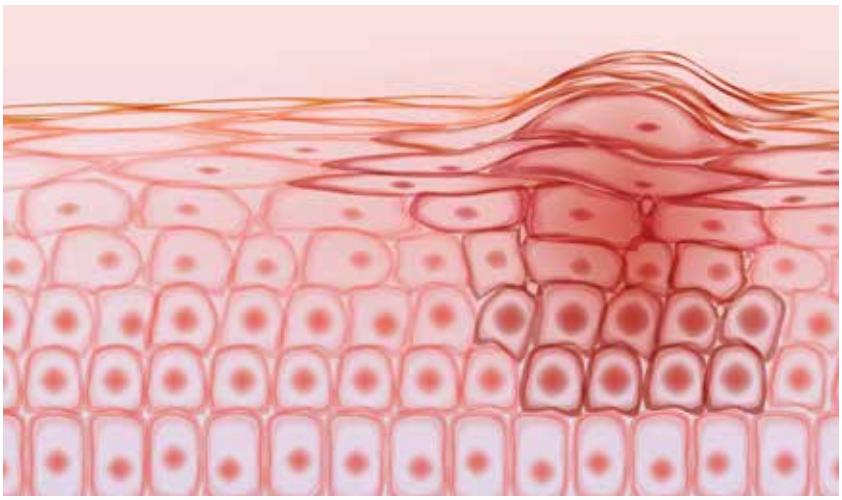
procedures validated in accordance with the requirements of the Umbrella EUA for SARS-CoV-2 Molecular Diagnostic Tests for Serial Testing.

In the case of serial testing, additional confirmatory testing for negative results may be necessary if there is a high likelihood the individual has COVID-19—e.g., because the individual had suspected exposure to SARS-CoV-2. Additional confirmatory testing for positive results may also be necessary if there is a low likelihood of COVID-19, such as in individuals without known exposure to the virus or who reside in communities with low prevalence of infection.



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MYRIAD GENETICS' BRACANALYSIS DIAGNOSTIC SYSTEM GAINS JAPANESE APPROVAL AS COMPANION DIAGNOSTIC

Japan's Ministry of Health, Labour, and Welfare has granted expanded coverage for use of Myriad Genetics' BRACAnalysis Diagnostic System as a companion diagnostic to identify patients with germline *BRCA*-mutated and HER2-negative high-risk recurrent breast cancer who may benefit from Lynparza (olaparib).

The BRACAnalysis Diagnostic System is designed to detect and interpret germline *BRCA1* and *BRCA2* variants, including deleterious or suspected deleterious variants in patients with HER2-negative high-risk early breast cancer. In the OlympiA trial, Lynparza demonstrated a statistically significant and clinically meaningful improvement in invasive disease-free survival, reducing the risk of invasive breast cancer recurrences, new cancers, or death.

With this expanded coverage, more patients with breast cancer now qualify for *BRCA1/2* testing in Japan, Myriad officials said.

CE MARK GRANTED TO SKYLINEDX SKIN CANCER TEST

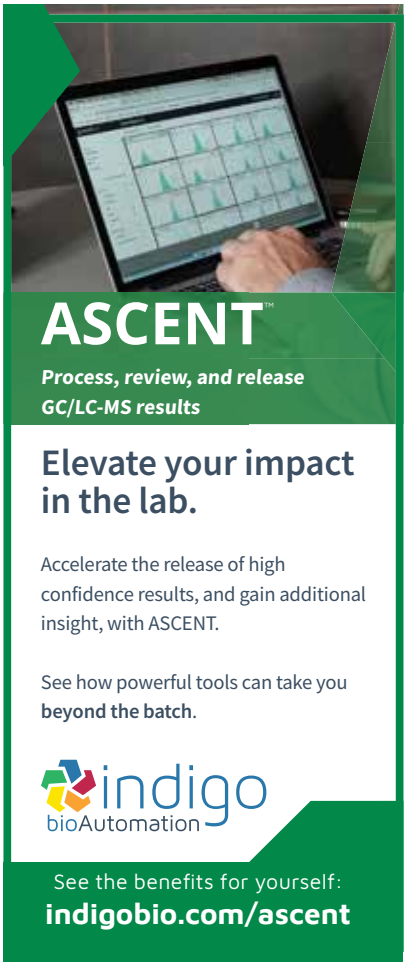
SkylineDx has received the CE mark for the Merlin Assay, which identifies melanoma patients who have low risk for nodal metastasis and who can forgo invasive sentinel lymph node biopsy surgery, a procedure that is used to determine metastatic spread of cancer for staging purposes. Based on quantitative PCR, the Merlin Assay uses a proprietary algorithm that calculates the risk of metastasis in a patient's sentinel lymph nodes. This model can calculate risk on an individual basis through a combination analysis of eight genes from the patient's primary tumor, the tumor thickness, and the patient's age.

Additionally, the company noted that Medicare recently began covering the Merlin Assay's U.S. counterpart.

COLON CANCER ASSAY GETS CHINESE APPROVAL

China's National Medical Products Administration (NMPA) has approved Pillar Biosciences' oncoReveal Dx Colon Cancer Assay. With this approval, the test is now available in China, the U.S., and Europe as a companion diagnostic. It is intended to identify patients with colorectal cancer whose tumors express wild-type *KRAS* status and who may also benefit from treatment with specific targeted therapies, including Erbitux (cetuximab) or Vectibix (panitumumab). The assay utilizes Pillar's SLIMamp next-generation sequencing technology.

OncoReveal Dx Colon Cancer Assay is Pillar's first NMPA-approved diagnostic product. Pillar's oncoReveal Dx Lung & Colon Cancer Assay previously received CE-IVD certification in Europe in April 2020 and Food and Drug Administration premarket approval in July 2021.



Industry Playbook

Sense and TECOmedical Sign European Distribution Agreement

Sense Biodetection has announced a strategic agreement with TECOmedical for nonexclusive distribution of Sense's Veros COVID-19, the first test on the Veros molecular testing platform.

Effective immediately in Germany and Austria, and pending regulatory approval in Switzerland, the agreement is the latest in Sense's planned European Union distribution partnerships as it commercializes its Veros platform.

The self-contained, single-use Veros COVID-19 product produces polymerase chain reaction (PCR)-quality results in about 15 minutes and is unconstrained by a reader or need for external power. Veros is the first instrument-free, single-use, rapid, point-of-care molecular COVID-19 diagnostic testing platform that produces lab-quality results in approximately 15 minutes, according to the company.

Veros COVID-19's clinical performance was established in a multicenter study that prospectively enrolled nearly 300 evaluable subjects during both the delta and omicron variant surges of the pandemic. All study sites represented near-patient testing or point-of-care environments, with all test operators reporting no prior formal laboratory training or experience.

Operators reported that the Veros COVID-19 was user-friendly and provided clear results with minimal hands-on time required, according to Sense officials.

LABCORP ACQUIRES NEW JERSEY OUTREACH LAB BUSINESS

Labcorp recently announced that it has acquired RWJBarnabas Health's outreach laboratory business and select related assets.

RWJBarnabas Health is New Jersey's largest academic health system. Labcorp officials say the expanded relationship with RWJBarnabas will allow the system's physicians and patients access to Labcorp's expanded test menu and its extensive network of patient service centers, including those in Walgreens locations.

In addition, Labcorp will offer patients served by a RWJBarnabas Health laboratory expanded health plan coverage. Labcorp also offers enhanced service to rural markets and the potential for reduced out-of-pocket lab costs for patients. Same-day and stat testing will also be available in local communities, according to Labcorp officials.

RWJBarnabas officials said the acquisition is a strategic business decision that "enables a high-performing, streamlined outreach network to support its community."

ILLUMINA TO APPEAL EUROPEAN COMMISSION'S DECISION ON GRAIL DEAL

After the European Commission's (EC) recent decision to prohibit Illumina's acquisition of Grail, Illumina

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announced that it intends to appeal the decision.

Illumina officials said they are disappointed with the EC's decision prohibiting the acquisition. They added that Illumina can make Grail's multicancer early-detection Galleri test more available, more affordable, and more accessible and can help save lives and lower healthcare costs.

Illumina said that a merger of the two companies would usher in a transformational phase in the detection and treatment of cancer by facilitating equal and affordable access to the Galleri test. The blood test can screen asymptomatic patients for more than 50 types of cancer and can identify the tissue where a cancer has developed. The company says Galleri is suitable for general population screening.

The merger would not only accelerate multicancer early detection in the European Union but would also reduce inequity in cancer care by making early diagnosis affordable and widespread, another key priority of Europe's Beating Cancer Plan, Illumina officials said.

GENOMENON INTEGRATES CLINVAR DATA INTO ITS SEARCH ENGINE

Genomenon, an artificial intelligence (AI)-driven genomics company, has integrated all variants and pathogenicity interpretations from the ClinVar database into its Mastermind Genomic Search Engine.

This integration allows access via a single Mastermind search to patient variants found by genetic testing labs and submitted to ClinVar, along with the scientific evidence for these variants found across medical literature, the company said.

Mastermind has indexed more than 9 million publications containing over 19 million genetic variants, including about 18 million variants found in the medical literature but that are missing from the ClinVar database. More than 2,000 diagnostic labs currently use Mastermind, which is integrated into 18 clinical-grade decision support platforms and reference databases across the globe, according to Genomenon.

The company said that the integration allows Mastermind's clinical users to contain their workflow within a single, searchable interface, accelerate diagnosis, and enrich clinical reporting with actionable insights not found in ClinVar. The integration also allows searchers to identify evidence in Mastermind that is otherwise missing from ClinVar, with the potential to change patient diagnoses and ensure proper treatment. Mastermind allows users to easily search using any variant nomenclature, which can lead to finding more evidence.

Genomenon officials added that integration of ClinVar data into Mastermind makes genomic analysis for clinical decision support faster, easier, and more effective.

PRELUDEDX AND GALAXY HEALTH NETWORK AGREEMENT FOCUSES ON NOVEL DUCTAL CARCINOMA IN SITU TEST

Prelude Corporation (PreludeDx) recently announced that it has signed an agreement with Galaxy Health Network to provide coverage for the company's novel DCISionRT test for ductal carcinoma in situ (DCIS), also known as stage zero breast cancer. In the U.S., more than 60,000 women are newly diagnosed with DCIS each year.

Under the agreement, Galaxy's more than 3.5 million members and 400,000-plus providers will have access to DCISionRT. PreludeDx officials said that DCISionRT predicts personalized recurrence risk and radiation therapy (RT) benefit for patients with DCIS. Personalized results provide physicians and patients with critical information to optimize DCIS treatment plans and avoid over or under treatment.

DCISionRT was developed by PreludeDx on technology licensed from the University of California, San Francisco, and built on research that began with funding from the National Cancer Institute. The technology enables physicians to better understand the biology of DCIS. The test provides a score that identifies a woman's risk as low or elevated. Unlike other risk assessment tools, the DCISionRT test combines protein expression from seven biomarkers and four clinicopathologic factors using a non-linear algorithm to account for multiple interactions between individual factors to better interpret complex biological information. Clinicians receive a report of a woman's recurrence risk after breast-conserving surgery alone and with the addition of radiation therapy.

This new information may help patients and their physicians to make more informed treatment decisions, according to PreludeDx.

Index to Advertisers

Ask The Expert

Improving Utilization of Paraneoplastic Antibody Panels

EXPERT
By Brad Poore, PhD

What are paraneoplastic antibody panels?

A: Paraneoplastic antibody panels are laboratory tests used to aid in the diagnosis of paraneoplastic neurologic syndromes (PNS), which are autoimmune disorders that afflict the central or peripheral nervous system. Because of the rarity of PNS and resemblance to more common pathologies such as schizophrenia, stroke, or infection, diagnosing PNS can be challenging. Fortunately, many patients with PNS frequently have circulating antibodies against neuronal self-antigens that paraneoplastic antibody panels can detect.

Paraneoplastic antibody panels often consist of multiple antibodies known to cause or be associated with PNS. Due to the complexity of the testing and the low prevalence of these disorders, these panels are often only available at reference labs.

When should these antibody panels be used?

Ideally, antibody panels should only be ordered by a neurologist and only if there is a strong clinical suspicion of PNS. This often means excluding other disorders, such as a stroke or viral encephalitis, before proceeding with antibody testing. While it is tempting to use the panels as a screen, indiscriminate usage in low-risk patients can result in false positives, delaying an accurate diagnosis.

What are the pros and cons of paraneoplastic antibody testing?

Paraneoplastic antibody testing can be a useful diagnostic tool for patients with a strong clinical suspicion of PNS. For example, in a woman with rapid onset ataxia and ovarian cancer, a high titer of the PCA-1 antibody strongly indicates paraneoplastic cerebellar degeneration. It may also indicate a poor prognosis, and that the neuronal damage is likely permanent. It is important to note, though, that a diagnosis of PNS can be made without antibody testing.

As mentioned above, the problems with these panels arise when they are used indiscriminately or as a screening tool. In a study by Ebright MJ, et al. (Neurology 2018;91:e2057-66), patients with a moderate or low clinical suspicion of PNS yielded no true positive panels. In addition, only panels ordered by neurology contained true positives. However, even when ordered by neurology, multiple institutions have found that the positive predictive value of the panels is low, often <20%.

The high false positive rate can be attributed to multiple features of the test, including the methodology for antibody detection, the specimen type selected, and what antibodies are being evaluated. Many antibodies associated with PNS can be found in the general population and may not be pathogenic or are indicative of non-PNS diseases. For example, the GAD-65 antibody, which is associated with Stiff Person Syndrome and multiple other paraneoplastic disorders, is present in 1% of the general population and roughly 80% of type-1 diabetics.

What methods can be used to screen patients who are unlikely to benefit from these antibody panels?

The Antibody Prevalence in Epilepsy and Encephalopathy (APE2) Score, developed at the Mayo Clinic, can be a very useful screening tool. In a retrospective study, Dartmouth Hitchcock Medical Center found that the APE2 score was able to identify approximately 90% of patients who would have had a true positive paraneoplastic antibody panel result, and approximately 80% of patients who would have had a false positive or negative panel (J Appl Lab Med 2021;7:36-45). However, the APE2 score can only be applied to certain PNS disorders, meaning that it cannot be used as a universal screen for antibody testing.

How can laboratorians work with clinicians to use these panels more effectively?

The most important thing the lab can do is to maintain an open dialogue with clinicians. Working with neurology, the lab needs to educate ordering providers on how the panels are intended to be used, and the problems associated with using them as a screen for low-risk patients. In addition, the lab can utilize various ordering practices, such as restricting PNS panel testing to neurology, or encouraging use of the APE2 score.

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CLN Clinical Laboratory News

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BETTER DIABETES CARE

11.5%

Reduction in HbA1c for patients in new clinical care pathway

PAGE 7

Teams from Seven Countries Recognized with Achievement

From innovative algorithms to improved biomarker monitoring, the evidence shows integrated teams make a difference in patient outcomes globally.

BY KIMBERLY SCOTT

Across the globe, clinicians and laboratory medicine professionals are measurably improving patient lives by implementing care pathways that employ laboratory testing in new ways. From enhancing diagnosis of myocardial injury in babies to detecting cardiovascular risk in blood donors to identifying acute kidney injury and chronic kidney disease, the interdisciplinary teams below have implemented care initiatives that are having a measurable impact on outcomes.

The seven initiatives highlighted below have been recognized "with achievement" by AACC, Abbott, and other leading healthcare organizations through the UNIVANTS of Healthcare Excellence program. This prestigious global awards program recognizes teams who collaborate across disciplines and transform healthcare delivery and, ultimately, patient care.

IMPROVING MULTIPLE MYELOMA DIAGNOSIS

Multiple myeloma (MM), a blood cancer of mature plasma cells, predominantly presents in primary care with relatively non-specific symptoms. As a result, crucial diagnosis often can be delayed or missed if appropriate tests or actions are not performed.

Using diagnostic criteria developed by the International Myeloma Working Group (IMWG), Hampshire Hospitals National Health Service Foundation Trust in Basingstoke, United Kingdom, conducted an internal audit to determine how providers could do a better job of identifying MM. The audit highlighted two key improvement areas: requests that missed appropriate tests and inappropriate referrals being made to hematologists (or missed altogether).

Hampshire Hospitals put together a multidisciplinary working group to review the existing pathway. According to Kate Fenna, principal biochemist in the clinical laboratory, the first significant improvement made was the introduction of an electronic request profile with all required tests, sample types, and instructions accessible on all platforms. The next and largest task was writing a complete interpretation algorithm with supporting information technology (IT) rules and a risk category escalation protocol. The aims were to ensure that every sample had all tests analyzed (reducing repeats), reduce manual intervention, improve result turnaround times, and reduce variation in action.

The IT element included result entry drop down, auto-reflex testing rules, and a way to automatically send critical result reports to the hematologist on duty. This not only reduced paper use but also significantly reduced the time taken for patient review.

Another key aspect of the initiative was the creation of coded interpretive comments that were concise, informative, and referred clinicians to the most appropriate clinical guidance, Fenna said. In addition to these large changes, the team introduced several smaller IT improvements, including patient flags, ability to quantify multiple paraproteins, and therapy flagging. Team members wrote a simplified algorithm to enable biomedical scientists "first read" interpretation. And to improve communication, the hospital started a monthly pathology newsletter. The initiative relied heavily on three clinical disciplines and the clinical laboratory, with a significant amount of IT work.

Prior to implementing the initiative, the lab sent urgent patient reports to the requesting physician, often a general practitioner, for appropriate action. The requesting clinician would have to review the results and initiate an urgent patient referral to the hematologist. Under the new protocol, the duty hematologist reviews all urgent positive patient results within 24 hours of result generation. This has reduced urgent patient review from 2 weeks to 24 hours. In addition, the lab now sends all patient reports with clinical comments that guide the requesting clinician on the most appropriate next steps, which has improved clinician satisfaction.

Also prior to implementation, about 64% of patient requests had all the required tests at initial presentation. Now, that number has increased to 87% and is expected to continue to increase as the profile use becomes embedded. Inappropriate secondary care hematology referrals and queries have gone down by 10% since introduction and are expected to continue decreasing.

"Since introducing the simplified algorithm, four biomedical scientists have been trained on electrophoresis first read and interpretation," said Fenna. "Increasing the skill set and test repertoire of the laboratory staff has significantly improved staff morale and engagement, particularly as this is a manual laboratory technique with which many are unfamiliar."

While the use of IT, diagnostic algorithms, and coded commenting is not novel, its use in this context for this diagnostic pathway is, she noted. The principles applied to this diagnostic pathway could easily be transferred to other diagnostic pathways where clear criteria and guidelines exist.

Improved patient pathway for diagnosis, follow-up, and monitoring of multiple myeloma

2 weeks to 24 hours

Reduction in time for review of urgent positive patient results

Enhanced discrimination of myocardial injury in the pediatric population

52.62% to 82.88%

Safe exclusion of myocardial injury in babies from birth to 2 years of age

Hampshire Hospitals is currently in the process of implementing a similar approach to thyroid function testing.

ENHANCED DIAGNOSIS OF MYOCARDIAL INJURY IN CHILDREN

Pediatric heart disease is a significant concern in the children's healthcare system. Physicians use biomarkers of myocardial injury, echocardiography, and electrocardiogram readings to form a clinical diagnosis and appropriate treatment plans. High-sensitivity cardiac troponin I (hs-cTnI) is the most common biomarker in pediatric heart disease workups. However, most clinicians use the reference interval of hs-cTnI in adults to diagnose pediatric heart disease.

Due to the similar clinical presentation of disease states, such as neonatal patent ductus arteriosus, viral myocarditis, and congenital heart disease, clinicians often find it challenging to diagnose a myocardial injury. This makes it critical to improve myocardial injury discrimination in a pediatric population.

Understanding that age-specific reference intervals for hs-cTnI would increase the accuracy of myocardial injury diagnosis in pediatric patients, a multidisciplinary clinical care team at Shandong Yantai Yuhuangding Hospital in Yantai, China, established a pediatric hs-cTnI reference interval to improve diagnosis.

Since the level of hs-cTnI in peripheral blood varies significantly between children and adults, physician use of adult reference values in assessing a child led to many children having their hs-cTnI levels re-examined after testing showed elevated levels during hospitalization. Parents were told that their child might have heart disease and were referred for follow-up cardiac assessments.

"The level of hs-cTnI in peripheral blood varies significantly between children and adults," said Lei Chen, vice director of the laboratory at Yantai Yuhuangding Hospital. "For example, the highest hs-cTnI reference value for newborns (114.16 ng/L) was about 4.3 times for adults (26 ng/L). Physicians' use of adult reference values for myocardial injury in assessing pediatric patients results in misdiagnosis in many children."

Because direct determination of reference ranges in pediatric populations is difficult due to the inability to obtain enough healthy children to participate in the study, the multidisciplinary clinical care team established a reference interval for hs-cTnI in young children by mining laboratory data using the indirect Hoffmann method. The team established reference ranges of hs-cTnI corresponding to the specific age (days, months, or years) and provided this information to clinical departments through the laboratory information system.

After implementing the initiative, the safe exclusion of myocardial injury increased from 52.62% to 82.88% in patients from birth to 2 days of age, from 55.66% to 96% in patients ages 2 to 7 days, and from 59.6% to 82.59% in patients from 7 days to 2 months of age. Overall, the hospital saw an 84% reduction in the number of blood samples drawn for cardiac marker tests in neonatal and pediatric medicine departments.

Use of the new pediatric reference ranges for hs-cTnI has made a significant improvement in assessment of myocardial injury in children, Chen said. In addition, ruling out myocardial injury early in a child's life eliminates the need for prophylactic nutritional drug therapies, which is estimated to save about $248 dollars (US) per patient.

EARLY DETECTION OF CARDIOVASCULAR RISK IN BLOOD DONORS

Cardiovascular disease (CVD) is the leading cause of hospitalization and death in Italy, according to World Health Organization estimates. Current tools used for cardiac risk stratification have several advantages, but also limitations, such as general correlation to risk of heart disease, inaccurate risk prediction, cutoffs that put the majority at moderate risk, and heavy dependence on age.

Cardiac-specific biomarkers, in conjunction with clinical and diagnostic findings, can help overcome these limitations, allowing an early identification, categorization, and prediction of who is at risk of future cardiovascular events.

Considering the importance of cardiovascular risk stratification for early prevention, Villa Sofia Hospital of Palermo implemented a CVD prevention initiative involving apparently healthy individuals, starting from blood donors without history of CVD, symptoms, or known risk factors, regardless of age. Together with tests performed on blood donors, Villa Sofia Hospital also included hs-cTnI as a cardiac-specific biomarker to more accurately identify and stratify early cardiovascular risk in this asymptomatic population, explained Patrizia Carta, a laboratorian in the transfusion medicine department.

Values of hs-cTnI greater or equal to 6 ng/L for men and 4 ng/L for women, in conjunction with other diagnostic findings, identified blood donors at medium/high risk of future CVD events, triggering a follow-up visit with cardiology and further investigations with imaging diagnostics, if required. The initiative generated measurable benefits, including early identification of 89 asymptomatic individuals who were newly identified at medium/high risk of future CVD events.

Since implementing the initiative, 3% of blood donors (89 out of 3,340) who were asymptomatic and without any know risk of CVD have

Early detection of unsuspected cardiovascular risk in asymptomatic blood donors

3%

Blood donors who were asymptomatic and had no known risk factors identified as medium-to-high risk for future CVD events

Vajirawich Wongpuvarak / iStock

been identified as medium-to-high risk for future CVD events, triggering follow up by cardiology and imaging diagnostics for more investigation. In the most extreme case, investigation results and clinical evaluation led to identification of a structural cardiomyopathy, ensuring early treatment and avoiding worse outcomes.

Another benefit is that the addition of a cardiac-specific biomarker to all blood donors regardless of age has helped drive blood donations at a time when it can be difficult to find people willing to donate. In addition, the estimated cost savings for the entire Sicily Healthcare Regional System was between 267,000 Euros and 445,000 Euros, based on mitigated outcomes associated with early risk assessment and intervention of the 89 medium-high risk blood donors.

"Our center was the only one in Italy to implement a cardiovascular risk prevention study," Carta said. "Our initiative allows us to screen a healthy population—as blood donors are by definition—allowing us to find that the healthy population could suffer from pathologies unknown to them."

RENAL OSTEODYSTROPHY MONITORING

Chronic kidney disease – mineral bone disorder (CKD-MBD) is a major cause of excess morbidity and mortality in hemodialysis patients. In Croatia, there are about 150,000 patients with chronic kidney disease (CKD), more than 2,000 of whom are on dialysis. Global clinical practice guidelines recommended by the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines endorse routine monitoring of bone biomarkers, including alkaline phosphatase and parathyroid hormone (PTH) every 3–6 months in patients undergoing hemodialysis.

In patients receiving treatment for CKD-MBD, or in patients with CKD and biochemical abnormalities, more frequent monitoring can enable enhanced identification of biomarker trends, early assessment of treatment efficacy, and mitigation of associated side effects.

The integrated care team at the University Hospital Center in Zagreb, Croatia, follows this best practice of more frequent testing of bone biomarker levels, which are monitored every 4 to 5 weeks in patients on calcimimetics (CINET) and vitamin D (or vitamin D analogs, such as ZEMPLAR). In addition, monthly PTH monitoring occurs in all children on dialysis with CKD-MBD.

"Using this approach, better titration of drug dosing is possible, preserving bone density and avoiding potential side effects for our patients," said Sanda Jelisavac Cosic, a biochemistry and laboratory medicine specialist in the department of nuclear medicine and radiation protection. With accelerated intervention in more than 60% of patients undergoing monthly PTH monitoring, the program enhances wellness, mitigates long-term risk, and reduces overall health care costs, she noted.

More frequent visits for patients who are undergoing therapy enable faster dosage adjustments, improving overall patient care and satisfaction, Cosic added. Better PTH control also has resulted in a decrease in the number of hyperparathyroid patients who need to have their parathyroid glands removed.

Patient surveys found that 100% of respondents were less stressed and feeling healthier when coming to regularly scheduled checkups. Almost all (98%) of nephrologists associated with this best practice indicated that they feel more secure in prescribing therapy and treating patients on dialysis due to more frequent PTH checkups.

"More frequent monitoring of PTH contributes to better calcimimetic titration and vitamin D analogs, slowing down the development of secondary hyperparathyroidism and preventing calcium bone loss," said Ninoslav Leko, head of nephrology at the hospital.

The best practice also has helped reduce healthcare costs. The cost of dialysis is $26,400 annually, while the cost of bone-saving therapy is an additional $10,300 annually. The reduction in cost ranged from $291 to $524 per patient per month, according to Cosic.

SCREENING HEALTHCARE WORKERS FOR COVID-19 ANTIBODIES

By November 11, 2021, the COVID-19 pandemic had resulted in more than 739,847 cases of confirmed infection in Jordan and more than 9,530 deaths. Because healthcare workers (HCWs) are considered at an elevated risk of infection, vaccination strategies of many countries, including Jordan, have focused on treating HCWs as a priority group.

At King Hussein Cancer Center in Amman, Jordan, a team went one step further. Knowing that antibody levels produced after vaccination begin to decrease over time—and there is no assurance that vaccinated HCWs are immune to COVID-19—the center adopted an initiative to screen them to ensure their vaccination succeeded in generating protective immunity against SARS-CoV-2. The idea was that this, in turn, might convey some protection for the center's cancer patients as well.

The cancer center chose the most sensitive, full automated, and practical test available to quantitatively measure IgG antibodies that attach to the virus's spike protein on the virus surface in serum and plasma, according to Lina Souan, director of the clinical immunology laboratory. The center also established a COVID-19 convalescent plasma and database bank for treating COVID-19 patients.

After the initiative was implemented, 5.3% of healthcare workers at the cancer center were identified as

Early diagnosis of acute kidney injury in hospitalized patients with comorbidities

60%

Patients with elevated SCr levels who would not have a documented clinical diagnosis without the algorithm

mixetto / iStock

lacking a protective antibody response to COVID-19. Those workers were strongly advised to get the vaccine or take a third booster shot. Otherwise, these workers were required to bring in a SARS-CoV-2 negative PCR test every 72.

The antibody testing also helped the cancer center determine which vaccines were most effective at inducing neutralizing antibodies for a longer period. According to the data, 43.9% of HCWs vaccinated with Sinopharm lost their vaccine induced neutralizing antibodies at 7 months after vaccination; 99.6% of HCWs vaccinated with Pfizer maintained their vaccine-induced neutralizing antibodies; and 98.2% of those vaccinated with AstraZeneca maintained their protective antibodies.

The cancer center also collected 484 convalescent plasma units to use in treating SARS-CoV-2 infected cancer patients, which led to decreased hospitalization and helped patients recover faster.

Mitigating avoidable complex procedures in cancer patients with chronic illnesses and underlying health conditions saves considerable costs while decreasing patient morbidity and mortality, noted Osama Abu Atta, section head of infectious diseases. For every cancer patient who did not contract COVID-19, the center saved an average of JD 1,200 per day.

"Improving and reducing the length of stay improves financial, operational, and clinical outcomes by decreasing the costs of care for a patient," he said. "It can also improve outcomes by minimizing the risk of hospital-acquired conditions."

Keeping patients healthy is the best practice for cancer care, added Souan. "By understanding how employees are affected by the vaccine, we can better ensure patient safety and the safety of our frontline healthcare workers. We also learned more about the effectiveness of each vaccine in our healthcare worker population and were able to build a convalescent plasma bank to help cancer and COVID patients."

EARLY DIAGNOSIS OF KIDNEY INJURY

Acute kidney injury (AKI) is a spectrum of heterogenous conditions that develop due to rapid impairment in renal function owing to a complex, multifactorial etiology. AKI is hard to diagnose, due to its asymptomatic presentation, with about 50% of cases being missed. Without timely diagnosis and intervention, the disease may progress to chronic kidney disease (CKD) and end-stage rental disease (ESRD). This disease is of public health importance because of its association with increased complications (life-threatening electrolyte imbalances, pulmonary edema, metabolic encephalopathy), mortality rates (as high as 40%-70%), and cost of healthcare. Optimal management of AKI can help improve patient outcomes and reduce mortality rate by 20%.

To tackle this issue in India, the biochemistry and immunology department of Kokilaben Dhirumbhai Ambani Hospital and Medical Research Institute (KDAH) created a pilot project for an alert system to facilitate early diagnosis and timely intervention for AKI. The department created an algorithm to track an increase in serum creatinine (SCr) according to the KDIGO guidelines, explained Barnali Das, a lead consultant heading the biochemistry and immunology sections in the laboratory medicine department of KDAH.

Patients older than 18 years with a baseline of SCr less than 4 mg/dl were evaluated and positive alerts were generated for 214 of 4,439 hospitalized patients screened over a 45-day period. Of these, 75.2% were critically ill, with primary diagnosis of cardiac, pulmonary, and nephrological events and co-morbidities such

Screening healthcare workers for neutralizing SARS-CoV-2 IgG antibodies

5.3%

Healthcare workers identified as lacking a protective antibody response to COVID-19

Renal osteodystrophy monitoring by monthly PTH determination in hemodialysis CKD-MBD patients

$291-$524

Savings in drug and PTH costs per patient per month

as hypertension, diabetes mellitus, and CKD. Approximately 60% of patients with elevated SCr levels would not have a documented clinical diagnosis without the clinical algorithm.

Executing the AKI alert system in real time is imperative to assist physicians in early diagnosis of AKI, Das said. Algorithms that implement the recommendations from the KDIGO guidelines offer visibility to physicians about AKI risks that may have previously gone unnoticed under the usual standard of care. Accuracy of the system was 91.4%.

"To our knowledge, this is the first attempt to create and implement an alert system to facilitate early diagnosis and timely intervention for management of acute kidney injury in India," said Urja Parekh, a research scholar on the pilot project.

Das and the team from KDAH recently received a $37,500 grant from Koita Centre for Digital Health of IIT Bombay and started a collaborative project with Siuli Mukhopadhyay of IITB to develop a risk prediction algorithm and web-based model for an AKI e-alert system.

The initiative enhanced clinician confidence in their ability to detect AKI even when creatinine levels are normal, noted Kiran Shetty, a consultant intensivist in the intensive care unit. "Early alert is especially useful in patients with nephropathy, diabetes, and hypertension and helps with management of these patients," he said. "The AKI alert system also contributes to the assessment of drug-dosage modifications, informing primary consultants on early identification of AKI and potential necessary action."

Identifying AKI early also has helped the hospital reduce costs. The average length of stay for AKI patients is 12 days with an average cost of $466 per day at KDAH. Treatment of critically ill AKI patients in the ICU costs $602 per day on average. Progression of AKI to more advanced stages would require dialysis at a cost of $444 to $619 per round of dialysis. And AKI screening ranges between $13 and $35 per patient, which results in a significant savings when AKI is caught and treated early.

OPTIMIZING DIABETES TREATMENT

The expanding prevalence of diabetes mellitus (DM) and the number of patients living with DM and its comorbidities has brought about new socioeconomic challenges. DM is a significant health problem that is associated with serious complications. Even prediabetes has shown to be associated with various complications, including increased macro and microvascular damage. Patients presenting with critically uncontrolled diabetes, acute diabetes-related complications, and diabetes-related comorbidities are subject to increased risk of mortality, increased incidence of chronic complications, increased length of stay in a hospital, and increased costs per admission.

Zulekha Hospital in Dubai, United Arab Emirates, formed a working group to focus on these challenges. The group developed a systemized, five-stage multidisciplinary clinical care pathway based on international guidelines and adapted to the hospital's patient population with the aim of supporting optimal DM care and preventing anticipated complications, according to Mariam Younan, a pathologist, and head of the hospital laboratory department.

"The battery of lab tests included in the pathway was very well chosen to address all aspects of clinical care of diabetes patients," Younan noted. All critical results were automatically alerted by the software with an automated message sent to the requesting doctor's mobile, together with a phone call. All tests were flagged in the final report to easily identify when abnormally low or high. Test

Optimizing care of diabetes patients through a 5-stage multidisciplinary clinical care pathway

4.5-Fold

Reduction in cardiovascular risk due to early detection of diabetic complications

results, once authenticated by the lab, were simultaneously viewed by the treating doctor on the electronic healthcare record and by the patient on the hospital patient portal. "All the above assisted in prompt and adequate patient care with early detection of complications and timely decisionmaking," she said.

Since being implemented in January 2021, the clinical care pathway led to a 30% increase in patient engagement, 11.5% reduction in HbA1c levels, as well as enhanced early detection of DM complications like diabetic nephropathy (11% to 19%), retinopathy (6% to 14%), and neuropathy (14% to 36%). It also led to earlier detection of diabetic foot infection with no amputations after the start of the initiative, according to Magdy Allam, head of the hospital's endocrinology department.

There were other positive outcomes related to the DM clinical pathway as well. Patient obesity declined by 6.45%, dyslipidemia dropped by 21%, systolic and diastolic blood pressures were reduced by 9% and 6%, respectively, and detection of vitamin B12 deficiency increased fivefold.

Not only were patients satisfied with the new pathway, but clinicians also expressed support. "Increased detection rate of neuropathy in diabetic patients after the pathway implementation increased my confidence in preventing a further chain of potential complications, including diabetic foot infection as neuropathy usually presents first in this chain," said Mohamed Elshafei, a specialist neurologist.

Prior to implementation of the pathway, 4% of patients with diabetes required hospital admission due to moderate to severe hypoglycemia (and one case was admitted with diabetic ketoacidosis). Since implementation of the initiative, no patients have experienced unanticipated hospital admissions due to diabetic complications.

Moreover, cardiovascular risk scores have improved more than 4-fold, mitigating long-term risk and associated diabetic complications. The score predicts the 10-year risk of the following atherosclerotic cardiovascular disease events: nonfatal myocardial infarction, coronary heart disease death, and fatal or nonfatal stroke. All these illnesses would incur healthcare costs and increase patient morbidity and mortality.

INTEGRATED TEAMS MAKING A DIFFERENCE

Each of these initiatives demonstrates how laboratory testing has a crucial role to play in improving patient care and outcomes. Beyond simply providing test results, clinical laboratories are working closely with interdisciplinary teams to help diagnose health conditions earlier when they can be treated most effectively, thus potentially reducing morbidity and mortality. Not only are these teams improving patient care, but they also are helping to develop integrated care practices that improve standards of care for their communities.

To learn more about the UNIVANTS program and other winners, go to www.univantshce.com.

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UNIVANTS 2021 Teams Recognized In This Issue

Improved Patient Pathway for Diagnosis, Follow-up And Monitoring of Mulitple Myeloma: A Multi-Disciplinary Collaboration to Improve the Pathway from the Initial Request to Long-Term Monitoring
Hampshire Hospital NHS Foundation Trust, Basingstoke, U.K.
Kirsty Gordon
Ross Sadler
Alex Kelly
Noel Ryman
Kate Fenna

Enhanced Discrimination of Myocardial Injury in a Pediatric Population Using Age-Specific Biomarker Reference Intervals
Yantai Yuhuangding Hospital, Yantai, China
Guozhen Chen
Chenming Sun
Lei Chen
Yanjie Ding
Guangyu Zhou

Early Detection of Unsuspected Cardiovascular Risk in Asymptomatic Blood Donors
UOC Medicina Trasfusionale Villa Sofia-Cervello, Palermo, Italy
Patrizia Carta
Francesco Arcoleo
Francesco Gioia
Calogero Falletta

Renal Osteodystrophy Monitoring by Monthly PTH Determination in Hemodialysis CKD-MBD Patients
University Hospital Centre Zagreb, Croatia
Sanda Jelisavac Cosic
Drasko Pavlovic
Boris Kudumija

Early Diagnosis of Acute Kidney Injury in Hospitalized Patients with Comorbidities
Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute, Mumbai, India
Sharad Sheth
Urja Parekh
Niranjan Kulkarni
Santosh S Shetty
Barnali Das

Improving Safety, Confidence, and Clinical Care of Cancer Patients Through Screening Healthcare Workers for Neutralizing COVID-19 IgG Antibodies and Establishing a COVID-19 Convalescent Plasma Bank
King Hussein Cancer Center, Amman, Jordan
Maher Sughayer
Hala Al Salahat
Lina Souan
Mohammed Owdeh
Alaa Al-Shorman

Optimizing the Care, Safety, and Wellness of Patients with Known Diabetes Through Laboratory Medicine and a 5-stage Multidisciplinary Clinical Care Pathway
Zulekha Hospital, Dubai, Dubai, United Arab Emirates
Magdy Allam
Mohamed Abdelhamid
Mariam Younan
Eman Yousef
Muhammad Khan

ADD-141680-GBL-EN

CLINICIANS

24.1%
INCREASE
in preoperative diagnostic accuracy[1]

11%
INCREASE
in clinical satisfaction[2]

PATIENTS

50%
REDUCTION
in AKI (acute kidney injury) complications[3]

3.9%
INCREASE
in number of patients with controlled diabetes[4]

ADMINISTRATION

24%
REDUCTION
in hospital admissions for patients who are not experiencing a heart attack[5]

$80K
INCREASE
of incremental revenue over 3 years[6]

PAYORS

€250K
in mitigated costs and procedures[7]

NZ$530K
per annum in mitigated healthcare costs[8]

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