

October 2021

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News

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## Your BURNOUT Is Real



### The State of Cybersecurity in Labs



### Diagnosing Financial Toxicity



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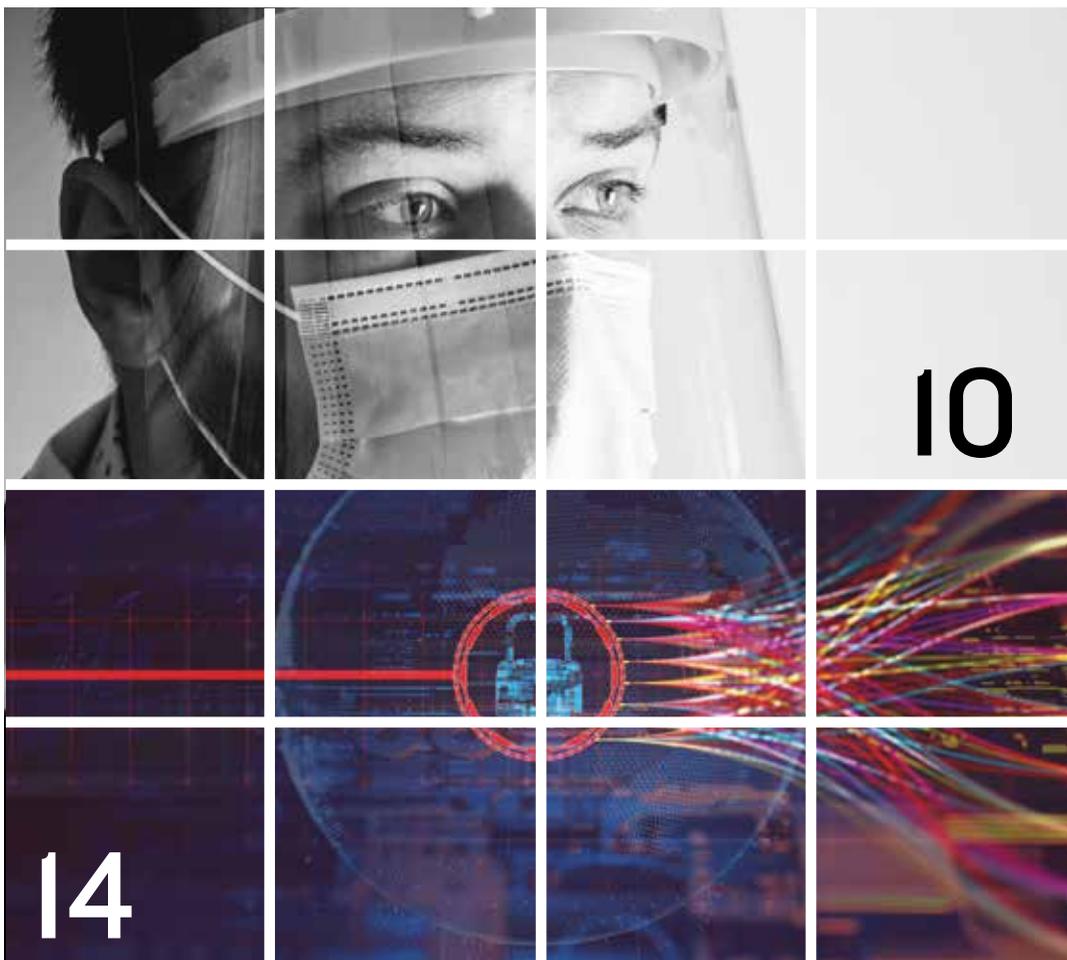
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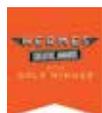


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Clinical practice continues to change, and the CDC CVD program is continuing to adjust its program to meet the clinical laboratory community's needs.

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## Health Centers Get \$48 Million to Fight HIV

The Department of Health and Human Services (HHS) and the Health Resources and Services Administration (HRSA) announced they have awarded more than \$48 million to 271 health centers across 26 states, Puerto Rico, and the District of Columbia to expand HIV prevention and treatment. The funding will support testing, pre-exposure prophylaxis (PrEP) related services, outreach, and care coordination.

The new spending is part of an HHS program called Ending the HIV Epidemic in the U.S. The agency says the program could reduce the number of new HIV infections in the United States 90% by 2030. The latest funding will expand HIV prevention services that decrease the risk of HIV transmission in counties, territories, and states that are seeing substantial HIV diagnosis.

Through this initiative, HRSA-funded health centers have already provided some 2.5 million HIV tests to patients. Of those who tested positive for the first time, more than 81% were successfully linked to treatment within 30 days. Nearly 190,000 patients living with HIV received medical care services at health centers, and over 389,000 patients received PrEP-associated services, HHS said.



### RECORD ENROLLMENT, EXPANSION FOR GOVERNMENT HEALTHCARE MARKETPLACE

A new report released by the Department of Health and Human Services (HHS) shows that an additional 2.8 million people gained access to healthcare insurance through the Biden administration's 2021 special enrollment period on HealthCare.gov and state-based marketplaces. This brings the total number of people in the U.S. enrolled through these programs to a record-breaking 12.2 million. Medicaid enrollment is also growing rapidly: More than 82.3 million people now use Medicaid.

According to HHS analysis, the expanded premium tax credits in the American Rescue Plan reduced premiums, increased savings, and provided consumers greater access. For example, more than 90% of consumers who enrolled during the special enrollment period saw their premiums reduced, and 48% of new HealthCare.gov consumers received a monthly premium of \$10 or less

after the law's tax credits. Likewise, since February 2020, the month before the COVID-19 public health emergency was declared, enrollment in Medicaid and related programs increased by more than 11.6 million, or 16.4%.

The administration is working on new ways to keep these programs growing. Beginning this year, consumers will have an extra 30 days to review and choose health plans on the government website, from November 1, 2021, through January 15, 2022. CMS is also expanding its marketplace navigators program, with experts who help consumers understand their choices and enroll.

### FEDS FINE HOSPITALS THAT DON'T GIVE PATIENTS QUICK ACCESS TO MEDICAL RECORDS

The Department of Health and Human Services (HHS) continues its crackdown on healthcare providers that won't give patients their healthcare records in a timely manner, with the agency's Office for Civil Rights (OCR)

recently announcing the resolution of its twentieth investigation in its HIPAA Right of Access Initiative this year.

Children's Hospital & Medical Center (CHMC) in Omaha, Nebraska is the latest organization in OCR's crosshairs. The hospital has agreed to take corrective actions and pay \$80,000 to settle "a potential violation of the HIPAA Privacy Rule's right of access standard."

The case is from May 2020, when a parent filed a complaint with OCR alleging that the hospital had failed to provide her with timely access to her minor daughter's records. The hospital provided some records but did not provide all of the records the parent requested.

The HIPAA right of access standard requires a covered entity, such as a hospital or independent laboratory, to act on a patient's access request within 30 days of receipt (or within 60 days if an extension is applicable).

In addition to the monetary settlement, CHMC will undertake a corrective action plan that includes 1 year of monitoring.



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## Turning Leftover Specimens Into Treasure



**L**eftover specimens are valuable resources for medical and translational research. The Food and Drug Administration (FDA) defines a leftover specimen as “the remnant of a human specimen collected for routine clinical care or analysis that would otherwise have been discarded.” An extended description could also include specimens obtained from repositories or biobanks and remnant specimens previously collected for other, unrelated research. The specimen types include, but are not limited to, biofluids such as serum or plasma, saliva, urine, and CSF, as well as tissues.

### How Can Laboratories Use Leftover Specimens?

Clinical laboratories routinely use leftover specimens for quality improvement and method development, validation, and verification purposes. For researchers, leftover specimens can be a springboard to carry out pilot studies and test novel ideas. IVD manufacturers also use them to generate data in support of premarket submissions to regulatory agencies.

Leftover specimens are particularly precious in vulnerable patient populations such as pediatric, elderly, and pregnant patients, from whom an extra blood draw for research could be challenging or sometimes impossible. For example, an isobaric tags for relative and absolute quantitation technique was employed to reveal the proteomic changes in leftover sera from pregnant women suspected for developing preeclampsia (Hypertension Research 2020; doi:10.1038/s41440-020-0484-3); potential miRNA markers were discovered for ectopic pregnancy using leftover samples from pregnant women visiting the emergency room (Clinical Chemistry 2012; doi: 10.1373/clinchem.2011.179283); leftover specimens from pregnant women were used for quantifying nine antimicrobials and studying the exposure of pregnant women to antimicrobials (Journal of Clinical Laboratory Analysis 2021; doi:10.1002/jcla.23539); and distinct antibody responses to SARS-CoV-2 were identified in children using their leftover specimens submitted as part of routine care (JAMA

Network Open 2021; doi:10.1001/jamanetworkopen.2021.4302).

Under certain situations, such as the COVID-19 pandemic, scientists are eager to obtain specimens from patients to study the molecular mechanisms and pathophysiology of the disease. However, prospective patient recruitment and sample collection for research could be impermissible, especially in patients under urgent care in the emergency room (ER) and critically ill patients in the intensive care unit (ICU) due to risk of infection and contamination. Moreover, longitudinal samples from those patients are extremely difficult to obtain even during non-pandemic times. Alternatively, as ICU patients' blood work is performed daily as part of routine clinical care, longitudinal specimens are available after routine testing is done.

Using leftover specimens for COVID-19-related studies could dramatically accelerate medical research. In one study, we used longitudinal, leftover serum specimens obtained on the first, second, and third day of hospital stays and identified distinctive cytokine signatures that predicted the development of acute respiratory distress syndrome, acute kidney injury, and mortality in COVID-19 patients (Scientific Report 2021; doi:10.1038/s41598-021-91859-z). In another study, early antibody responses were evaluated in leftover sera obtained from 120 COVID-19 adult ER patients (Biosensor and Bioelectronics 2021; doi:10.1101/2020.11.19.20235044). We found that higher baseline SARS-CoV-2 total antibody and neutralizing antibody activity positivity rates and more robust antibody responses were seen in patients who survived COVID-19 than in those who died in the hospital.

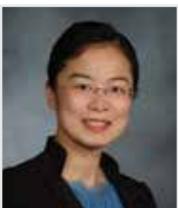
Laboratories also can use archived specimens from previous, unrelated studies and repositories or biobanks for method development and biomarker evaluation. For example, at the beginning of the pandemic, there



By Boyan Song,  
PhD



Zheng Cao, PhD



Zhen Zhao, PhD

were a lot of controversies over test accuracy, particularly specificity of the SARS-CoV-2 antibody assays. The specificity validation could be achieved using archived specimens collected prior to the pandemic.

### Regulatory Considerations

Although using leftover specimens usually does not involve direct patient interaction or intervention, they still should be deidentified, saved, and used for research purpose only with meticulous control and care to protect patients' privacy and confidentiality. A careful evaluation should be made to determine whether the activity qualifies as research involving human subjects that must be reviewed by an institutional review board (IRB), and whether informed consent or the documentation of informed consent can be waived. Researchers in the U.S. can use "Human Subject Regulations Decision Charts: 2018 Requirements," created by the U.S. Department of Health & Human Services, or consult the IRB with study specific details.

For leftover specimens obtained from clinical laboratories, researchers should recognize compliance requirements and policies to which these laboratories must adhere, such as how long patient samples must be kept before research or other uses. Researchers should coordinate with the clinical laboratory to obtain the specimens as soon as possible while remaining in compliance with the clinical laboratory's policy.

### Limitations

Using existing leftover specimens might sound like an easier approach than conducting prospective collection from study participants. However, their use often is limited in scope because they have not been collected for specific research purposes. In some cases, it is not possible to find sufficient demographic, diagnostic, and clinical information to determine whether leftover specimens are within the intended use.

Among other considerations, researchers must define clear scientific requirements when designing a study using leftover specimens. Researchers should determine if the quality and associated existing demographic and clinical data of the leftover specimens fit within the scope of the proposed study and if the specimen type, processing, handling, and storage conditions are suitable for the proposed analysis. In addition, in their publications, researchers should give greater attention to the description of the specimens in methods and interpretation of findings.

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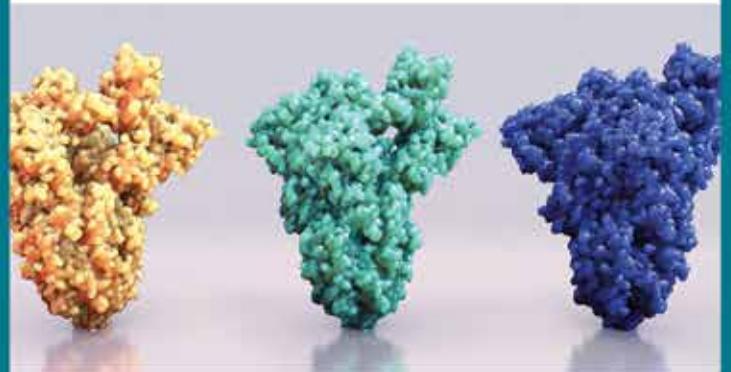
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## The Sample

## Rapid Point-of-Care Antigen Assay Could Aid Hospital Infection Control

A new assay might detect SARS-CoV-2 antigens with enough sensitivity and specificity to inform infection control measures and potentially inform novel, point-of-care testing methods, according to a recent *Clinical Chemistry* paper (Clin Chem 2021; doi:10.1093/clinchem/hvab158).

Many nucleic acid-based methods are sensitive enough to detect acute COVID-19 infections. However, persistent nucleic acid positivity after symptom resolution and disease recovery complicates infection control measures. This is true especially in immunocompromised patients who show long periods of nucleic acid positivity and have diverse presentations.

Previous research has shown that antigen results correlate better with viral culture results than nucleic acid determinations. These previous findings suggest that positive antigen results predict risk of transmission. However, most rapid antigen tests have low sensitivity and low positive percent agreement in high viral load cases, compared with real-time (rt) PCR.

The researchers developed the Microbubbling SARS-CoV-2 Antigen Assay (MSAA) as a screening test to identify patients who are likely to have active, ongoing replication and need close viral sequence monitoring. The assay relies on a smartphone's camera and readout and has a limit of detection (LOD) of 0.5 pg/mL (10.6 fmol/L) for the nucleocapsid antigen or 4,000 copies/mL inactivated SARS-CoV-2 virus in nasopharyngeal (NP) swabs. The authors also developed a computer vision and machine learning-based automatic microbubble image classifier to accurately identify positives and negatives.

In a clinical validation study on 372 residual clinical NP swabs from intensive care unit COVID-19 patients and immunocompromised COVID-19 patients, the researchers compared MSAA and rtPCR performance.

Positive MSAA results agreed with positive rtPCR results, and negative MSAA results agreed with negative PCR results, at rates of 97%. In patients who were not immunocompromised, swabs' antigen positivity rate decreased as days-after-symptom-onset increased, despite persistent nucleic acid positivity. MSAA detected antigens for longer, variable periods of time in immunocompromised patients with blood cancers. MSAA also detected viral sequence variations in patients with long duration of high antigen burden. Total microbubble volume—a quantitative marker of antigen burden—correlated inversely with cycle threshold values and days-after-symptom-onset.

The MSAA can provide insights into antigen dynamics in various patient populations, the researchers wrote.

### LEVEL OF BILE ACIDS DURING PREGNANCY MIGHT POINT TO COMPLICATIONS

**E**levated maternal serum total bile acids are associated with increased risk of intrauterine growth restriction (IUGR) and low birth weight (LBW), which appears higher in

pregnant individuals with hypertensive disorders, according to a recent study (JAMA Netw Open 2021; doi:10.1001/jamanetworkopen.2021.17409).

Bile acids play essential roles in metabolic modulation. Excessive serum total bile acid (sTBA) levels during pregnancy are associated with adverse perinatal outcomes.

However, their association with the risk of intrauterine growth restriction (IUGR) has been unclear.

The researchers conducted a retrospective cohort study that included regular prenatal exam records on 68,245 singleton pregnancies—delivered from 2014 to 2018—at a hospital-based center in Shanghai, China.

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Nonlinear regression models suggested an inverted J-shaped association between maternal sTBA level during pregnancy and fetal birth weight, with a steep decrease in birth weight at high sTBA levels. The estimated mean birth weights of infants born to mothers with sTBA of 40.8 µg/mL, 0.4 µg/mL, and 4.1 µg/mL were 2,879 g, 3,290 g, and 3,334 g, respectively.

The researchers observed lower birth weight and a higher incidence of IUGR in patients with gestational elevated bile acids, known as gestational hypercholanemia (sTBA of 4.08 µg/mL or higher). The estimated mean birth weight of infants born to mothers with gestational hypercholanemia was 3,309 g, versus 3,338 g for infants born to mothers without the disorder. Incidence of IUGR among women with gestational hypercholanemia was 1.4%, compared with an incidence of 0.5% among women without gestational hypercholanemia.

Compared with patients with sTBA concentrations less than 4.08 mg/mL, those with gestational hypercholanemia had increased risk of LBW (with an adjusted odds ratio of 1.29), and IUGR (with an adjusted odds ratio of 2.18). The highest risk for LBW and IUGR was among pregnant individuals with both hypertensive disorders and hypercholanemia, compared with those with sTBA concentrations less than 4.08 µg/mL. For LBW, the adjusted odds ratio was 9.13. For IUGR, the adjusted odds ratio was 19.14.

Clinicians should monitor bile acid concentration during follow-up for pregnancies with potential IUGR, the researchers wrote. They call for more research to confirm both their findings and benefits of drugs that lower sTBA concentrations.

#### STUDY HIGHLIGHTS BENEFITS OF MULTITARGET FECAL IMMUNOCHEMICAL TEST

**A** multitarget fecal immunochemical test (FIT) better detects advanced colorectal neoplasia and adenomas than an older FIT assay, a recent study found (Ann Int Med 2021; doi:10.7326/M20-8270). Many screening programs use the older FIT because of its overall performance characteristics, logistics, and cost-effectiveness, but its sensitivity for cancer precursors, including advanced adenomas (AAs) and advanced serrated polyps (ASPs), is far lower than its sensitivity for cancer.

The researchers developed a new, protein-based multitarget FIT (mtFIT) using a combination of hemoglobin, calprotectin, and serpin family F member-2. This was intended to outperform FIT in the detection of advanced neoplasia (AN) at an equally high specificity. The researchers tested the assay on leftover FIT material in 1,284 participants from a screening and referral population, classified by their most advanced lesion. Forty-seven had colorectal cancer, 135 had AA, 30 had ASP, 250 had nonadvanced adenoma, and 53 had nonadvanced serrated polyps. The study also included 769 controls.

The researchers used classification and regression tree (CART) analysis on biomarker concentration to identify the optimal combination for detecting AN. The researchers cross-validated the mFIT test's performance using a leave-one-out approach and compared mFIT performance with a FIT test with equal specificity.

The CART analysis showed that mFIT had a cross-validated sensitivity for advanced neoplasia of 42.9%, versus 37.3% for FIT. The two tests both had sensitivity of 96.6%. In particular, cross-validated sensitivity for AAs increased from 28.1% to 37.8%. Using these results, the researchers performed an early health technology assessment that showed that screening via mFIT may be more cost-effective than FIT.

The researchers noted that their study is limited by enrichment with a referral population. A prospective screening trial of mFIT is being prepared, they added.



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The pandemic revealed the fearless commitment and ingenuity of clinical laboratorians and the IVD industry, but stress and burnout have left them wounded.

BY JEN A. MILLER

# Your Burnout Is Real

**B**urnout among healthcare workers has reached a crisis level. But while many reports have focused on physicians and nurses, few have considered the impact on clinical laboratory professionals. "The laboratory is often behind the scenes supporting the patient's clinical care," said Melissa Allen, MS, program administrator, pathology and laboratory medicine at the University of Rochester Medical Center in Rochester, New York. "We have a supportive leadership team, but lab

personnel in general tend to fly under the radar because we lack visibility."

Even if burnout among doctors and nurses does get the most attention, especially when hospitals are full of COVID-19 patients, the evidence shows that burnout in clinical laboratorians is also severe: 85.3% of respondents to a 2020 survey from the American Society for Clinical Pathology (ASCP) reported having felt burnout.

That study was conducted before COVID-19 became a pandemic, and all evidence points to the pressure on

laboratorians increasing dramatically. Working in a job that has a small margin for error plus high demand for mental acuity is demanding enough without pandemic-level work. "Laboratory science has exacting technical standards and places high cognitive demands on the individual, plus there's a societal expectation that leads to hesitancy to recognize and address fatigue and burnout," said Kathryn Gibson, MD, medical director of health and wellness at ARUP Laboratories.



If left unchecked, burnout compounds and leads to new problems. Fatigue and burnout “lead to an increased number of errors and decreased quality, which in turn lead to higher resource utilization, decreased margins, and increased pressure on the system,” Gibson said. “At ARUP, we’re figuring out how to interrupt this cycle with a focus on changing the culture around mental health.”

The ASCP survey also found that 44.4% of respondents were considering changing careers altogether, 33.4% thought about finding a job in a related field, and 24.9% were considering retiring—ominous signs considering the already dire clinical laboratory labor shortage. What would help? Not surprisingly, 58.9% said better wages, but 27.1% also said better work-life balance.

“The fundamental culture of wellbeing has to shift,” Gibson said. “Everyone talks about putting on your oxygen mask first, but our cultural norms are so strong that even if someone knows it logically, we have a hard time engaging with that thought emotionally or behaviorally.”

#### **PUTTING PEOPLE FIRST**

Breaking this cycle isn’t going to happen by changing the nature of clinical laboratory work, Gibson said. It can’t, not if laboratorians are going to continue maintaining superb patient care. “We’re not going to change the requirements of standardization, high

mental acuity, and attention to detail,” she said. “What we can do is change the hesitation to acknowledge the stress and burnout and put the structure in place for peers to support each other, and for supervisors to support their teams.”

During the first and second waves of the pandemic, Allen said that she noticed the extreme stress among technologists who were working to clear the backlog on the bench and outrun an onslaught of pending tests. She said she “tried to encourage staff to take time to step away from the

workplace to go outside and take a walk in the sunshine.” She also encouraged mindfulness moments when employees did get a break.

There are no easy fixes. The University of Rochester’s employee wellness team ran webinars about burnout and, prepandemic, organized mindfulness sessions and yoga. That helped some employees, but Allen also saw that some of these initiatives caused stress itself as staff “wanted to keep the work moving, get one more patient sample through,” she said. “We

**“Everyone talks about putting on your oxygen mask first, but ...**

**we have a hard time**

**engaging with that thought emotionally or behaviorally.”**

**—Katherine Gibson**



tried having ice cream trucks come through, little things to lift their spirits. But often, it's good for one group but creates stress for another group because they can't get away and participate."

What has helped most, she said, was expanding employee assistance and mental health resources, and making therapists available to all staff, whether they used the University of Rochester health insurance products or not. "Our organization took a big step to open mental health resources to all staff regardless of insurer, which was really helpful," she said. "We need to increase our availability and access to things like employee assistance programs and therapy and practical resources that can help people navigate this emotional onslaught."

In addition to making therapy more widely available, revamping employer-provided leave programs to cover not just physical but also better cover mental health is critical. Longer term, the government can help by making the Federal and Medical Leave Act (FMLA) more inclusive of mental health, she said.

"Taking a leave for physical health concerns is far more straightforward than for mental health concerns, as there's not a well-established timeline to improved mental health," Gibson said.

Education and awareness of burnout coming from a leadership level also makes a difference, she added. "Talking about mental wellbeing really does open the door for other people to talk about it. Psychologically, it's a safe place to go to if your leadership engages the topic," she said. "I know that education and awareness sound dry, but when you really think about it, what that means is awareness that you're not alone, and awareness of how other people deal with that."

Allen hopes that the pandemic has also opened leaders' eyes to the key role clinical laboratory professionals play in overall patient care and they recognize that they are affected by the increased demands and stress of the current situation, too. "COVID has really brought forth a spotlight on the clinical laboratory and the part we

take in treating and diagnosing our patients," she said.

If anything good has come of this, it's that when elective surgeries were canceled during peak COVID-19 hospitalizations, laboratories had the opportunity to cross-train staff in other areas of the lab, "which is something we don't often get to do because of our day-to-day workload," Allen said. That can potentially help with the staff shortage.

### WELLNESS AWARENESS, FOR THE NEXT GENERATION

While the median age of a range of medical professionals continues to get older, younger professionals remain a force for change in all fields, and they are approaching potential burnout and fatigue in ways that make more sense to them. That includes wellness.

"Younger professionals are very interested in how we can maintain what, in many ways, is a satisfying and fulfilling career, without succumbing to the potential for burnout," said Sarah Hackenmueller, PhD, technical director of rapid response laboratories at the Providence Oregon Regional Laboratory and chair of the AACC Society for Young Clinical Laboratories Core Committee (SYCL).

Members of the SYCL Core Committee (which defines "younger" as under 40 years old) had been informally sharing what wellness tactics worked for them. "We talked about different challenges that we were encountering and how some of us were able to overcome them even if we weren't all susceptible to the same frustrations or same challenges," she said. They realized that "there must be others in our professional community and within AACC who feel the same way."

They started a new wellness initiative to share tips and tricks for making the most of time and energy. The goal is to share what peers know works for them, in the hopes that creating a database of options will help other members find something that might work for them as well.

In January 2020, the committee launched the monthly Wellness Tip community on the AACC SYCL Artery forum, with the goal of



fostering an environment where wellness-related topics can be discussed in a practical and broadly applicable way, and where members can freely share what has worked for them.

"We can't deal with anything specific in terms of staffing limitations or schedules at a particular institution, but we can provide tools that are broad and generic enough that they can be added to each person's internal toolkit for resilience," Hackenmueller said.

She also hopes that wellness and resiliency are included in more training programs for the next generation, so that they know that, yes, they will encounter stress, "but here are some ways you can really start to prioritize your own wellbeing," she said. "It seems obvious, but people need to be told it's OK, you can and should prioritize your own wellbeing at some point. That doesn't mean you can disregard your job, but there needs to be more awareness and more focus on that earlier in the training process." ■

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# Why Cyber Threats Won't Let Up

The relentless drive for smaller, faster, and more connected devices is running up against what could be a permanent state of cybersecurity threats.

BY SARAH MICHAUD



In October 2020, the federal government issued a dire warning of increased ransomware attacks on hospitals in the United States. The joint alert from the Cybersecurity and Infrastructure Security Agency, the Department of Health and Human Services (HHS), and the Federal Bureau of Investigation called the situation an “increased and imminent cybercrime threat.”

Following this report, researchers at the IT firm Check Point reported a 45% increase in cyberattacks against healthcare organizations—more than double the average increase seen across other industries.

Clinical laboratories’ data and operations have been no exception, and the risk could be growing, according to experts. For lab medicine, a wave of mobile technology and other trends are driving a more digital and connected ecosystem. Without cybersecurity controls, networked laboratory devices can be compromised and lead to patient harm.



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# Nova POC Creatinine/eGFR Method is More Accurate than Laboratory Method: Large Medical Center Study

In a 670 patient study funded by the International Society of Nephrology, the South Africa Medical Research Council and the University of Witwatersrand, Johannesburg, South Africa, the Nova POC StatSensor Creatinine/eGFR meter was more accurate than the central laboratory IDMS-traceable Jaffe methodology in estimating GFR when both methods were compared to MEASURED GFR (iohexol).<sup>1</sup>

- StatSensor measurements showed less proportional and constant error than respective IDMS Jaffe measurements when compared to iohexol measured GFR (mGFR).<sup>1</sup>
- StatSensor showed better accuracy than the IDMS Jaffe methodology at identifying patients with mGFR's <90 mL/min/1.73 m<sup>2</sup>.<sup>1</sup>
- Of particular interest in the study, StatSensor showed better accuracy than the laboratory Jaffe methodology in the 60-89 mL min/1.73 m<sup>2</sup> range, where individuals with early disease may benefit renal protective measures.<sup>1</sup>



Nova Biomedical StatSensor Creatinine Meter

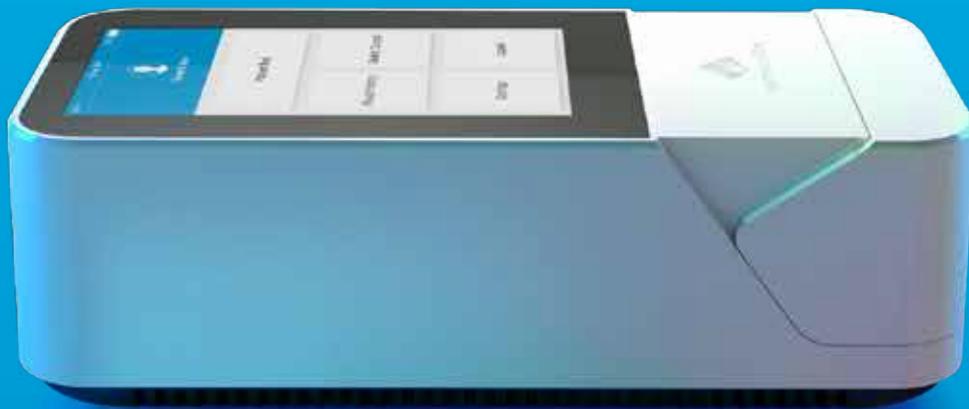
1. George J et al. Evaluating chronic kidney disease in rural South Africa: comparing estimated glomerular filtration rate using point of care to iohexol measured GFR. CCLM 2021.



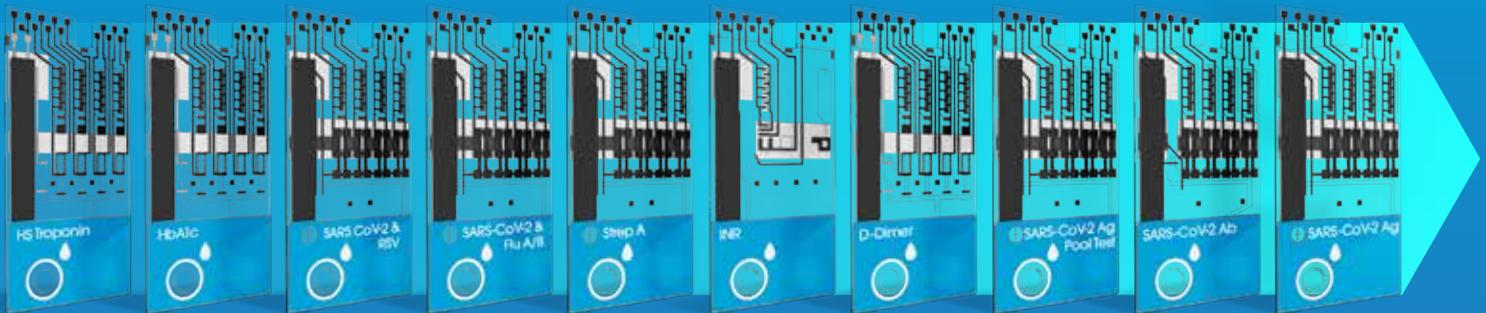


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In development	In development	In development	In development	In development	CE Mark	CE Mark	CE Mark	FDA EUA*	FDA EUA*	FDA EUA*

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\*The LumiraDx SARS-CoV-2 Ag test and the LumiraDx SARS-CoV-2 Ab test have not been cleared or approved by FDA. The LumiraDx SARS-CoV-2 Ag test has been authorized by FDA under an EUA only for the detection of SARS-CoV-2 nucleocapsid protein. The LumiraDx SARS-CoV-2 Ab test has been authorized by FDA under an EUA only for detecting the presence of total antibodies to SARS-CoV-2. They have not been authorized for use to detect any other viruses or pathogens. The tests are authorized in the United States for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostic tests for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

organization's security protocol will negatively impact clinical workflow. That conversation is so important, and it gets overlooked."

For laboratory professionals who want to help their organization prevent breaches or who have general questions about medical device security, Brennan recommends reaching out to the security team directly and asking for a briefing. If the laboratory is not associated with a system or hospital that has its own security team, there are some free resources. Brennan, who sits on the board for the American Association for Medical Instrumentation, recommends the association's free cybersecurity resources page and the HHS Office for Civil Rights Security Risk Assessment.

For specific instruments, the best way to learn about cybersecurity

issues is directly from the manufacturer, according to Jacobson. He also recommends getting software patches directly from the manufacturer. Many companies have customer portals that labs can use to check device performance or enter repair and maintenance tickets. Jacobson points out that Siemens Healthineers also posts security white papers to their customer portal that describe security factors in detail.

#### STAY HOPEFUL, STAY VIGILANT

Despite the growing number of cybersecurity risks, laboratorians have many reasons to be hopeful. Technical advances are emerging that will protect patient care and detect security breaches before they happen. For example, manufacturers are working on artificial intelligence applications built into devices that can alert users

to anomalous behaviors that might indicate a cyber adversary at work.

"Try not to panic when you see cyberattacks on the news," Jacobson said. "Not all of the ransomware you hear about are going to impact medical devices, and there is a good chance your device manufacturer is going to be on top of the latest vulnerabilities and is developing mitigation strategies to thwart security breaches."

The threat will continue to be an issue for the foreseeable future. While manufacturers, information security staff, and IT professionals work to stay one step ahead of cyber adversaries, it is essential for laboratories to stay current with and use cybersecurity best practices. ■

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**AACC**





BY MICHAEL ASTION, MD, PHD,  
AND BRIAN R. JACKSON, MD

## Patient-Centered Laboratory Stewardship Can Reduce Financial Toxicity

**A**ccusations of financial malfeasance related to coronavirus testing have been the subject of numerous news stories. The alleged abuses include overcharging for coronavirus testing both nationally and internationally (1, 2, 3), and loopholes in U.S. federal law allowing patients to be charged when the law's intention is complete financial coverage (4). In the U.S., problematic medical fees and billing practices are not restricted to coronavirus testing: They are commonplace throughout the healthcare system.

In a previous article, we described lab stewardship as a set of activities, policies, and procedures that improve five elements of lab testing: access to testing, test ordering, result retrieval, result interpretation, and financial fairness for patients (5). We also explained why lab stewardship must be patient-centered. Here we describe how laboratories can help patients with financial decisions and avoid subjecting them to financial toxicity.

The concept of financial toxicity in medicine was first described in oncology, where patients disproportionately experience financial harm from their care (6, 7). Financial toxicity both hurts the patient financially and harms the patient's health due to stress and the avoidance of necessary care (8). Table 1 presents financial fairness goals for lab stewardship programs and builds on the work of Elizabeth Rosenthal, MD, who has advocated for a patient financial bill of rights (9).

### Pricing and Financial Toxicity

The list price of laboratory testing is highly variable. It is not uncommon to see list prices substantially above costs. These high fees can result in financial toxicity to patients, especially if patients are uninsured or underinsured, or if testing is out of

network for the patient's health plan (13). Hospitals sometimes raise prices in order to increase revenue from the subset of uninsured patients who have the ability to pay, as well as insured patients who have to pay out-of-pocket when testing is not covered by their health plan or is out-of-network. High prices also lead to higher reimbursement when insurance plans are contracted to pay hospitals a percentage of billed charges. Hospitals' justifications for high prices usually focus on the availability of charity care, and the fair prices available to patients who are insured and in-network.

While clinical laboratory leaders rarely determine the pricing for lab

tests, that need not prevent them from influencing pricing behavior. Clinical laboratory leaders practice patient-centered stewardship when they involve themselves in health system finances to advocate for fair pricing. Reasonable pricing directly decreases financial toxicity.

### Price Transparency and Out-of-Pocket Expenses

Most commercially insured patients cannot rapidly determine out-of-pocket expenses for lab testing because price lists are confusing and difficult to access. Many hospital websites do not provide easy calculation of out-of-pocket expense based on insurance plan

#### T1 How Good Laboratory Stewardship Helps Patients Avoid Financial Toxicity

Goal	Purpose of goal
Ensure price list is fair and readily available	<ul style="list-style-type: none"> <li>Test pricing is easily available and understandable</li> <li>Pricing reflects market value and does not exploit situational vulnerability</li> <li>Facility fees, when present, are in the price list</li> </ul>
Provide an estimate of costs and coverage requirements prior to testing	<ul style="list-style-type: none"> <li>Benefits investigation is available to patients to determine insurance coverage and prior authorization requirements</li> </ul>
Provide an itemized, comprehensible bill	<ul style="list-style-type: none"> <li>The patient understands what test(s) were performed and what they owe</li> <li>The patient can easily detect any billing errors</li> </ul>
Eliminate surprise out-of-network billing	<ul style="list-style-type: none"> <li>The patient does not receive a large bill when physician sends testing to a lab that is out-of-network for the patient's insurance plan (10)</li> </ul>
Establish your lab as a stable in-network lab for your major payers	<ul style="list-style-type: none"> <li>The patient has stable, adequate insurance coverage for lab testing at your facility</li> <li>The patient avoids a large increase in expenses if your lab goes from in-network to out-of-network</li> </ul>
Provide adequate charity care and coaching on financial incentives from outside labs	<ul style="list-style-type: none"> <li>The patient understands eligibility for charity care and at what level</li> <li>The patient is retained within your institution's billing and charity care system, so they avoid multiple charity care policies and inaccurate offers of free testing or financial forgiveness (11, see insert)</li> </ul>
Decrease the stress of collections	<ul style="list-style-type: none"> <li>The patient avoids being hassled by a collection agency or becoming the target of a lawsuit, especially while disputing a bill</li> </ul>
Provide support for insurance procedures, including grievances	<ul style="list-style-type: none"> <li>Maximize the patient's likelihood of insurance coverage, including prior authorization support</li> <li>Minimize the amount of work the patient has to accomplish to access that coverage</li> <li>Help the patient win ethical grievances (12)</li> </ul>

(or lack thereof), let alone communicate eligibility for charity care. Thus, healthcare remains one of the few purchased services where a person does not know the estimated payment before a service is rendered.

Fortunately, some hopeful examples of better pricing and estimating practices have appeared. For example, the website for Prevention Genetics provides a well-formatted, accurate price list of their tests and test panels (14). The state of New Hampshire provides a price transparency tool that provides patients with estimated test costs at different hospital and commercial labs based on the patient's insurance plan (15).

### Improving Insurance Coverage

A patient-centered lab stewardship program has numerous ways to help patients obtain better coverage for medically necessary testing. For example, laboratory experts, including lab genetic counselors, can guide providers to write medical notes that support the necessity of testing, emphasizing how the test influences medical care. The medical documentation should align with plan-specific coverage criteria.

Another way labs can help patients is to regularly meet with commercial and government payers to provide updates on medical necessity. For example, Seattle Children's, as well as other labs in the PLUGS collaboration, have successfully worked with commercial payers and state Medicaid systems to improve coverage for genetic testing. These interactions with payers build trust, which has the added benefit of increasing the likelihood that your lab will remain in-network for the patient's insurance.

Lab experts also can support appropriate grievances, in which the patient disputes a noncoverage decision. Some insurance plans will allow patients to give the lab permission to appeal on behalf of the patient. When that is not possible, labs still can provide guidance and tools. For example, the PLUGS collaboration has produced a free tool to help patients win ethical grievances for coverage of their laboratory tests (12).

### When Laboratories Put Patients First, It Makes a Difference in Their Care

Clinical laboratories practice patient-centered laboratory stewardship when

they decrease the financial toxicity of testing. Clinical laboratories can pursue a variety of goals to prevent financial toxicity and increase financial fairness. When patients are treated fairly by laboratories, they are more likely to obtain and benefit from medically recommended testing. ■

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**LABORATORY  
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BY JANE DICKERSON, PHD, DABCC,  
 AND JESSIE CONTA, MS, LGC  
 WITH HEATHER AGOSTINELLI

## Is a Benefits Investigation Really Beneficial? An interview with Heather Agostinelli

**T**he U.S. health insurance system is increasingly complex, affecting providers' ability to offer coordinated care and cost transparency. Patient-centered lab stewardship tackles this complexity through targeted efforts to improve access to medically necessary testing, as well as improving coverage for those tests. In an influential New York Times op-ed, Elizabeth Rosenthal, MD, proposed a patient financial bill of rights, noting that "twenty percent of people with insurance say they have trouble paying their medical bills, a figure that rises to above 50% for the uninsured" (1). Even for patients with insurance, and for whom testing is considered a "covered benefit," the actual cost to the patient is not transparent because of copays, coinsurance, and unmet deductibles (2).

As clinical laboratory professionals who prioritize patient care, we believe patients deserve to understand how much a service will cost, whether insurance will cover the cost, and whether they will be financially liable. Tools to support pricing transparency for lab testing align with these stewardship principles. So, how can we find out what a test will cost? We invited Heather Agostinelli, vice president of strategic revenue operations at XIFIN, to share her expertise.

### In your own words, what does a thorough benefits investigation for a laboratory test entail?

A good benefits investigation (BI) entails understanding the cost of the test and the expected reimbursement of that test at that specific point in

time. What type of deductibles are involved? Is there a separate deductible, perhaps for genetic testing? Are there applicable co-pays? What is the co-insurance that will be applied to this test? Those things are all very important to a thorough BI. Most smaller labs are making phone calls to payers for BI and may be on that call for 30 to 60 minutes to do that. In addition, they usually make multiple calls back to see if they get the same story from that payer because there is so much misunderstanding, and often speaking to two different people yields two different answers.

this is the estimate at that exact time, because claims will come in and be processed within hours sometimes and that can affect the estimate. In many instances, it changes it for the better in the sense that more of the deductible has been met, but I've seen where we've had a reverse effect.

### Could you share an example of why this issue is important?

There is a patient that comes to mind—a young mother who had a child born with Down syndrome. She became pregnant again and was interested in testing to see if this

**Even for patients with insurance, and for whom testing is considered a "covered benefit," the actual cost to the patient is not transparent.**

We're very fortunate, because we have an estimator tool that is a big help. However, it is also predicated on the insurance returning all the necessary information. In the instance of an out of network lab, it can be inaccurate if we do not have access to an expected amount for that payer and that test. We do, however, have an analytics program that can determine what that insurance typically allows for that test, helping eliminate the error in BI for out of network labs. This tool is key, as many labs are out of network and do not have expected pricing as there are no contracts in place with payers.

When we provide an estimate back to a patient, we explain that

baby would have Down syndrome. A BI wasn't really in play at that time, so patients just had the test and hoped for the best. She ended up with a large bill, and when I met her, she was seriously upset and confused about her insurance benefits. She told me that she would not have had some of the tests had she known what they were going to cost, and she assumed they were all covered by insurance.

Her story still resonates with me, especially since her testing was covered, but not through the out-of-network laboratory where she had the test. That's why I think BI is so important and is increasingly relevant.

### What are the barriers to answering this clearly for each patient encounter?

Some of the complexity comes from dealing with out-of-network plans. Dealing with specific plans can be difficult because you submit to the state plan, but they forward to the home plan, and they might have discrepant policies. In addition, when calling the plan directly, the discrepancies in information could be the result of inadequate training.

This issue of inaccurate information recently caused a problem with our tool. The insurance carrier provided all the appropriate information to the vendor, who in this case was the intermediary between the payer and XIFIN. The vendor filtered out some of the pertinent information that was returned to XIFIN, thus causing an inaccurate BI. In this instance the coinsurance responsibility was filtered out. This example highlights the importance of validating the accuracy of the information, whether you do it manually, through a phone call, or with an automated tool. When we identify inconsistencies in our investigation, we usually work through the payer relations team to investigate the root cause.

### In a perfect world, what would labs implement to support a patient-centered approach to billing transparency for laboratory testing?

Many labs manage their own BI process, but I do have several large labs where we manage their BI as well as prior authorization. When you are dealing with a patient who has no out-of-network benefits, most laboratories offer a self-pay rate that is less expensive than if they had gone through their insurance. Pursuing a self-pay option must be determined prior to billing insurance. Once insurance is billed from a compliance standpoint, you really can't touch that bill.

In a perfect world, automation is key. Taking out the human element can be beneficial—with a machine at our end hooked up to the machine at the payer's end that knows how much of a deductible this patient has, how much of their deductible was met this year, this

is the coinsurance percent, and this is their copay. We're not necessarily having the conversation with the patient, but at least it's machine to machine, and you're not talking to a person who may understand what is covered by insurance today but a colleague may not the next day.

The ability to do a BI from a system standpoint, and using what we call our estimator tool, is a trend well-received among our stakeholders. In the example I shared with the estimator tool filtering issue, I was pleasantly surprised to find that the insurance provider was very willing to help us figure out what happened. They wanted to make sure that we had received the right information so that we were giving the patient the appropriate information for the BI.

### How do you push the field towards tools that really are as effective as possible, including standards that consumers should expect?

Accessibility and usability are key. You want to make sure that it is for somebody who doesn't live and breathe benefit investigations. I always think of my dad who is brilliant and gets frustrated whenever he must deal with Medicare. The tools should be user-friendly and easy to find. Ultimately, if you have a good tool and it is accessible and easy to get to, it really does

cut down on all those phone calls. Automation is key for error-prone elements, but human interaction to educate the consumer is still necessary. Overall, consumer expectations, including price shopping and user experience, will drive the field to improve. ■

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## Regulatory Roundup

### FDA Clears NYU Langone Test to Guide Solid Cancer Treatment

The Food and Drug Administration has cleared a NYU Langone Health next-generation sequencing test that guides treatment decisions for cancer patients. Cleared under a 510(k) designation, the NYU Langone Genome Profiling of Actionable Cancer Targets (PACT) test detects variations in 607 genes associated with various cancers. At this time, the test is cleared for use only in NYU Langone Health patients.

The PACT test is designed for integration into electronic records. Its development included a collaboration with the healthcare technology company Phillips on genomic processing and interpretation. The collaboration produced an interface between the new test and NYU Langone Health's electronic medical records system.

The PACT assay includes genes with established roles in cancers and with relationships to targets of currently approved cancer drugs. The assay also includes genes related to currently studied compounds or strongly linked to cancers in basic science studies, with an eye toward genetic variants that may be important in diagnosis and treatment of cancer over the next 5 to 10 years.

PACT is designed to be part of ongoing efforts by the NYU Langone research community to find previously unknown changes in genes that further improve diagnoses or yield new pathways to target with drugs.



#### AMAZON COVID-19 KIT GETS EUA

The Amazon COVID-19 Test Collection Kit DTC has received emergency use authorization (EUA) from the Food and Drug Administration. The direct-to-consumer kit enables self-collection of nasal samples, which users send via pre-paid UPS next-day shipping to Amazon's Hebron, Kentucky diagnostics laboratory for polymerase chain reaction testing. Customers will receive test results within 24 hours of their sample's arrival at the lab, and results are available through Amazon's secure website AmazonDx.com.

The collection kit is for use by individuals ages 18 and older and requires registering the collection kit via a U.S. mobile phone with text messaging.

#### FDA GRANTS EUA FOR THERMO FISHER SCIENTIFIC NEXT-GENERATION COVID-19 ASSAYS

The Food and Drug Administration has granted an EUA for the TaqPath COVID-19 Fast PCR Combo Kit 2.0 and the TaqPath COVID-19 RNase P Combo Kit 2.0, both marketed by Thermo Fisher Scientific. The tests are designed with increased target redundancy to compensate for current and emerging SARS-CoV-2 variants. The two tests leverage an updated design from the original TaqPath assays, targeting eight different genes across three regions of the virus that causes COVID-19.

The TaqPath COVID-19 Fast PCR Combo Kit 2.0 assesses raw saliva. Results are returned in about 2 hours to

enable broad, high-frequency testing.

The TaqPath COVID-19 RNase P Combo Kit 2.0 is designed with an approximate 3-hour turnaround time and can detect SARS-CoV-2 from individuals suspected of COVID-19 by their healthcare provider, as well as from patients who are asymptomatic.

#### PILLAR BIOSCIENCES RECEIVES FDA PMA FOR LUNG AND COLON CANCER ASSAY

The Food and Drug Administration (FDA) has granted premarket approval (PMA) for the oncoReveal Dx Lung and Colon Cancer assay, marketed by Pillar Biosciences. The assay is a next-generation sequencing, tissue-based companion diagnostic test for the qualitative detection of somatic

mutations in DNA derived from non-small cell lung cancer (NSCLC) and colorectal cancer (CRC) tumors.

The PMA covers the test as a companion diagnostic for all FDA-approved epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapies for NSCLC targeting exon 19 in frame deletions and exon 21 L858R substitution mutations in EGFR. The PMA also allows use as a companion diagnostic for KRAS wild-type tumor tissue with absence of mutations in codons 12 and 13 for metastatic CRC patients, when targeted treatment with Erbitux (cetuximab) or Vectibix (panitumumab) is warranted.

This panel assay is intended to be used on the Illumina MiSeq Dx instrument.

#### SPEEDX RECEIVES CLEARANCE IN AUSTRALIA FOR COVID-19 DIAGNOSTIC TEST

The SpeedX PlexPCR SARS-CoV-2 test has received clearance from the Australian Therapeutic Goods Administration. The two-gene, single-well test detects all known current circulating variants of SARS-CoV-2. The test offers scalable 96- or 384-well capacity, automated software reporting, and liquid handling robotics in the form of the SpeedX PlexPrep. The combination of PlexPrep robotics and automated software analysis can support a scalable workflow for throughputs of 480 to 1,920 patient samples in an 8-hour shift.

#### ONCOTYPE DX BREAST RECURRENCE SCORE PROGRAM APPROVED IN JAPAN

Japan's Ministry of Health, Labor, and Welfare (MHLW) has approved the Oncotype DX Breast Recurrence Score Program. It helps guide chemotherapy treatment recommendations and provides risk of distant recurrence in patients with hormone receptor-positive, HER2-negative early-stage breast cancer with up to three positive lymph nodes. The approval is a critical step in making Oncotype DX, marketed by Exact Sciences, accessible to breast cancer patients in Japan.

The Oncotype DX Breast Recurrence Score Program approved in Japan combines the Oncotype DX Breast Recurrence Score test and software developed for the Japanese market. Exact Sciences plans to pursue coverage under Japan's universal healthcare insurance system and launch the test through its Japanese affiliate, Exact Sciences K.K.

According to Exact Sciences, Oncotype DX is the only test validated to determine which patients will benefit from chemotherapy and provides critical information beyond traditional prognostic factors. The test is supported by prospective outcomes data that show most patients with either node-negative or node-positive disease can be spared chemotherapy when decisions are guided by Oncotype DX.

#### TWO NEXT-GENERATION HIV-1 TESTS GET CE-IVD CLEARANCE

CE-IVD clearance has been granted to two next-generation extended-coverage (XC) tests for HIV testing marketed by Cepheid. Xpert HIV-1 Viral Load XC is intended to assess viral load levels, which are used to monitor effectiveness of antiretroviral treatment. It provides extended strain coverage to improve performance and address the risk of false negative results due to gene mutations or deletions. Xpert HIV-1 Qual XC has also been cleared for use. The test facilitates dried blood spot sample processing and a simplified workflow. Both tests are designed for use on any of Cepheid's GeneXpert Systems.

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## Qiagen and OncXerna Therapeutics Ink Companion Diagnostic Deal

Qiagen and OncXerna have entered into an agreement to advance development of the Xerna TME panel as a potential next-generation sequencing (NGS) companion diagnostic for OncXerna's experimental drug navicixizumab. OncXerna is developing navicixizumab as a treatment for patients with ovarian cancer. Clinicians can order the test to determine if ovarian cancer patients whose dominant tumor type is driven by angiogenesis are more likely to benefit from treatment with the drug.

The Xerna TME panel uses proprietary RNA-based gene expression data and a machine learning-based algorithm to classify patients—based on the dominant biology of their cancer—so that they can be matched with therapies.

Under a nonexclusive license, which is for research use only and clinical development programs, OncXerna has granted Qiagen the rights to integrate the Xerna TME panel into their NGS workflow solution.

The companies say the deal will advance the Xerna TME panel toward regulatory approval as an NGS companion diagnostic and adoption into medical practice.



### BIOREFERENCE LABS ACQUIRES ARIOSIA LAB PRENATAL BUSINESS FROM ROCHE

**B**ioReference Laboratories announced that it has acquired the U.S. Ariosa centralized laboratory prenatal testing business from Roche. Ariosa's noninvasive prenatal screening (NIPS) test, the Harmony Prenatal Test, is one of the most widely studied tests used in prenatal screening and has been performed in over 1.5 million patients, the company said. GenPath, BioReference's specialty health division, currently

offers ClariTest Core, a NIPS test that uses the same core technology as the Harmony Prenatal Test. The acquisition of Ariosa will complement this current NIPS offering, according to BioReference Labs.

The company added that in 2020, there were about 6 million pregnancies in the U.S., and prenatal screening for Down syndrome had become common practice. Acquiring Ariosa allows BioReference Labs to expand its NIPS offerings and further underscores the company's commitment to prenatal screening, it said.

### PROMEGA AND HENLIUS DEVELOPING MICROSATELLITE INSTABILITY COMPANION DIAGNOSTIC

**P**romega and Henlius Biotech announced they will develop and commercialize a microsatellite instability (MSI) in vitro diagnostic kit to identify cancer patients likely to benefit from serplulimab, a novel anti-PD-1 monoclonal antibody (mAb).

MSI is a form of genomic instability caused by the insertion or deletion of repeating bases called

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microsatellites during DNA replication and the failure of the mismatch repair system (MMR) to correct these errors. MSI status is a measure of MMR deficiency commonly found in solid tumors. Tumors with MSI-high (MSI-H) status have shown higher response rates for immune checkpoint inhibitor therapies such as anti-PD-1 mAb drugs. Serplulimab was developed by Henlius for the potential treatment of MSI-H solid tumors.

For now, the kit will be available to doctors in China for MSI screening and immunotherapy options. China's National Medical Products Administration recently granted priority review to a new drug application for serplulimab. The companion diagnostic method now being developed by the two companies is a multiplex polymerase chain reaction by capillary electrophoresis.

#### ILLUMINA ACQUIRES GRAIL TO SPEED ACCESS TO MULTICANCER EARLY-DETECTION TEST

■ Illumina announced acquisition of Grail, a healthcare company focused on early detection of multiple cancers. Illumina will hold Grail as a separate company during the European Commission's ongoing regulatory

review of the Galleri blood test, which detects many different cancers before they are symptomatic, according to Illumina.

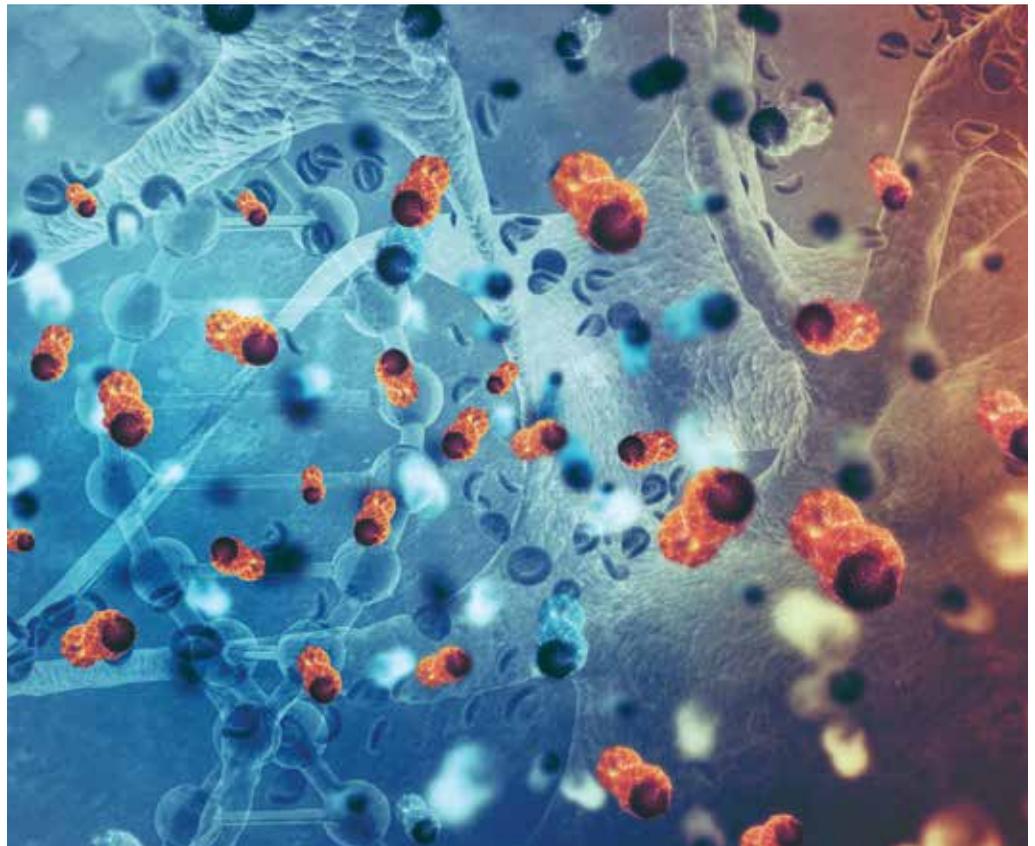
The review was prompted by concerns that Illumina's vertical takeover of its former spinout could harm research and development efforts at competing diagnostic companies, according to Fierce Biotech.

In August, the U.S. Federal Trade Commission said it seeks to undo Illumina's \$7.1 billion acquisition of Grail, alleging it would harm innovation and boost prices, Reuters reported.

Illumina officials say that the decision to make the acquisition and hold the companies separate permits the regulatory processes to proceed while safeguarding the deal without it expiring. The company says the deal will also accelerate the global adoption of next-generation sequencing-based multicancer early detection tests, increase accessibility, and improve patient outcomes. Information from the company says that 71% of all deadly cancers do not currently have a screening test. Grail's Galleri test can detect more than 50 cancers across all stages. In 89% of the positive results, the test correctly identified the tissue of origin, with a specificity of 99.5%.

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## Ask The Expert

# CDC's Progress on CVD Biomarker Standardization



EXPERT

Uliana Danilenko, PhD

**What are the steps of CDC's standardization process?**

**A:** Standardization, as we define it at the Centers for Disease Control and Prevention (CDC), is a process in which the accuracy, precision, and other relevant analytical performance parameters of a laboratory test are assessed, improved, and maintained to meet certain clinical needs.

The CDC Clinical Standardization Program (CSP) for Cardiovascular Disease Biomarkers (CDC CVD Program) is doing that with three main components. First, the CDC Lipids Reference Laboratory (LRL) operates internationally recognized reference measurement procedures for total cholesterol, total glycerides, and HDL- and LDL-cholesterol that are traceable to SI in accordance with ISO 17511. Second, the certification program uses the serum materials characterized by LRL to maintain metrological traceability of the members of the Cholesterol Reference Method Laboratory Network (CRMLN). The CRMLN members work with assay manufacturers to establish and verify metrological traceability. Finally, CDC's Lipids Standardization Program (LSP) monitors the analytical performance assays in clinical laboratories to ensure the accuracy achieved at the manufacturer level reaches patient care.

The LSP is different from external quality assurance (EQA) programs, as it collects weekly data from individual laboratories. In one example, this detailed data enabled CSP to detect a small shift in calibration with an assay manufacturer. CDC identified the source of the shift, and the manufacturer was able to correct the calibration before it affected patient care.

**How are CVD programs evolving?**

Clinical practice continues to change, and the CDC CVD program is continuing to adjust its program to meet the clinical laboratory community's needs. Most notably, treatment targets for LDL-cholesterol are now much lower. However, analytical performance criteria for blood lipid measurements did not change accordingly. CDC does not define analytical performance criteria. It considers and adopts, where feasible, recommendations made by relevant stakeholders. For lipids, the last recommendations were developed more than 20 years ago. CDC is supporting stakeholders and experts who are revising current performance criteria to help support new practice guidelines.

With new data now available about limitations of LDL-C and HDL-C measurements, CDC introduced new requirements in its program, such as providing measurement data on

samples from patients with certain diseases and conditions. Furthermore, CDC is changing its protocols to better assess analytical performance at lower lipids levels. Data from CDC's CVD certification program show that establishing metrological traceability through appropriate calibration notably improves calibration bias. However, the bias observed in individual samples can still be high. This situation can only be addressed efficiently using individual donor specimens in the evaluation and certification process. The CDC CVD program is including bias of individual samples in its certification process.

The CDC CVD program is also addressing the need for traditional reference materials by collaborating and supporting the work conducted at the national and international Institute of Standards and Technology, France's Laboratoire National de Métrologie et D'essais, and other metrology institutes.

**What are the new CVD biomarkers that need standardization?**

Measurements of traditional blood lipids do not fully capture CVD risk in all patients, and lipoproteins can provide more detailed information about a person's risk for CVD. CDC CVD is responding to this need by including Lp(a), ApoB, and ApoA1 in its programs in close collaboration with the IFCC working group for Apolipoproteins by Mass Spectrometry.

*The author thanks Hubert W. Vesper, PhD, director of the CDC Clinical Standardization Programs, for his contribution to the article. CDC CSP thanks the CRMLN Laboratories for their support with manufacturers standardization. The findings and conclusions in this article have not been formally disseminated by CDC and should not be construed to represent any agency determination or policy. Use of trade names and commercial sources is for identification only and does not constitute endorsement by the U.S. Department of Health and Human Services or CDC.*

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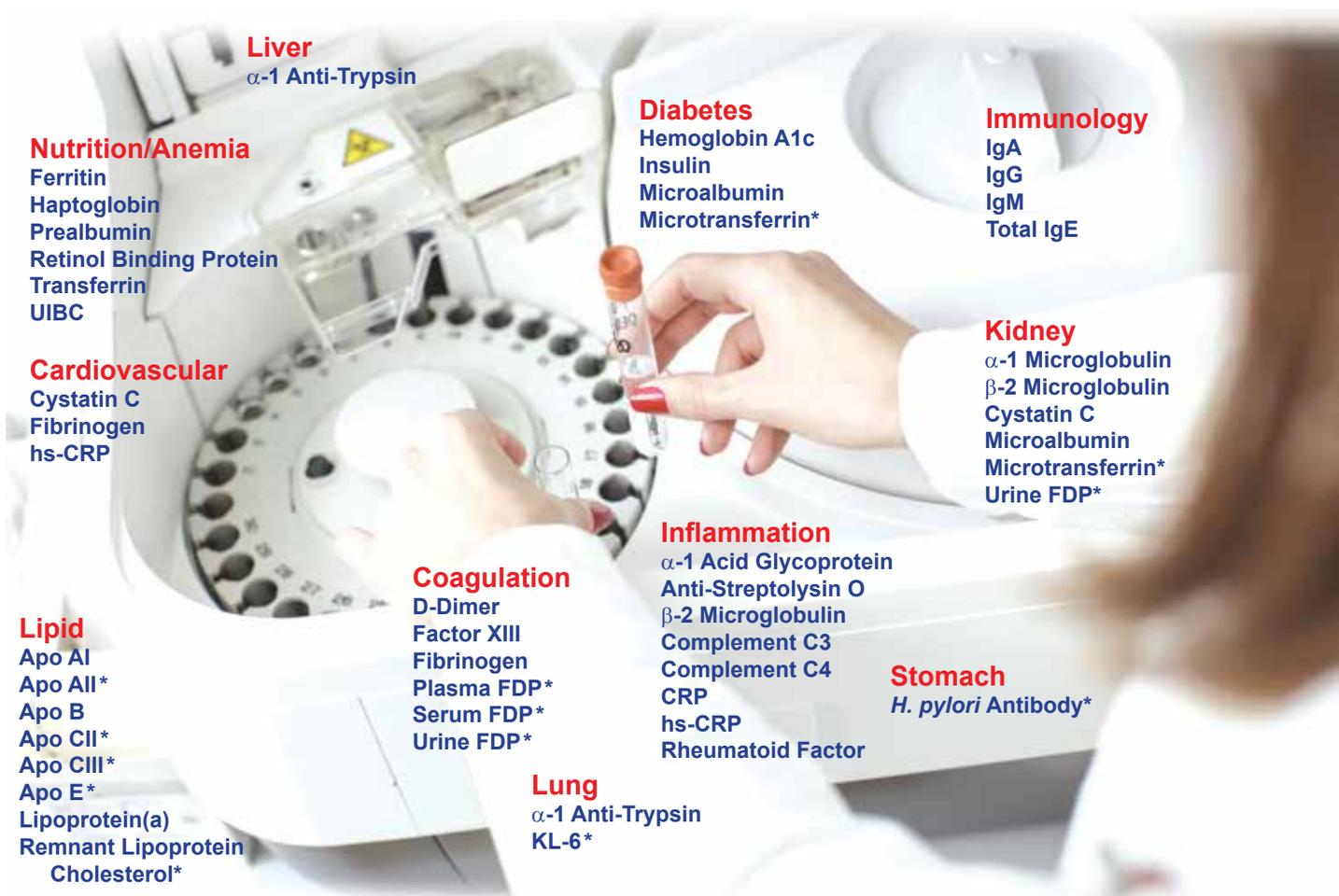
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