September/October 2024

CLN Clinical Laboratory News

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MACHINE LEARNING FOR HEMOGLOBINOPATHY DIAGNOSIS

88%

Discriminative performance of new eXtreme Gradient Boosting model

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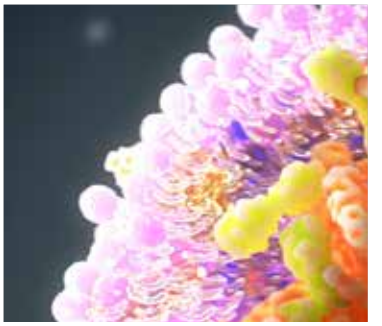
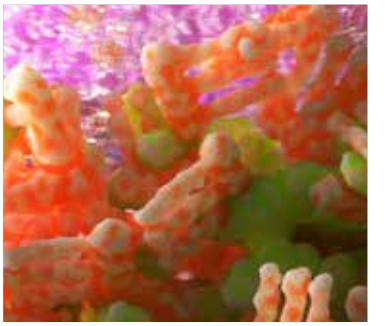
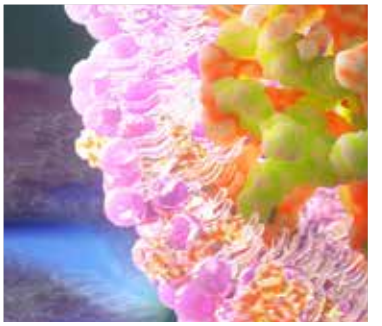
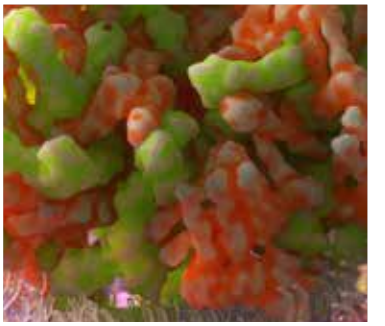
Reimagining lipid testing









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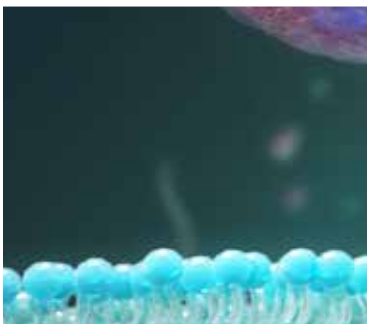

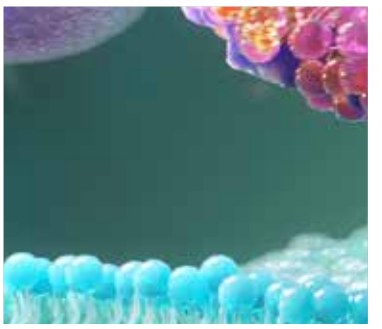

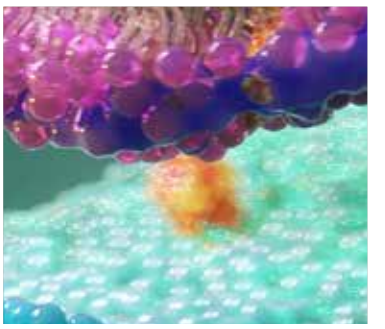

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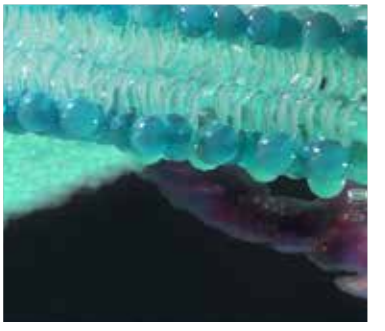

ADLM Association for Diagnostics & Laboratory Medicine™ Formerly AACC

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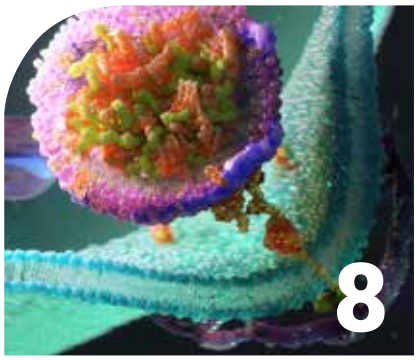

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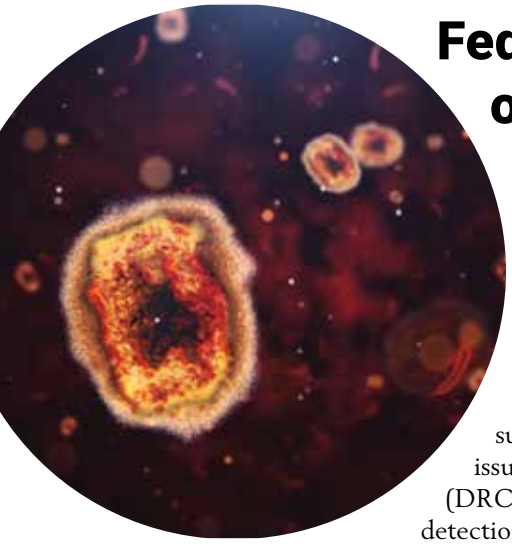

Federal government targets clade I mpox outbreak in Africa

The Africa Centres for Disease Control and Prevention (Africa CDC) has declared the outbreak of clade I mpox as a Public Health Emergency of Continental Security. The World Health Organization (WHO) similarly classified it as a Public Health Emergency of International Concern. According to the Department of Health and Human Services, the U.S. government has pledged continued collaboration with African governments, Africa CDC, and WHO to mount a response.

The risk of clade I mpox spreading to the U.S. remains very low, with no known domestic cases, according to the Centers for Disease Control and Prevention (CDC). The U.S. has a strong surveillance system in place and encourages vaccination for individuals at high risk. The CDC has issued updated guidance for clinicians and travelers to the Democratic Republic of the Congo (DRC) and surrounding regions. According to the WHO, the preferred laboratory test for mpox is detection of viral DNA by PCR.

In 2022, the clade II mpox outbreak led to more than 95,000 cases across 115 non-endemic countries. Clade I mpox is more severe, with a higher mortality rate. Data from endemic countries like the Democratic Republic of the Congo (DRC) suggest that while clade I mpox may cause significant health impacts in the region, it is likely to result in lower morbidity and mortality in the United States compared to the DRC.

The DRC is currently facing its highest annual number of suspected mpox cases ever recorded, with the disease spreading to neighboring countries that previously had no reported cases, according to the WHO.

In addition to diagnostics, vaccination is a key element in controlling the outbreak. The U.S. is donating 50,000 doses of the Food and Drug Administration-approved JYNNEOS vaccine to the DRC and is collaborating with international partners to bolster vaccination efforts.

CONGRESS RESPONDS TO ADLM ADVOCACY ON PEDIATRICS, LABORATORY DEVELOPED TESTS

The Association for Diagnostics and Laboratory Medicine (ADLM, formerly AACC) has made progress over the last few months in its campaign to improve pediatric reference intervals (PRIs) and oppose the Food and Drug Administration (FDA) final rule on laboratory developed tests (LDTs).

In a significant advocacy effort on PRIs, ADLM led a coalition of 42 professional societies, clinical laboratories, and manufacturers to push for federal funding dedicated to this cause at the Centers for Disease Control and Prevention (CDC). The effort targeted key congressional offices, emphasizing the urgent need for more accurate diagnostic standards for children. On July 10, persistence paid off. The House Appropriations Committee approved the Fiscal Year 2025 Labor, Health and Human Services, Education, and Related Agencies Appropriations Act. The committee's report language explicitly supported the CDC's work to improve PRIs. The congressional committee's report language also referenced a 2022 CDC study that revealed significant discrepancies between current PRIs and actual child development, underscoring the need for this research.

This work gained further momentum on August 1 when the Senate passed the Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriation Bill for 2025. The Senate report mirrored the House's support for enhancing pediatric reference intervals. The Senate report also went a step further by instructing the CDC to include cost estimates for these improvements in the agency's next budget request.

On the LDT front, the House also advanced on July 10 the Fiscal Year 2025 Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act. The accompanying report urged the FDA to halt its final rule on LDTs, which ADLM argues will lead to restricting patient access to critical testing.

While reports from Congress are non-binding, Congress uses them to provide detailed guidance and accountability for federal agencies.

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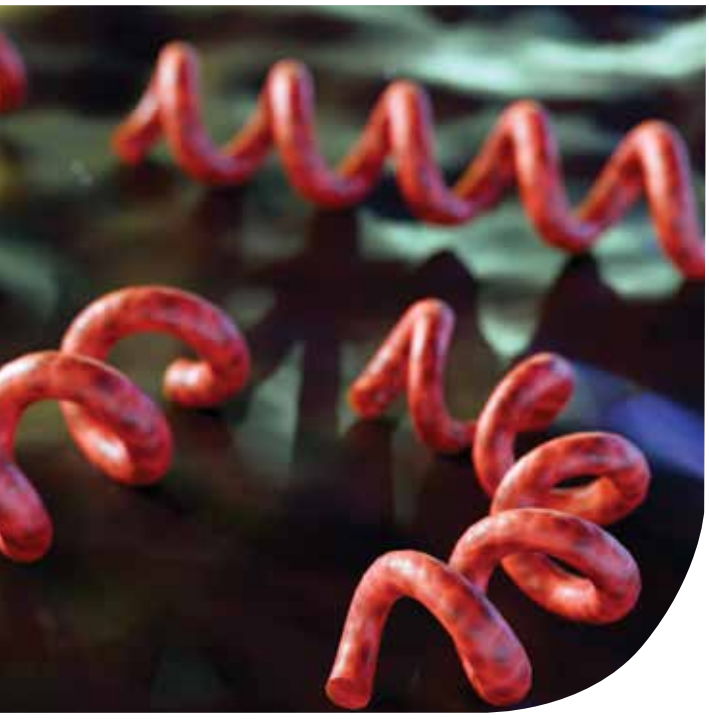
CDC updates on syphilis testing for the clinical laboratory

Sarah Wheeler, PhD FADLM, CC(NRCC)

The recent release of the 2022 Sexually Transmitted Infection (STI) Surveillance Report by the Centers for Disease Control (CDC) has confirmed the continuing increase in reported syphilis cases, which have reached numbers not seen since 1950. These statistics correlate with the ongoing opioid epidemic and the CDC calls the two "intersecting epidemics." The data also confirm that syphilis continues to disproportionately affect minoritized racial and ethnic populations.

The rise in syphilis among women of childbearing age is particularly alarming, with congenital syphilis rates increasing by 937.3% since 2013. The clinical laboratory has a significant opportunity to help reduce the spread of syphilis by providing timely, accurate, and appropriate screening and treatment monitoring.

With the increase in syphilis and the recognized importance of clinical laboratory testing, the CDC in February 2024 released the first ever recommendations for syphilis testing in the clinical laboratory (MMWR Recomm Rep 2024; doi: 10.15585/mmwr.rr7301a1). This extensive document provides a review of current research on syphilis biology and clinical laboratory tests, as well as specific recommendations for clinical laboratories. Here we'll review a few highlights in updates of the science and terminology, as well as the recommendations from the CDC for performing testing.



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USING THE RIGHT TESTS FOR SYPHILIS

Syphilis diagnosis relies on two types of serologic tests that detect the host's antibody response to the infection. The first type, known as treponemal tests, identifies antibodies (usually IgM and IgG) specific to proteins found on Treponema pallidum. These antibodies typically remain detectable for life, even after successful treatment.

The second type, non-treponemal tests, has been thought to detect antibodies generated in response to tissue damage caused by infection. More recent work, highlighted in the CDC guidelines, indicates that the lipoidal antigens used in non-treponemal tests (cardiolipin, cholesterol, phosphatidylcholine) are found in the membranes of T. pallidum and hosts alike. These tests therefore are more properly termed "lipoidal antigen" tests.

Unlike treponemal antibodies, non-treponemal (lipoidal antigen) antibodies generally decline after treatment, making these tests useful for monitoring treatment effectiveness and distinguishing between new, active infections and those that have been previously treated. Non-treponemal tests include the rapid plasma regain (RPR) and Venereal Disease Research Laboratory (VDRL) tests. Positive tests are titrated to provide a semi-quantitative titer result.

Importantly, these lipoidal antigens are also found in host cell membranes. As a result, reactive tests may not be associated with syphilis, resulting in biological false positive tests. Biological false positives can account for as much as 11% of positives tests in some populations, thus a positive non-treponemal test alone is insufficient to diagnose syphilis.

FOLLOWING THE CDC-RECOMMENDED ALGORITHM

With these two types of tests available, CDC recommends that laboratories perform screening through algorithmic testing (Figure 1). The original CDC-recommended screening algorithm is the forward or traditional algorithm, which starts with a non-treponemal test and, when positive, is assessed by treponemal testing to ensure the reactive test is specific for syphilis.

As treponemal testing became more automated, the reverse algorithm was introduced. In this algorithm, a reactive treponemal test is followed by a non-treponemal test to determine whether the infection is active. If the non-treponemal test

is negative, the laboratory performs a second treponemal test to ensure that the first treponemal test was not falsely positive. Each algorithm has limitations; however, the reverse algorithm may be more likely to catch early and late syphilis infections.

KEY CDC RECOMMENDATIONS

The laboratory recommendations for syphilis testing from the CDC that pertain to serologic testing are listed below in italics.

Recommendation for endpoint titers. This is a reporting recommendation that all non-treponemal (lipoidal antigen) titers be reported down to a 1:1 titer and up to an end point titer (i.e. – no ">" or "<" in result reporting). For laboratories using automated RPR testing that may not report down to a 1:1 titer, these specimens are recommended to be reflexed to a manual RPR method. Many laboratories do not currently perform endpoint titers, but rather dilute to a specific titer and report as ">".

Recommendation for syphilis serologic testing algorithm. Full forward or reverse syphilis serologic algorithms should be used for diagnosis (Figure 1). This recommendation highlights the need for clinical laboratories to incorporate reflex testing algorithms that facilitate compliance with either a forward or reverse algorithm without requiring the ordering provider to select the subsequent test. This approach also reduces the need for patients to return to their healthcare provider or a blood draw site for a final diagnosis.

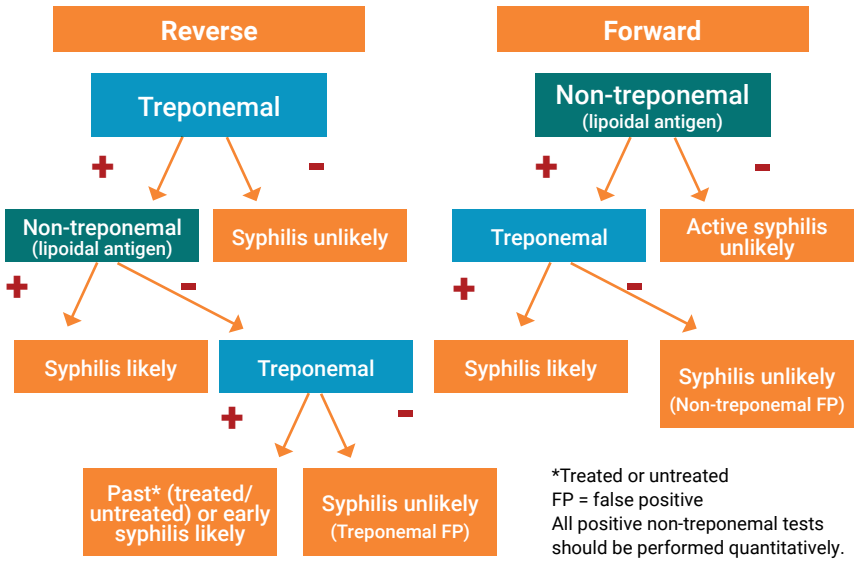
Recommendation for serologic syphilis testing. The same non-treponemal (lipoidal antigen) test should be used when monitoring patients for treatment response or reinfection; RPR and VDRL titers are not interchangeable. The second treponemal test in the reverse algorithm — and the treponemal test in the forward algorithm — is often a manual test with high specificity, and the Treponema pallidum particle agglutination (TPPA) test is the preferred manual treponemal test based on performance characteristics compared to other manual treponemal tests.

It is notable that there is little published data on the performance of automated treponemal tests stratified by syphilis stage. Available literature seems to indicate comparable performance overall with TPPA; however, additional data are needed.

Recommendation for syphilis serologic testing in pregnant persons and recommendation for syphilis serologic testing in persons living with HIV/AIDS. Historically there has been a lack of clarity on the best testing and interpretation in these populations. Current evidence indicates that these populations should receive the same testing and interpretation regardless of pregnancy or HIV status.

The CDC Laboratory Recommendations for Syphilis Testing is a comprehensive document with additional information on test choice, test performance, recommendations for sample processing, result reporting, and current research. Amid this ongoing epidemic, the CDC emphasizes that laboratories are critical in the public health response. Implementing the CDC recommendations is an important first step for clinical laboratories in reducing the public health burden.

Figure 1: Syphilis testing algorithms



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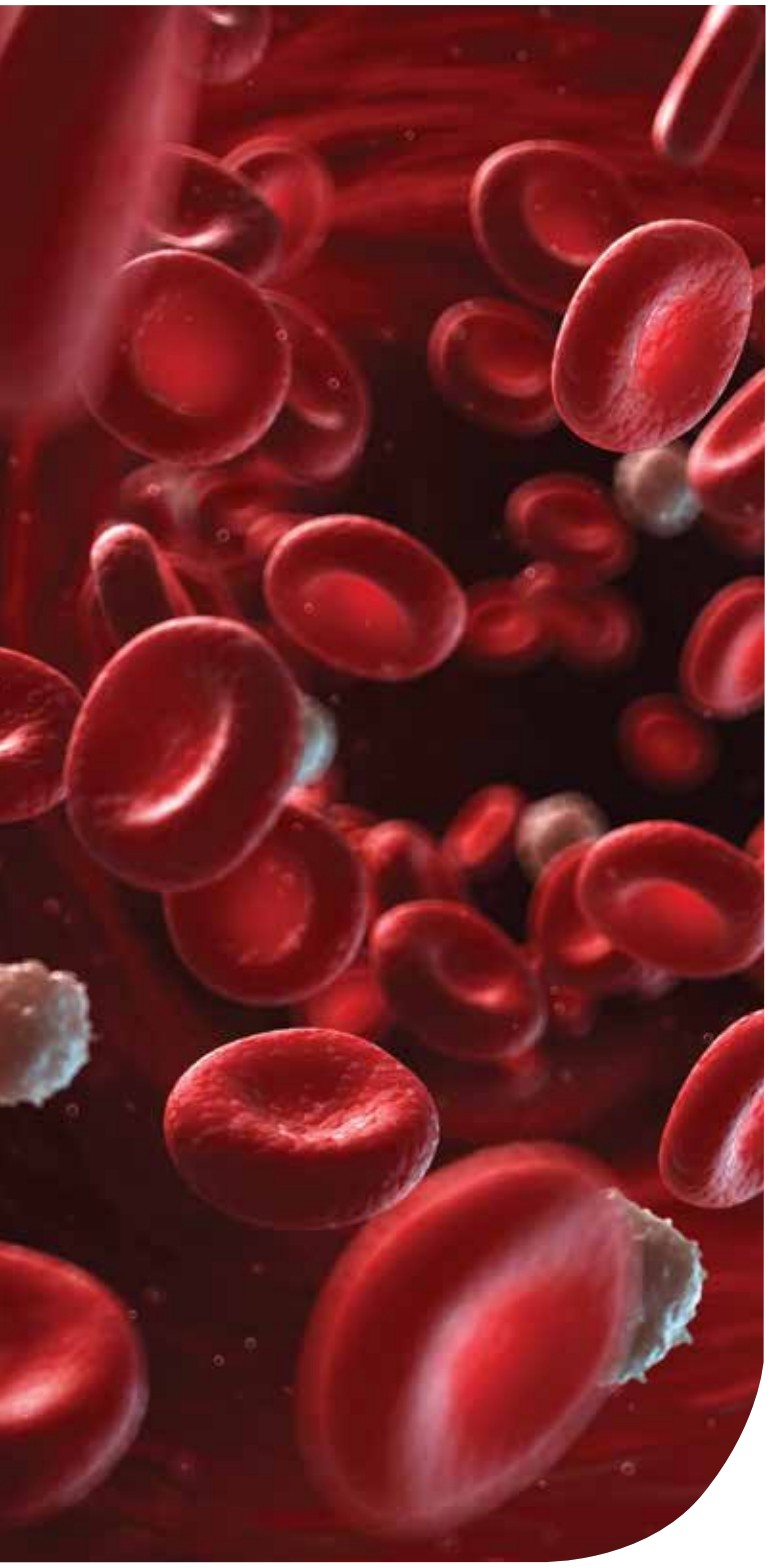

Machine learning models aid hemoglobinopathy diagnosis

Both eXtreme Gradient Boosting (XGB) and logistic regression models can make highly accurate predictions about a broad range of hemoglobinopathies and differentiate them from iron deficiency anemia (IDA), according to recent research. (Clin Chem 2024; doi: 10.1093/clinchem/hvae081)

Hemoglobinopathies affect 5.2% of people worldwide and account for 3.4% of deaths of children younger than 5, but they often remain undiagnosed. Meanwhile, migration drives rising prevalence in areas where malaria is not endemic. Early identification of carriers of genetic variations leading to hemoglobinopathies is important for counseling at-risk couples.

Laboratories use specific changes in complete blood count (CBC) parameters to recommend diagnostic testing for hemoglobinopathy, including reduced hemoglobin and mean corpuscular volume. CBC changes caused by hemoglobinopathies can mimic those caused by IDA. Misdiagnosis may result in unnecessary iron supplementation.

To improve this situation, the researchers developed and validated a new machine learning model intended to differentiate between various hemoglobinopathies and IDA. The model covered a wide spectrum of hemoglobinopathies and was based on CBC testing.

The researchers retrospectively extracted hemoglobinopathy test results from 10,322 adults at eight laboratories in the Netherlands. The researchers developed XGB and logistic regression models to differentiate negative from positive cases using seven routine CBC parameters. The researchers performed external validation on a dataset from an independent laboratory in the Netherlands. To specifically differentiate thalassemia from IDA, the researchers performed additional external validation on a previously published Spanish data set including 2,629 test results, mainly from cases with microcytic anemia.

In distinguishing negative from positive hemoglobinopathy cases in the independent external validation set, the XGB and logistic regression models achieved areas under the receiver operating curve (AOCs) of 0.88 and 0.84, respectively. Subclass analysis showed that the XGB model reached an AOC of 0.97 for ß-thalassemia, 0.98 for α^0-thalassemia, 0.95 for homozygous α^+-thalassemia, 0.78 for heterozygous homozygous α^+- thalassemia, and 0.94 for the structural hemoglobin variants hemoglobin C, hemoglobin D and hemoglobin E. Both models attained ROCs of 0.97 in differentiating IDA from thalassemia.

These results showcase the machine learning algorithms' wide-ranging applicability in medical diagnostics, the researchers wrote.

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BLOOD TEST FOR ALZHEIMER'S DISEASE SHOWS PROMISE

A new blood test showed high diagnostic accuracy for Alzheimer's disease among individuals with cognitive symptoms in primary and secondary care.

Using predefined cutoff values, a new blood test showed high diagnostic accuracy for Alzheimer's disease (AD) among individuals with cognitive symptoms in primary and secondary care, according to a recent study (JAMA 2024; doi:10.1001/jama.2024.13855).

The assay is based on the ratio of plasma phosphorylated tau 217 (p-tau217) relative to non–p-tau217 (expressed as percentage of p-tau217), combined with the amyloid-β 42 and amyloid-β 40 plasma ratio (the amyloid probability score 2 [APS2]).

The researchers prospectively evaluated the assay in 1,213 primary and secondary care patients undergoing cognitive evaluation. The biomarker cutoff values had been established in an independent cohort and were applied to 307 primary care patients and 300 secondary care patients. Patients' mean age was 74.2, 48% were women, 23% had subjective cognitive decline, 44% had mild cognitive impairment, and 33% had dementia. In both the primary care and secondary care assessments, 50% of patients had AD pathology.

After analysis of a single batch of plasma samples in the primary care cohort using APS2, the AUC was 0.97 (95% CI, 0.95–0.99), the positive predictive value (PPV) was 91% (95% CI, 87%–96%), and the negative predictive value (NPV) was 92% (95% CI, 87%–96%). In the secondary care cohort, the AUC for APS2 was 0.96 (95% CI, 0.94–0.98), the PPV was 88% (95% CI, 83%–93%), and the NPV was 87% (95% CI, 82%–93%).

When the plasma samples were analyzed prospectively (biweekly) in the primary care cohort, the AUC was 0.96 (95% CI, 0.94–0.98) for APS2. APS2's PPV was 88% (95% CI, 81%–94%), and it NPV was 90% (95% CI, 84%–96%). In the secondary care cohort, the AUC for APS2 was 0.97 (95% CI, 0.95–0.98), the PPV was 91% (95% CI, 87%–95%), and the NPV was 91% (95% CI, 87%–95%).

Primary care physicians had a diagnostic accuracy of 61% (95% CI, 53%–69%) for identifying clinical AD after clinical examination, cognitive testing, and a computed tomographic scan, versus 91% (95% CI, 86%–96%) using APS2. Dementia specialists using usual methods had a diagnostic accuracy of 73% (95% CI, 68%–79%), versus 91% (95% CI, 88%–95%) using the APS2. In the overall population, physicians' diagnostic accuracy when using the APS2 (90% [95% CI, 88%–92%]) was similar to the diagnostic accuracy using the percentage of p-tau217 alone (90% [95% CI, 88%–91%]).

Although the blood test provided superior performance compared with standard clinical evaluation, studies should evaluate how the use of blood tests for these biomarkers influences clinical care, the researchers wrote.

FIFTY NEW GENETIC LINKS TO KIDNEY CANCER IDENTIFIED

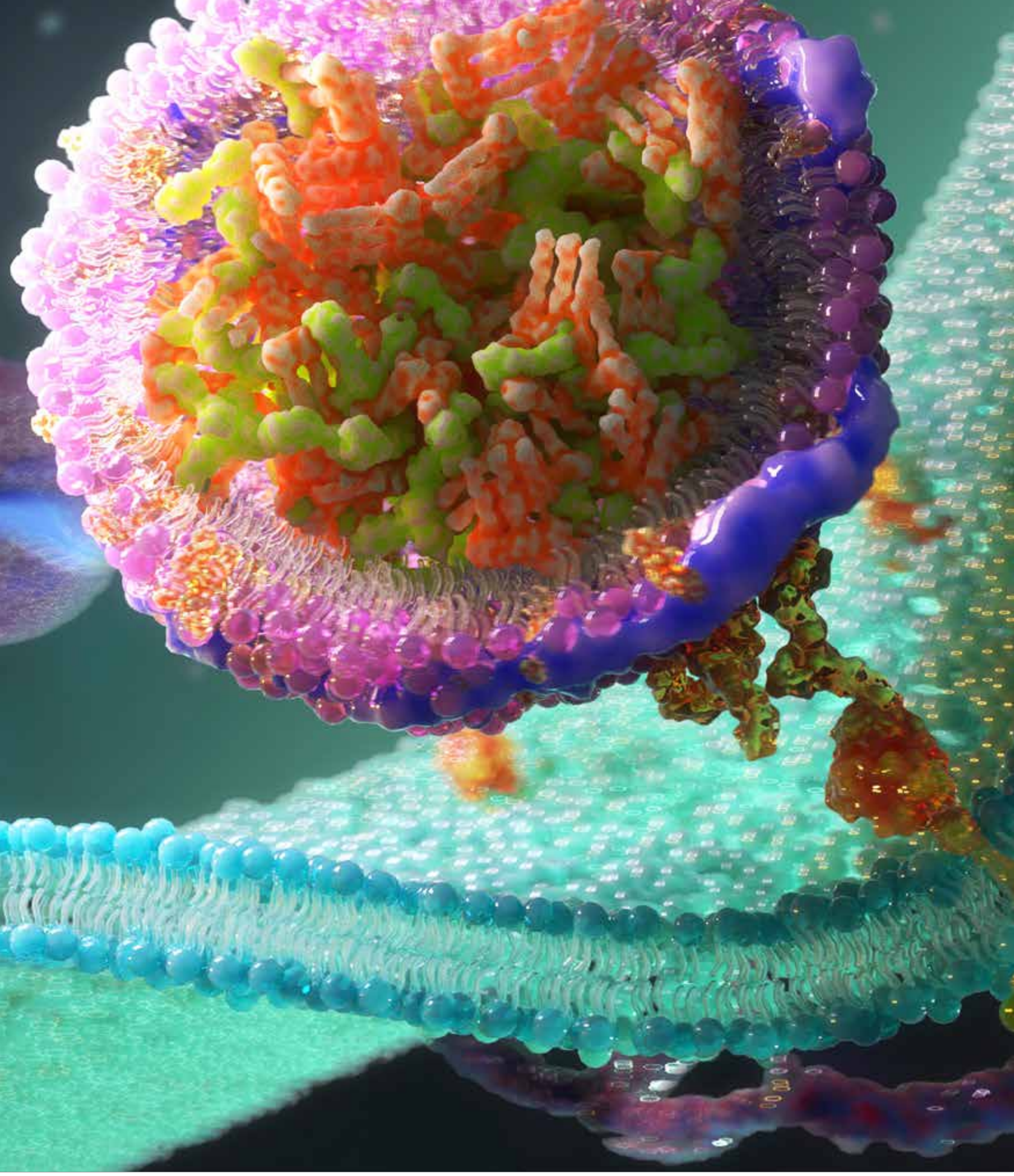
A recent genome-wide association study (GWAS) analysis identified 50 new areas across the genome associated with kidney cancer risk (Nat Genet 2024; doi.org/10.1038/s41588-024-01725-7).

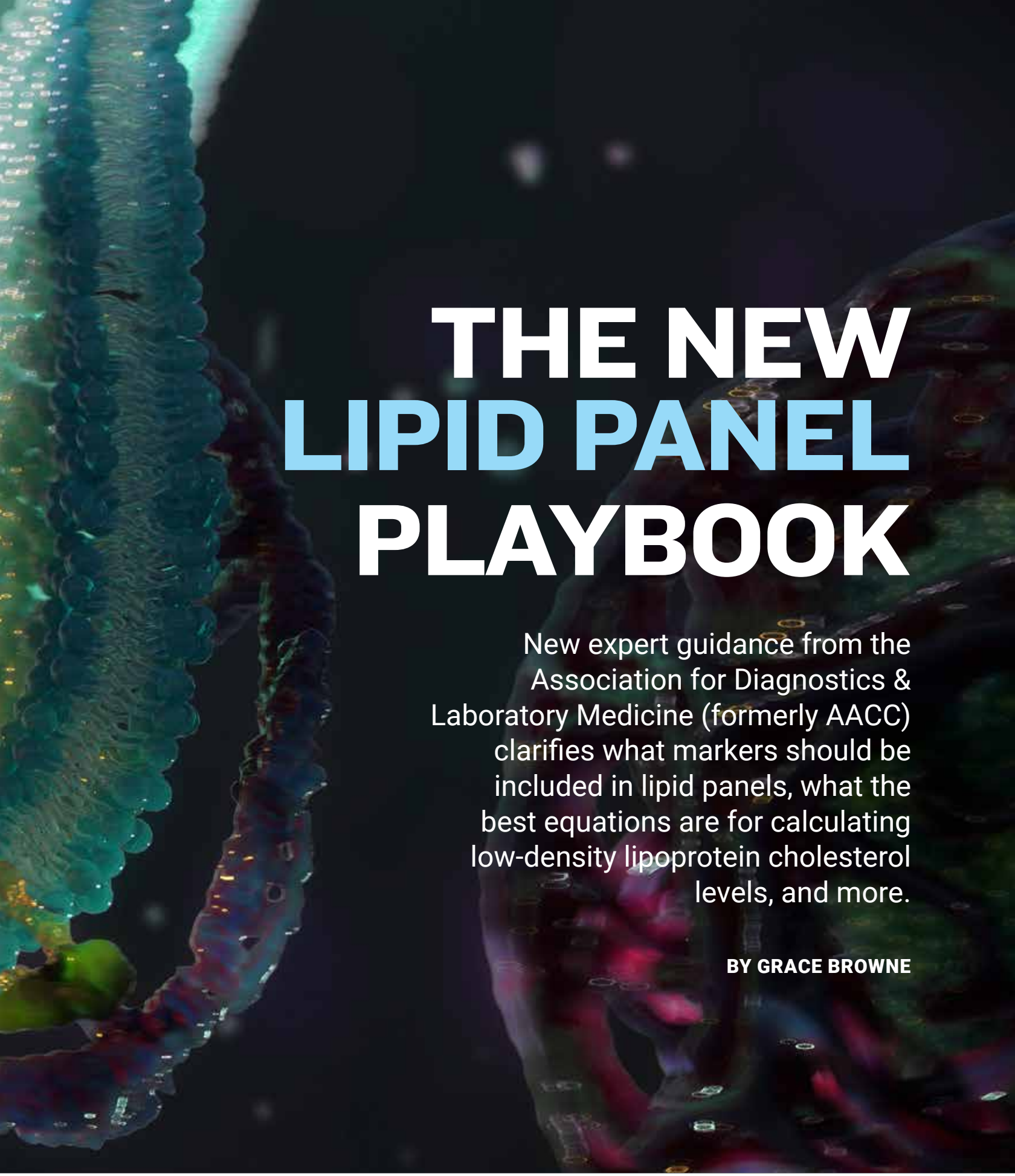
A previous GWAS of people of European ancestry identified 13 regions of the genome associated with kidney cancer risk. In contrast, the current study involved participants of many different genetic ancestries, including 29,020 people with kidney cancer and 835,670 people without kidney cancer. Including the newly discovered regions, 63 are now associated with the risk of developing kidney cancer.

Among the newly identified genetic variants were several associated with a risk of papillary renal cell carcinoma, the second most common subtype of renal cell carcinoma. Another variant in the VHL gene was common in individuals of African ancestry and associated with an estimated three times higher risk of developing clear cell renal cell carcinoma, the most common type of kidney cancer.

The researchers used the study data to develop a polygenic kidney cancer risk score. Combined with established risk factors such as high blood pressure, smoking, and high body-mass index, the score may enable earlier detection.

The researchers add that their data may eventually aid understanding of the molecular basis of kidney cancer, inform screening efforts, and identify new drug targets.





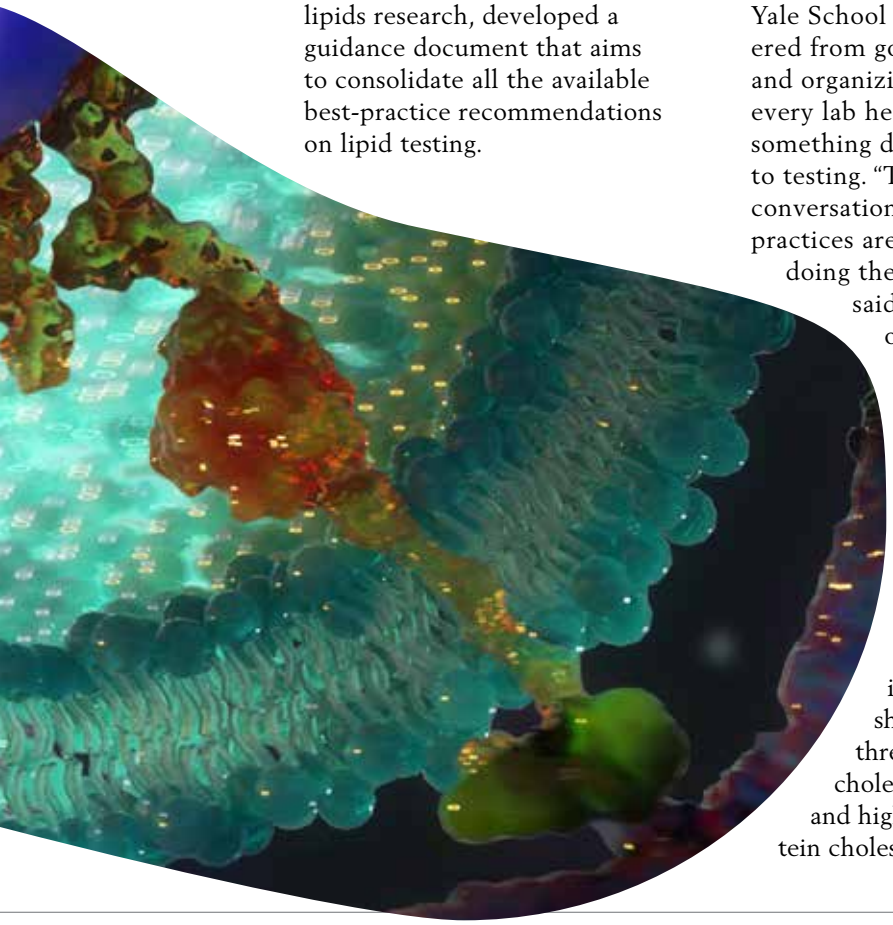
THE NEW LIPID PANEL PLAYBOOK

New expert guidance from the Association for Diagnostics & Laboratory Medicine (formerly AACC) clarifies what markers should be included in lipid panels, what the best equations are for calculating low-density lipoprotein cholesterol levels, and more.

BY GRACE BROWNE

It is crucial to catch atherosclerotic cardiovascular disease (ASCVD) early, as it can lead to severe complications and death and is a leading cause of morbidity and mortality worldwide. The standard approach to identifying individuals at high risk for developing ASCVD who may benefit from therapy is to measure their blood lipids and lipoproteins using a lipid panel.

However, the test has suffered from a lack of standardization, which consequently leads to variability in the way results are reported. And advances in lipid testing in recent years have led to some standard practices becoming dated. To address this heterogeneity, a group of experts from the Association for Diagnostics & Laboratory Medicine (ADLM, formerly AACC), along with a physician who specializes in lipids research, developed a guidance document that aims to consolidate all the available best-practice recommendations on lipid testing.



"There are piecemeal recommendations in different documents, textbooks, or even clinical guidelines that touch on laboratory testing for lipids," said Leslie Donato, PhD, DABCC, the co-lead author of the guidance document and assistant professor in the department of laboratory medicine and pathology at Mayo Clinic in Rochester, Minnesota. "But there's no overarching one-stop-shop for how we test and report lipids." The guidance document is her and her co-authors' attempt to meet that need — and to bridge the gap between the physicians interpreting the test results and the laboratory professionals who run the testing.

Joe El-Khoury, PhD, DABCC, FADLM, a co-author of the guidance and associate professor of laboratory medicine at Yale School of Medicine, discovered from going to conferences and organizing roundtables that every lab he talked to was doing something different when it came to testing. "There needed to be a conversation about what the best practices are instead of everybody doing their own thing," he said, "and getting a group of experts together to address this issue was, I felt, the priority for this field."

"THERE NEEDED TO BE A CONVERSATION ABOUT WHAT THE BEST PRACTICES ARE INSTEAD OF EVERYBODY DOING THEIR OWN THING."
— JOE EL-KHOURY

WHAT A LIPID PANEL SHOULD MEASURE

One of the major recommendations in the new guidance is that a lipid panel should always have three measures: total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C). Two other biomarkers are often included: low-density lipoprotein cholesterol (LDL-C) and non-HDL-C. However, "many labs still do not report non-HDL-C," El-Khoury said.

Beyond the classic lipid panel, the new guidance recommends testing for other biomarkers such as lipoprotein(a), also called Lp(a). The guidelines recommend testing Lp(a) in patients who have premature atherosclerosis, patients who have a family history of premature atherosclerosis as well as elevated Lp(a), with very high LDL-C levels or familial hypercholesterolemia, and finally in individuals at very high risk of ASCVD. Canadian and European guidelines recommend population-wide screening for Lp(a), meaning that Lp(a) should be checked at least once

Left and previous page: NANOCLUSTERING / SCIENCE PHOTO LIBRARY / Getty Images

in everybody as Lp(a) concentrations are genetically determined. Lp(a) has historically flown under the radar, Donato said, but ongoing clinical trials for new medication for high expressors of Lp(a) mean that testing for the marker is going to "expand dramatically," she said.

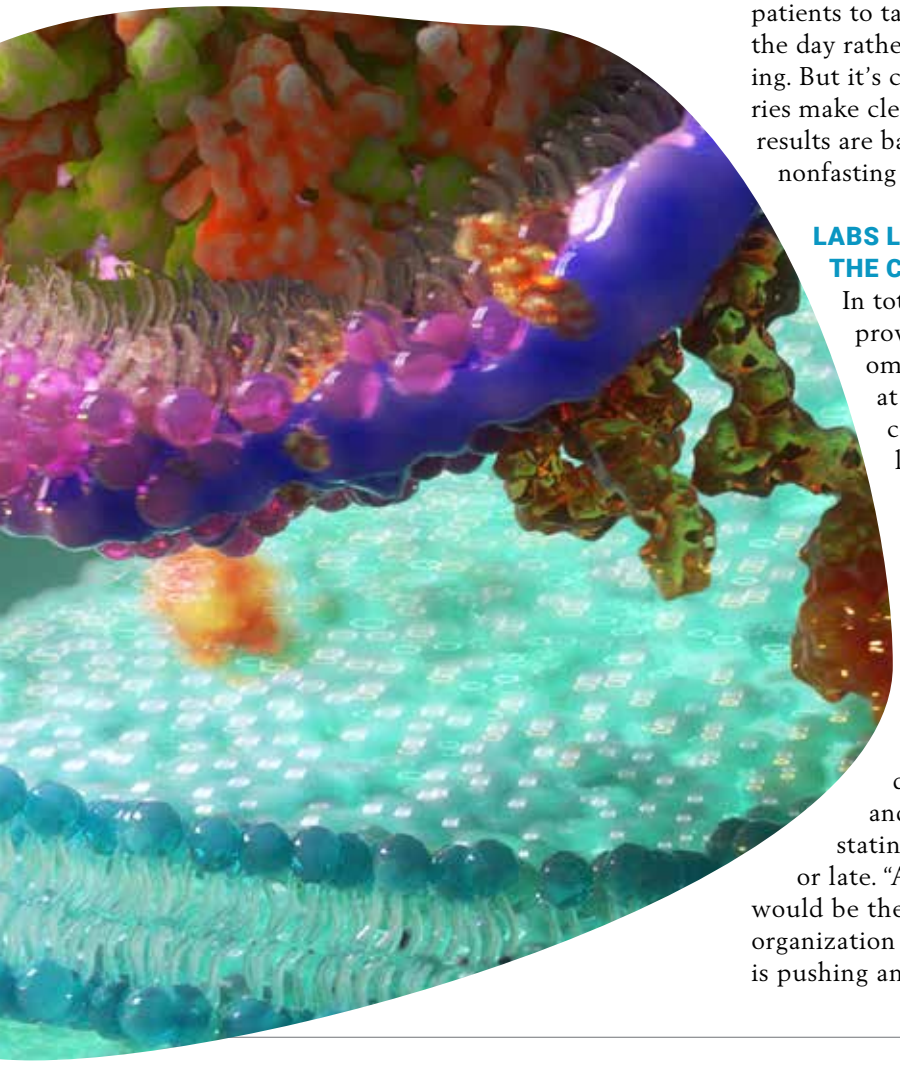
The guideline also makes the recommendation to test for the lipoprotein apolipoprotein B (apoB), which is a structural protein of low-density lipoproteins. A growing body of research has found that apoB can be a better and more reliable assessment of atherosclerosis risk than testing simply for LDL-C, particularly when apoB and LDL-C levels disagree.

EQUATIONS AND TEST PREPARATION

The ADLM guidance also focused on how LDL-C levels are calculated. The most common way of calculating LDL-C for decades has been the Friedewald equation, which states: LDL-C = [Total Cholesterol] – [HDL-C] – [Triglycerides/5]. "People have used it for a long time, and no one has thought this needed any changing," El-Khoury said. However, the equation has certain limitations, such as lowered accuracy with very low LDL-C levels as well as with high triglyceride levels. It also requires a fasting sample. "It's an imperfect calculation," Donato said. "And there are just better methods."
In its place, the guideline recommends two alternative equations: one called the Martin equation, and the other one called the Sampson equation, both of which are more modern and accurate.

Another new change that the authors recommend has to do with the way that patients prepare for the test. Traditionally, patients have had to fast before a lipid panel

"IT'S AN INGRAINED DOGMA THAT EVERYONE THINKS YOU HAVE TO BE FASTING TO HAVE A LIPID PANEL DRAWN."
— LESLIE DONATO



because measuring lipids on fasting samples was considered the most surefire way of getting an accurate reading. "It's an ingrained dogma that everyone thinks you have to be fasting to have a lipid panel drawn," Donato said. However, more recent research has shown that "you don't really need to do that for everybody," El-Khoury said, and that the alterations to triglycerides due to breaking the fast turn out to be negligible for most. And eliminating the need for patients to fast would offer various advantages. Fasting is inconvenient for older patients and patients who are dependent on medication already, and eliminating it would enable patients to take tests throughout the day rather than in the morning. But it's crucial that laboratories make clear in reports whether results are based on a fasting or a nonfasting example.

LABS LEADING THE CHARGE

In total, the guidance provides nineteen recommendations aimed at both the clinical community and the laboratory professional community when it comes to lipid testing.

The biggest issue at stake with different labs using different approaches, El-Khoury said, is the risk of misdiagnosing patients, and starting them on statin therapy too early or late. "As far as I know, this would be the first laboratory-organization based guideline that is pushing and emphasizing the need for labs to lead this change, and implement these things that are well under their control," El-Khoury said.

"What we tried to do in the document is really tie it to clinical guidelines and clinical practice, so that it's easy to understand why what we're doing in the laboratory can then be translated to the clinical setting," Donato said. Clinical guidelines are really geared toward physicians and how to interpret results — but they really don't specify how the physician gets those results.

El-Khoury acknowledged that some laboratories may not have the resources to implement all the changes recommended in the guideline. But he emphasized that lab professionals cannot make these changes alone: "We cannot work in a silo and start making changes to these things without working with our clinical colleagues," he said. The transition will also take some education, Donato said. "We just have to figure out how to implement these changes and make sure everyone is aware of the change and educated on how to use the testing after the change is made."

"This is now the home for anything related to lipid testing," El-Khoury said. "We hope that the guideline will serve as a guidance for change and updating our practices so that we're all essentially doing as close as possible to the same thing when it comes to these tests."

Grace Browne is a freelance journalist who lives in London. She currently has a fellowship funded by the International Center for Journalists through the Health Innovation call.

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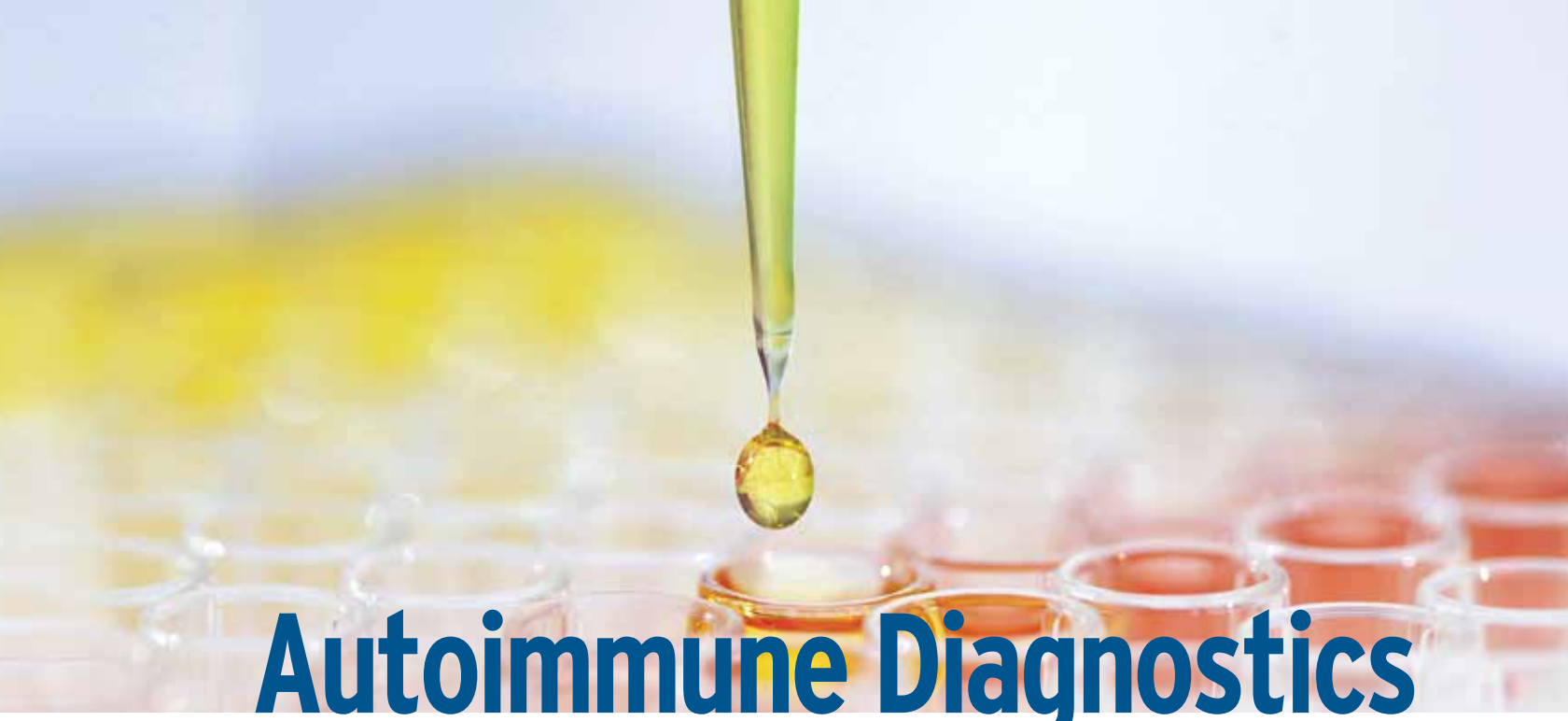

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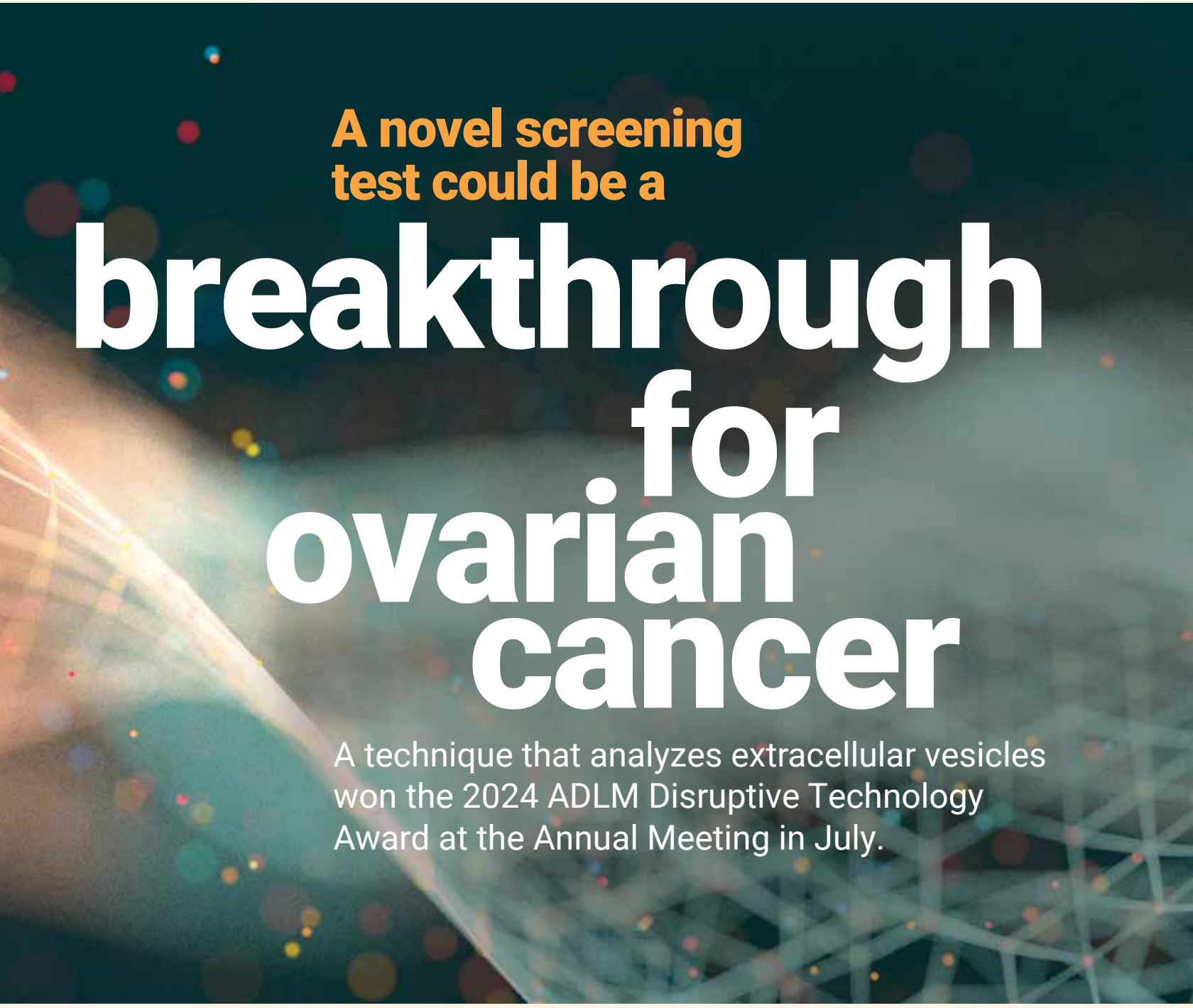
BY KAREN BLUM



A novel screening test could be a

breakthrough for ovarian cancer

A technique that analyzes extracellular vesicles won the 2024 ADLM Disruptive Technology Award at the Annual Meeting in July.

A blood-based test from Mercy BioAnalytics that has the potential to become the first FDA-approved test for ovarian cancer screening won ADLM's 2024 Disruptive Technology Award, presented at ADLM 2024 in Chicago. The honor recognizes innovative testing solutions that improve patient care.

"We were so thrilled," said Dawn Mattoon, PhD, chief executive officer of the company, based in Waltham, Massachusetts "It was unexpected. We applied thinking we were maybe a step too early. We know how much more work we have to do."

Most blood tests in development for early detection of cancers rely on identifying and measuring circulating tumor DNA (ctDNA) — genetic material shed from tumor cells. But that has limitations, Mattoon said. For one, ctDNA is released into circulation only when cells die. In the early stages of cancer, a tumor

mass is very small, and its cells are busy dividing and growing without a lot of cell death occurring.

Mercy's test, called Mercy Halo, instead analyzes extracellular vesicles (EVs) — small, membrane-bound particles shed continuously by all cells, which are abundant in circulation. For example, 1 mL of blood from a stage I cancer patient with a 1 cm tumor contains 100,000 tumor-derived EVs, according to company materials. The same sample may contain at most one copy of ctDNA.

The Mercy Halo assay is designed to detect multiple cancer-related biomarkers on the EVs' surfaces. When EVs are shed from tumor cells, they carry genomic and proteomic markers derived from their cell of origin, Mattoon explained. "Think of that kind of like a sphere, decorated on the outside with biomarkers."

HOW THE MERCY HALO TEST WORKS

The Mercy Halo assay introduces a magnetic bead coated with a capture antibody directed toward specific biomarkers decorating the EV surface. It pulls EVs with these biomarkers out of the sample for study. However, some of them may be healthy, noncancerous cells, Mattoon said. Then, to gain additional sensitivity and specificity, the test introduces two additional antibodies, directed against two additional biomarkers on the same EV, now sitting captured on the magnetic bead. Each detection antibody is conjugated to a double-stranded oligonucleotide with complementary, single-stranded overhangs. "When, and only when, they bind in close proximity to one another on the surface of that captured EV will those two oligos anneal," Mattoon said. "We do a ligation step, and that forms a template for PCR" that can be read on any qPCR instrument. "It's really through the selection of those three biomarkers that we're able to drive sensitivity and specificity for, in this case, early-stage ovarian cancer." The biomarker names are proprietary, she said.

The FDA in May granted the company Breakthrough Device Designation for the screening test in asymptomatic, postmenopausal women, and company staff are now working with the FDA on a pivotal study design, Mattoon said. "We want to make sure that we have really strong alignment with the FDA before we move into the pivotal study," she said. "It is absolutely our intention to submit this to FDA for approval, and we hope to do that in 2026."

There currently is no screening test for asymptomatic women to detect ovarian cancer, of which some 20,000 new cases are reported a year, according to the Centers for Disease Control and Prevention. More than 70% of ovarian cancers are diagnosed in women over age 50, and nearly 80% are diagnosed at an advanced stage of disease.

For women at high risk of developing ovarian cancer because they have a family history or a mutation in the *BRCA* gene, "the best we can do for them right now is recommend that they have their ovaries and fallopian tubes surgically resected," Mattoon said. "For the rest of us who don't have any of those risk factors, we basically just have to hope that we don't get ovarian cancer. There is no screening modality. That's what we are endeavoring to do."

FROM INSPIRATION TO CLINICAL EVIDENCE

The original technology was the brainchild of Joseph Sedlak, an MD/PhD candidate at Harvard University with his own unique story.

As an undergraduate at the University of Michigan, Sedlak was part of a dedicated program, the Blavin Scholars, for young adults who had spent time in foster care or were navigating education without support from parents or guardians. The program, started by financier and philanthropist Paul Blavin, provides mentors and other wraparound services. With Blavin's support, Sedlak graduated summa cum laude and entered an MD/PhD program at Harvard and MIT, along the way becoming Blavin's adopted son. It was during this graduate work that

Sedlak identified early detection as an area of significant unmet need to reduce cancer morbidity and mortality. Together, Sedlak and Blavin founded Mercy BioAnalytics in 2018 based on Sedlak's novel idea to leverage EVs in early cancer detection.

Because EVs are so abundant, the Mercy Halo test can detect them even in very small sample volumes, Mattoon said. For the ovarian cancer test in development, only 300 µL are needed. That enables the test to be run on material stored in biorepositories from previous clinical trials or research studies.

Recently, the company partnered with investigators from University College London to run the test on a retrospective of baseline blood samples from postmenopausal participants from the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). During that trial, participants were randomized to receive no screening, annual multimodal screening including serum measures of the biomarker CA125, or annual transvaginal screening. The study found a significant (10%) decrease in late-stage, high-grade serous ovarian cancer but no decrease in deaths from these screening options.

In the new study with Mercy BioAnalytics, among samples from over 1,300 women, investigators found that the Mercy Halo test was able to detect high-grade serous ovarian cancer up to 3 years prior to diagnosis. The sensitivity 0–12 months prior to diagnosis was 82% (and 85% for stages I and II), compared with 63% (46% for stages I and II) for CA125 at a cut-off of 15.5 U/mL established in an independent study. The specificity, in controls, of the EV-based blood test was 97.7% and of CA125 was 95.5%

"That blows the doors off CA125," Mattoon said. "It's really the most significant advancement in ovarian cancer early detection in 40 years." These results were presented in a poster in June at the American Society of Clinical Oncology's annual meeting.

In additional study findings, the AUC 0–12 months prior to diagnosis was 0.94 (0.98 for stages I and II) compared with 0.87 (0.80 stages I and II) for CA125. And, in samples from women who had a false positive transvaginal ultrasound who underwent trial surgery during the initial study and had benign pathology, Mercy Halo's specificity was 97.6%, compared with 89.5% for CA125.

The technology also could be suitable as an aid to diagnosis for a woman presenting with symptoms of ovarian cancer, Mattoon said. Ovarian cancer typically presents with nonspecific symptoms such as diffuse pelvic pain or a feeling of fullness. Combined with a lack of a screening test, she said, "Women are almost always diagnosed at an advanced stage of disease, and their outcomes are terrible. Most of these women, unfortunately, will succumb to their disease." If ovarian cancer is detected early, at a localized stage, she said, more than 90% of women will survive for 10 years.

The biomarkers targeted by Mercy Halo may be generalizable to other cancers, Mattoon said. The company is working on another indication, for early detection of lung cancer in individuals who are at high risk because of their smoking history. They also have feasibility data for breast, prostate, and colorectal cancers, she said.

It's pretty easy for companies to do case-control studies that include some people already diagnosed with a condition and some who are healthy, and many emerging technologies can discriminate postdiagnostic cases from healthy controls, Mattoon said. Where some start to falter is in translating early performance into asymptomatic individuals. But Mercy validated the performance of their test in the intended use population in their study with University College London, which makes Mattoon optimistic about their upcoming pivotal validation study.

"It's an amazing time to be in the space," she said. "I believe that blood-based cancer screening will come into the norm of clinical practice over the next decade. Who wouldn't want to be a part of that?"

The two other finalists for the award were Dionysus Digital Health for its Enlighten Test, an epigenetic test taken during pregnancy that predicts future risk of postpartum depression, and Vitestro, for its Vitestro autonomous blood-drawing device.

The Enlighten Test scans epigenetic biomarkers from a blood test during pregnancy, specifically looking at methylation status of two genes: *TTC9B* and *HP1BP3*. *TTC9B* is associated with estrogen activity while *HP1BP3* mediates anxiety. Pregnant people can then share results with their physicians and discuss screening for postpartum depression after the baby is born.

The Vitestro device combines artificial intelligence-based, ultrasound-guided imaging with robotic needle insertion to ensure accurate, secure blood collection. The procedure — from tourniquet to bandage application — is performed automatically.

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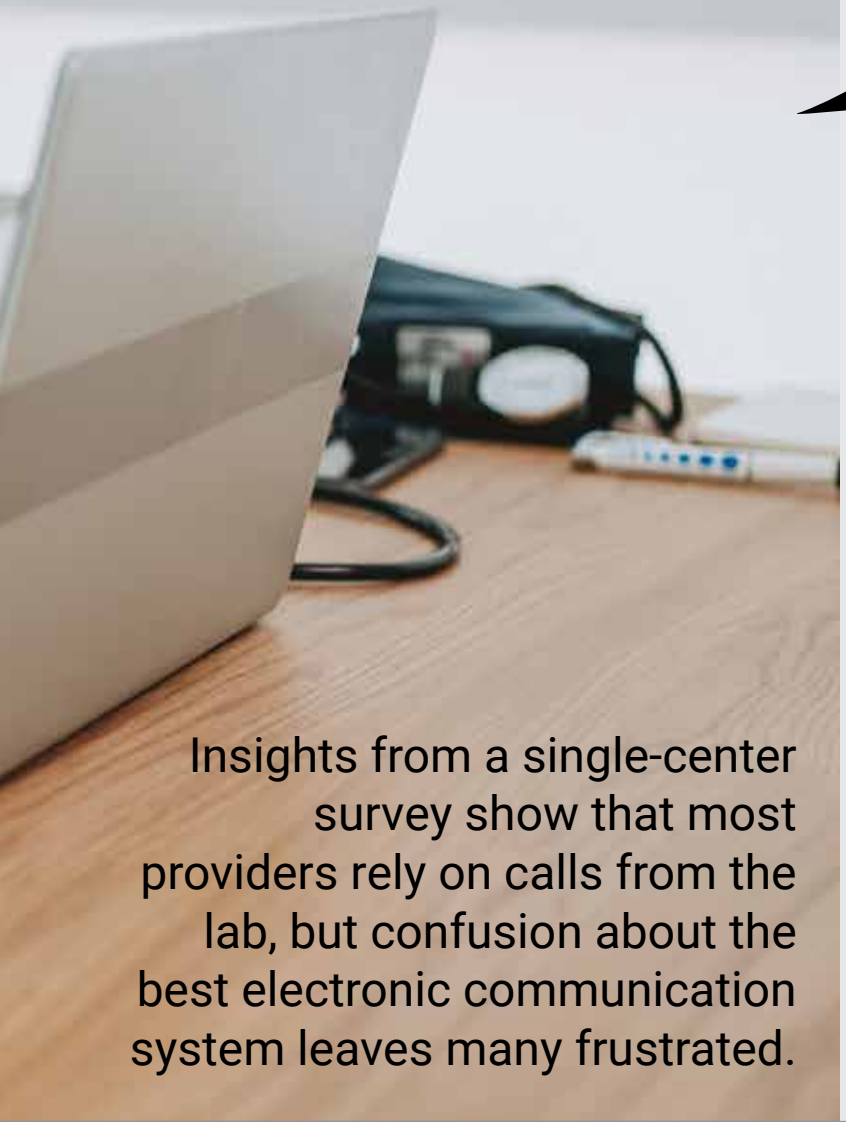
Critical result notification preferences



Insights from a single-center survey show that most providers rely on calls from the lab, but confusion about the best electronic communication system leaves many frustrated.

Timely communication of test results that fall significantly outside the expected range and pose potential life-threatening risks is crucial for effective patient care. However, as healthcare systems offer new methods of electronic communication, clinical laboratories must navigate not only regulatory requirements but also the increasingly noisy information environment providers experience.

The Joint Commission (TJC) defines a critical value as one requiring immediate communication of results. Regulations from agencies and accreditors such as the Centers for Medicaid and Medicare Services, TJC (National Patient Safety Goal NPSG.02.03.01), and the College of American Pathologists (CAP) Checklist statement (GEN.20316, COM.30000, COM.30100) mandate that laboratories develop and implement an alert system for critical values (CAP- critical values reporting QT10).

Although the regulatory considerations for implementing a critical value reporting system from these different agencies have a lot of commonalities, there are some notable

BY SRI BHARATHI KAVURI, MD, CARLOS CLARK, MD, ODUTAYO OLALEKAN, MSC, MBA, AND ANTHONY O. OKORODUDU, PHD, MBA

differences. CAP COM 3000 and CAP COM.30100 indicate critical results can be communicated by phone or electronically, whereas TJC requires that the communication be via telephone or verbal. Notably, both agencies accept electronic transmission of results. In addition, CAP requires that the recipient confirm receiving the information but does not specifically require that a "readback" of the result be electronically transmitted. TJC requires that a readback be done while communicating the critical result.

Only 6.8% of providers indicated that they depend only on phone calls from the lab.

Historically in our hospital system, like most others, this has been done through a telephone call to the "responsible licensed provider/licensed independent practitioner." The laboratory technician resulting the test is responsible for calling the ordering licensed independent practitioner (LIP) within 30 minutes. If the provider cannot be reached, communication is escalated according to a predefined algorithm indicated in our standard operating procedure. This current system has been in place for many years and has stayed the same through the electronic revolution in medical records in the past decade.

We conducted a survey to understand the perception of the providers who receive these critical results with the aim of understanding their readiness to utilize the newer options available for critical result notification. One such method we assessed was provider awareness of EPIC Haiku notification. Secure messaging has also become available at our hospital system since the completion of the survey. The results of the survey could guide healthcare systems in identifying potential areas of improvement. They also might inspire innovative solutions that will enhance the use of technologists' time and increase the efficiency of timely delivery of these results to the right provider, while minimizing unwanted distractions.

HOW WAS THE SURVEY CONDUCTED?

The survey was sent to all providers at the University of Texas Medical Branch across all campuses (one main campus on the island of Galveston and four smaller hospitals in the suburbs) via a broadcast email. It consisted of 10 questions, with some questions providing the option for a free-text input, some with required categorical responses, and others with multiple choice options. The survey was open to participants for a period of 4 weeks, with two reminder emails sent out at regular intervals. A total of 544 providers opened the survey, with 191 of them completing it (35.1%). Among the respondents, 84% were physicians (n=161), including faculty members, residents, and fellows. Fifteen percent (15%) of the respondents identified as advanced practitioners.

HOW PROVIDERS USE MULTIPLE COMMUNICATION METHODS

In the era electronic medical records (EMRs), multiple modalities exist through which physicians can track laboratory results of their patients. We attempted to analyze the most used methods with a multiple-choice question in which providers could check all that apply. The options were periodic check of EMR, phone call from the laboratory, checking before seeing the patient again, and using the patient list in the EMR and the flag feature to identify critical results.

The survey showed that 54.4% of our respondents use two or more methods, and around 21% responded that they only rely on periodic checks of the EMR (Figure 1). Only 6.8% of providers indicated that they depend only on phone calls from the lab, while around 2% responded that

Figure 1: How do providers at our institution check critical lab results for patients?

Providers use multiple modes to check critical results. Only 7% rely exclusively on phone calls from the laboratory.

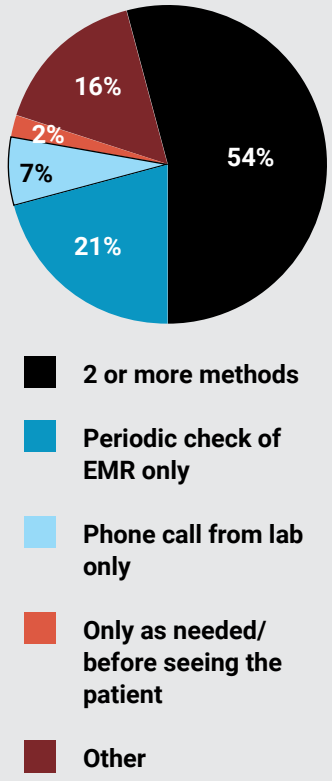
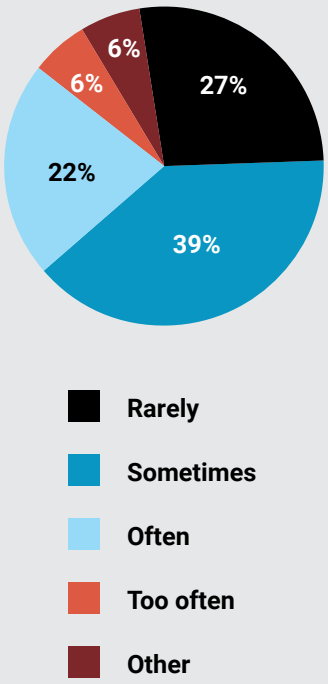


Figure 2: Clinician's perspective on the frequency of critical result notifications from the laboratory

Most respondents reported the laboratory called them "rarely" or "sometimes."



they check these results only before seeing the patient again, or only as needed. Only two providers reported using Haiku for checking critical results.

When asked to rate the perceived frequency of critical result notifications from the laboratory, 27% felt that they are called only rarely by the lab and 39% indicated that they were called "sometimes" (Figure 2). Twenty-two percent of the respondents reported that they were "often" called by the laboratory, with 6% specifying that they received these calls often even when they are not on call. The remaining 6% did not provide specific response about the frequency of phone notifications.

PROVIDERS REPORT DISTRACTIONS BUT STILL FIND CRITICAL RESULT CALLS USEFUL

More than a third (35%) of the respondents felt that the critical result calls distract them from patient care (Figure 3). Fifty five percent indicated that the calls did not distract (disagree/strongly disagree) from patient care. One provider wrote that it distracts them from their sleep which in turn takes away from patient care due to fatigue.

Most still find the calls useful: 58% reported they find them useful, with 14% indicating that they were indispensable to patient care. However, 38% of the providers felt that these calls are not useful, and 5% of those believed the disadvantages of the call outweighed the advantages.

Some went on to explain that sometimes these results are either expected or not a surprise because they are already being tracked and do not warrant immediate intervention. A few raised concerns about the current system of calling the ordering provider instead of the on-call provider, and a few others disagreed with the critical nature of some test results.

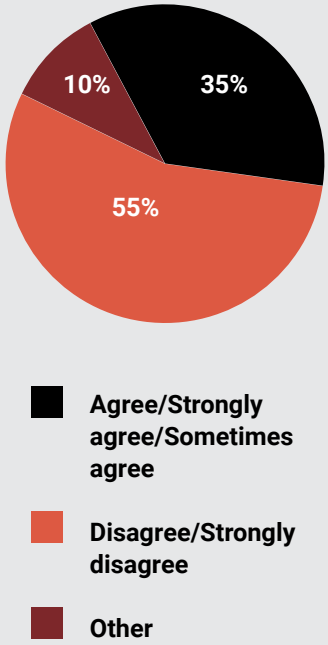
WHICH CRITICAL TEST RESULTS DO PROVIDERS THINK HAVE THE MOST UTILITY?

Forty percent of the respondents reported that they appreciate the calls about electrolyte levels the most, with potassium being the most frequently mentioned component. Approximately 25% of the respondents felt that hemoglobin results are very helpful as well. Approximately 20% of the respondents mentioned that receiving calls about positive cultures was of vital importance, with suggestions made to add all positive cultures in neonates to the critical value list, not just blood and CSF.

Blood glucose levels, specifically hyperglycemia, also were highlighted as an important call to receive by 15% of the providers. Approximately 10% of respondents mentioned the importance of specialized tests

Figure 3: When do critical result calls distract providers from patient care?

More than 1/3 of providers say they are distracted by critical result calls.



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relevant to their specific specialties. Most of the providers from the pediatrics department indicated that they appreciate the calls about bilirubin levels and reported that blood cultures in neonatal intensive care unit also were of vital importance.

Which results do providers believe have the least utility? Many of the respondents felt that none of the currently reported critical values should be excluded from the list. However, among those who responded, activated partial thromboplastin time was cited as the least useful laboratory results that is called in to physicians; most of the providers said that these can be reported to the nurses on the floor, as they manage the heparin drip.

More than 1/3 of the providers indicated that phone calls distract them from patient care.

Although the protocol in our laboratory is not to call a critical result if the same one has already been reported in the past 72 hours, some providers mentioned receiving phone calls for repeat critical values (perhaps outside the 72-hour window) and said it was not useful. Some suggested that low glucose levels, specifically those for outpatients, could be excluded from the list since several hours would have passed, and there would be nothing actionable resulting from the call.

PROVIDERS VIEWS ON SMARTPHONE ALERTS

Our hospital system utilizes the EPIC EMR system, with Haiku available as an application for smart phones and other electronic devices. The Haiku app is protected by a duo security system for multifactor authentication. It allows users to place orders on-the-go, as well as check the results as soon as they have been uploaded, by selecting the "notify me" option while ordering the test.

When asked if they were familiar with this option of choosing EPIC Haiku notifications for critical results, only 33% responded affirmatively. However, when asked how likely they would be to adopt a different system for the delivery of critical result notification from the laboratory, an overwhelming majority of providers (around 82%) said they would very likely/likely consider adopting a new system. Some providers went on to suggest secure text messaging systems, Microsoft teams, and EMR alerts as alternatives. A minority specified that they were uncomfortable or unable to get Haiku to work on their phones, pointing to a potential area of intervention.

HOW CAN THE LABORATORY IMPROVE CRITICAL RESULT NOTIFICATIONS?

Our conclusions from the survey are that most respondents do find the critical result notifications from the laboratory useful, but the current system could be improved to remove redundant laboratory tests and adopt secure smart systems to better communicate these results. An increase in providers' awareness of newly available modalities of notification seems to be the need of the hour, as they offer a tailored menu from which the clinician can choose to be notified about specific results for a specific patient.

Boosting provider awareness of these new systems seems to offer a good chance of success, as almost 82% of providers indicated that they would be willing to consider adopting a new system for critical result notifications.

It is also notable that more than a third of the providers indicated that the phone calls distract them from patient care. We believe this adds urgency to the need to work on alternative ways to communicate critical results.

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1. Mandelbaum T et al. Outcome of critically ill patients with acute kidney injury using the AKIN criteria. *Crit Care Med* 2011;39(12):2659-2664.
2. Kobayashi M et al. Prognostic Value of Estimated Plasma Volume in Heart Failure in Three Cohort Studies; *Clin Res Cardiol* 2019;108(5): 549-561.
3. Niedermeyer, et al. Calculated Plasma Volume Status Is Associated With Mortality in Acute Respiratory Distress Syndrome. *Critical Care Explorations*: September 2021, V3(9):1-9.
4. Kim HK et al. Prognostic Value of Estimated Plasma Volume Status in Patients with Sepsis. *J Korea Med Sci* 2020;9(37):1-10.
5. Soliman HM. Development of ionized hypomagnesemia is associated with higher mortality rates. *Crit Care Med* 2003;31(4):1082-7.
6. Wilkes NJ et al. Correction of ionized plasma magnesium during cardiopulmonary bypass reduces the risk of postoperative cardiac arrhythmia. *Anesth and Analg* 2002;95(4) 828-834.




BY JESSIE CONTA, MS, CGC, CAROLINA SOMMER, MAX BROWN, AND JOSHUA HENDERSON

Supporting the rare disease community: Insights from the NW Rare Disease Coalition Payer Forum

Approximately 1 in 10 Americans is affected by a rare disease. An estimated 80% of these conditions have known genetic origins, underscoring the critical need for access to genomic testing (1). Adding to the burden on patients, diagnostic odyssey — the time from symptom onset to diagnosis — can take more than 6 years and 17 medical interventions, on average (2). Diagnosis is not only a critical step in connecting patients with appropriate treatments, such as cell and gene therapies, but also provides a sense of purpose and community for those affected (3).

The NW Rare Disease Coalition supports the Pacific Northwest's rare disease community by providing educational programming, engaging in direct advocacy, and fostering industry partnerships. The coalition strives to end the diagnostic odyssey, improve access to care, and accelerate the development of new treatments. Since 2017, the coalition has hosted an annual educational event about the importance of rare disease research. New this year, the Payer Forum was a workshop designed to engage payers in discussions with industry, patients, and legislators around rare disease genetic testing and gene therapy access.

Perspectives on diagnostic journeys and care coordination

The forum panel discussions featured individuals with rare diseases and parents of children with rare diseases. Panelists highlighted the lengthy and challenging diagnostic journey, which often involves navigating complex healthcare systems and enduring significant financial and emotional strain. The time to diagnosis can be long. For many, the presenting features and symptoms in isolation didn't prompt a diagnosis; however, features taken together supported genomic testing that revealed a common underlying etiology.

Receiving a diagnosis, even in the absence of treatment, provides a sense of connection and purpose. Rare disease caregivers often assume multiple roles, including healthcare navigators, fundraisers, researchers, and advocates. The financial burden of expert consultations, therapies, and support for daily living is substantial, and obtaining insurance coverage for necessary tests and treatments remains a significant hurdle. Variable coverage policies result in inequitable access to genetic testing and counseling, which further highlights the need for streamlined and collaborative diagnostic approaches.

At the forum, panelists highlighted several initiatives, like Project Baby Bear (4) and UnitedHealthcare's Complex Care Concierge (5), that coordinate resources to improve patient access to genomic testing. Payers described how these successes served as a foundation to expand access to genomic testing within their organizations, including examples of expanded coverage for rapid genome sequencing within Blue Shield of California and United Healthcare plans.

Genetic counseling is also a critical component of testing and coordination in rare diseases, yet access is limited by inadequate reimbursement models.

Perspectives on cell and gene therapy

The afternoon session focused on cell and gene therapy access. Perspectives from patients, advocates, and researchers emphasized that cell and gene therapies, while transformative, are not always curative. Panelists discussed the importance of setting realistic therapeutic goals and involving patients in defining success criteria. Many shared stories of therapies providing significant benefits despite not meeting traditional endpoints. This hightlights the opportunity for engaging patients and caregivers in the study design process and integrating flexible outcome measures.

Panelists provided an overview of the science behind cell and gene therapies and explored the complexities of creating reimbursement models for high-cost, potentially one-time treatments. The value assessment of cell and gene therapies differs between providers, patients, and insurers, further complicating coverage

decisions. Individual's frequent switching of insurers also affects projections on return on investment, adding another layer of complexity. Panelists discussed the unique challenges in rare diseases, including small patient populations, evidence generation difficulties, failure rates of therapies, and long negotiation timelines for reimbursement.

Some organizations are piloting alternative payment models, such as outcome-based agreements and installment payments, to better allocate resources and ensure equitable access to therapies. Panelists agreed that is critical to make therapies affordable to guarantee that all patients benefit.

Payer views on access to care

In the final session of the event, payer representatives discussed access to genomic testing and cell and gene therapies. They reflected on the challenges of managing high costs, ensuring the effectiveness of tests and treatments, and dealing with fraud and abuse. Payers emphasized the importance of demonstrating the efficacy of tests and treatments to justify coverage.

Reconsidering evidence-generation models to better suit the small patient populations typical of rare diseases, and the need for robust data to support the clinical and economic value of treatments was a key recommendation. Payers also explored the idea of aggregating data across rare conditions to provide meaningful evidence to support access.

In the absence of universally accepted standards for medical necessity policies, payers utilize existing evidence to produce documents of varying content, structure, educational level, and accessibility. This variability results in inconsistent access for individuals with rare diseases. A PLUGS consensus statement seeks to increase standardization through a proposed framework that can be adopted by payers when creating policies (6).

Payers were moved by the chance to connect directly with rare disease patients and families and discussed how to secure representation within their respective organizations. Patient advocacy groups are increasingly involved with policy, research, diagnostics, and therapeutics for their disease of interest (7), and a natural extension is with payer organizations.

Moving forward: A call to action

Several themes emerged from the forum, including the need for a strong medical home for rare disease patients, insurance coverage for emerging diagnostic technologies, access to genetic counseling and care coordination, support for cell and gene therapies, and a seat at the table within payer organizations for patient advocates.

The NW Rare Disease Coalition's efforts underscore the importance of connection, advocacy, and data in improving the lives of those affected by rare diseases. The voices of patients and caregivers are indispensable in shaping effective healthcare policies and practices.

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References

1. Global Genes. RARE disease facts. https://globalgenes.org/learn/rare-disease-facts/ (Accessed July 9, 2024).
2. EveryLife Foundation for Rare Diseases. The Cost of Delayed Diagnosis in Rare Disease: A Health Economic Study. https://everylifefoundation.org/wp-content/uploads/2023/09/EveryLife-Cost-of-Delayed-Diagnosis-in-Rare-Disease_Final-Full-Study-Report_0914223.pdf (Accessed July 9, 2024).
3. Once Upon a Gene Podcast. Episode 231- The Power of Genetic Diagnosis - More Than Just a Label https://effieparks.com/podcast/episode-231-more-than-just-a-label (Accessed June 6, 2024).
4. Dimmock D, Caylor S, Waldman B, et al. Project Baby Bear: Rapid precision care incorporating rWGS in 5 California children's hospitals demonstrates improved clinical outcomes and reduced costs of care. Am J Hum Genet 2021; doi: 10.1016/j.ajhg.2021.05.008.
5. UnitedHealthcare. Complex Health Needs. https://www.uhc.com/news-articles/benefits-and-coverage/complex-health-needs (Accessed July 9, 2024).
6. Patient-centered Laboratory Utilization Guidance Services. PLUGS Consensus Recommendations and Framework for Development of Payer Medical Necessity Policies. https://www.schplugs.org/insurance-alignment (Accessed August 1, 2024).
7. Patterson AM, O'Boyle M, VanNoy GE, Dies KA. Emerging roles and opportunities for rare disease patient advocacy groups. Ther Adv Rare Dis.2023; doi: 10.1177/26330040231164425.

BY JOSH DIEGNAN, PHD, FACMG

Implementation of an automated EMR workflow to facilitate genetic consultation and review of inpatient genetic test requests

Inpatient genetic testing is generally only appropriate when the results will change the management of patients while they are in the hospital. When test results are available after a patient has been discharged, it can be unclear as to which provider is responsible for following up on the results.

Inpatient genetic testing can also create a financial burden to health systems since these costs are not typically covered by current reimbursement practices. A review of select inpatient genetic test orders at UCLA from 2020 to 2022 demonstrated that approximately 80% of the results were not available until after the patient was discharged, so we wanted to implement a workflow whereby select inpatient genetic test requests would be reviewed for appropriateness before the actual test orders could be signed.

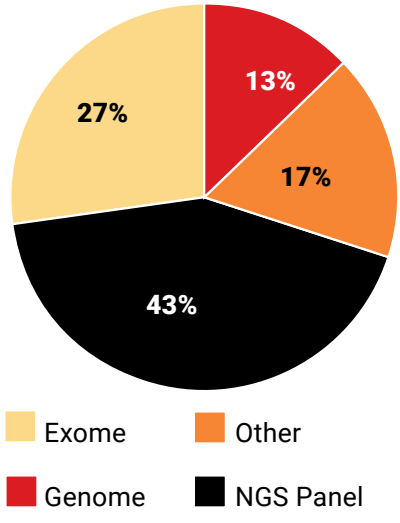
LABORATORY STEWARDSHIP FOCUS

Designing and Launching the Electronic Consultation Workflow

We developed an automated electronic consultation workflow within our electronic medical record (EMR) (Epic) that blocks providers from signing an order when they attempt to select list of inpatient genetic orders. In these cases, the EMR shows an alert requiring providers to consult the molecular diagnostics laboratories first; for the consult, the provider enters the desired test, the reason for ordering it, and a contact phone or pager number. After the provider signs the consult order, the molecular lab director team is notified by an e-mail with the information.

The molecular lab director on service then contacts the provider by phone by the close of the next business day to discuss whether the test request is appropriate for the inpatient setting. If it is determined to be appropriate, the molecular lab director then signs a note in the EMR that allows the provider to sign the genetic test order by suppressing the alert. If the order is deferred to the outpatient setting, then we recommend the provider document ordering the test in the discharge summary.

Figure 1. Type of Test Requested



We launched this workflow in October 2023 and applied it to seven specific germline genetic test orders (both in-house and sendout). Additional sendout test requests to four dedicated genetics labs were added to the workflow in February 2024. Based on previous ordering practices, the molecular diagnostics group expected approximately two consult requests per week. Consultations with providers focused on two main questions: 1) when is the patient expected to be discharged? and 2) how will the results from the test affect clinical management during admission?

Evaluating the Workflow and Outcomes

In the first seven months since the workflow was launched (up until June 3, 2024), we received 60 consult requests. This is approximately two per week, which is similar to the pre-intervention level. Other test orders have also presumably been prevented where the provider ultimately elected not to order the consult, though this can be difficult to determine.

The types of tests that providers requested are shown in Figure 1. As expected, trainees (residents or fellows) initiated the majority (64%) of the inpatient consults thus far. Approximately 18% of them have been initiated by clinical genetic counselors. Overall, genetics providers have been far

The laboratory regularly reviews a dashboard to evaluate changes in the volumes of inpatient genetic test orders, which can help identify additional tests to be added to this workflow.

more likely to order the inpatient genetic tests appropriately as compared to non-genetics providers, and their requests were less likely to be cancelled (see Table 1). In contrast, many of the requests involving non-genetics providers were canceled/deferred to the outpatient setting, with some of those requests being auto-canceled (due to the patient being discharged before the request could be discussed).

This automated EMR workflow has presumably reduced inappropriate inpatient genetic test orders, though some providers may have ended up ordering tests directly with the reference laboratory using their provider-facing portal outside of Epic. This is information we don't always have easy access to, and we have already initiated several efforts to reduce direct portal ordering as much as possible in the future.

Moreover, many educational discussions have occurred between providers and molecular lab directors during the time in which the workflow has been live; however, only a few clinical users have been involved in more than one consult, making it difficult to determine how much of an educational impact the intervention has had overall.

We are currently evaluating whether certain specialties, such as clinical genetics, should have the consult alert suppressed, as most of their requests have thus far been deemed appropriate. Other specialties could also have the consult alert suppressed in the future as needed. Revising the requirements for specific specialties is preferred to revising the requirements for specific providers, as the latter option would likely require additional ongoing monitoring and maintenance as providers and trainees come and go.

However, some clinical genetics providers have expressed a preference to retain the alerts for their orders too, as they are sometimes consulted to order tests for other services who are under the assumption that clinical genetics is already excluded from this workflow. Many of those requests are for tests that clinical genetics would not recommend ordering during the inpatient admission, and by keeping the alert in place, clinical genetics should receive fewer inappropriate requests from other providers to place those orders.

The laboratory also regularly reviews a dashboard to evaluate changes in the volumes of specific inpatient genetic test orders, which can help identify additional tests to be added to this workflow in the future. As was previously mentioned, many germline genetic tests are currently being sent directly from clinics to reference laboratories, and one of our overall goals is to continue building discrete tests and integrating additional laboratories into our EMR (e.g., through Epic Aura). As those efforts continue, we will establish better visibility of test utilization, and those additional tests can also be considered for inclusion in the inpatient genetic testing consult workflow.

Table 1. Outcome of new EMR workflow

	Genertics providers (n=31 tests)	**Non-genetics providers** (n=29 tests)	**Total** (n=60 tests)
Deemed appropriate and ordered	81% (25/31)	34% (10/29)	58% (35/60)
Deemed inappropriate but still ordered	6% (2/31)	17% (5/29)	12% (7/60)
Deferred/canceled	13% (4/31)	49% (14/29)	30% (18/60)

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AN INTERVIEW WITH SHANNON HAYMOND, PHD

Why data literacy is essential for laboratory professionals

By Jen A. Miller

In laboratory medicine, the strategic use of data can transform everything from operational efficiency to groundbreaking research discoveries. It can lead to insights in everything from identifying how to deploy phlebotomists more efficiently across a healthcare system to using statistics to identify patterns that lead to breakthroughs for better patient care.

But a large volume of data is only useful if you know how to use it. That's especially true in clinical laboratories, which produce reams of data.

CLN spoke to Shannon Haymond, PhD, Senior Vice President and Chief of Pathology and Laboratory Medicine and Arthur C. King Professor of Pathology and Laboratory Medicine at Ann & Robert H. Lurie Children's Hospital of Chicago, about what clinical laboratory directors should know about data, and how they can work with other departments across their institutions to make sure they're using data to the benefit of both patients and the institution.

How would you define data literacy?

To me, data literacy is the ability to interpret and communicate data so that you can make decisions or inform others' decision making.

It's important because there are so many things we can be informed about with data, and having this awareness helps you make better decisions. If you can understand what happened or why it happened, it can help you determine what you should do next, or what's likely to happen next. Those are all very powerful things that help you take the appropriate action.

How should data science be part of the lab director's role?

I think this should be a fundamental concept. Data science is transforming many aspects of our life. Our laboratories are no different, because laboratory directors are decisionmakers and innovators who will increasingly apply data-centric approaches to operational, quality, and clinical workflows. Additionally, more of the applications and instruments we use today will rely on data-driven technologies. So, data analytics and data literacy are critical skills for now and in the future. We must continue to advance our ability to collect, analyze, and consume data so we can glean valuable insights from data and effectively incorporate predictive and prescriptive methods to help automate our decision-making.

Who should be building out informatics pipelines, and what role can laboratory directors play?

There are many approaches to building pipelines for informatics and data analytics. One we found works best is a partnership with our institutional information technology group. That allows us to leverage institutional policies, processes, technologies, and people resources to do things most efficiently and, I think, effectively.

In this model, laboratory professionals are the experts on our workflows and challenges, and we can articulate our needs, and evaluate or develop tools and solutions. But we rely on our information technology or information management group and embedded analysts to help us implement those solutions within the hospital's informatics frameworks and governance policies. This also allows for better integration, so we're not limited to accessing only our own laboratory data or applications.

What is required to get hospital investment in laboratory informatics, and who should be championing this?

I've always encouraged people to start by finding out what is going on at their institutions already. There is an ongoing digital transformation happening in all industries, including healthcare. I've found that many institutions are viewing data as an asset, and they want to make sure people are maximizing that value. They've recognized that this requires resources and infrastructure

FOCUS ON **DATA SCIENCE**

and are investing in these areas. Laboratories can take advantage of work that is in process or that already exists at their institutions to get started.

Next, you have to find out who the decisionmakers are and then be able to articulate your use cases. How do you want to use the data? What data and tools do you have? Will these meet your needs? How is it going to impact your clinical and research initiatives? Once you know all that's happening in the institution, then you can start to figure out how these projects are funded and prioritized. Is it through operational funds? Some mix of operational and research funds? Or other sources of funding?

I personally feel that data science or data analytics — this falls under computational pathology for us — is a necessary function and a specialty of laboratory medicine that should be a part of all departments. Computational pathology at Lurie Children's is composed of bioinformatics, pathology informatics, data science, data literacy, and digital pathology. Just like the laboratory builds infrastructure for a point-of-care testing program, I feel every laboratory needs infrastructure for these computational efforts that is in addition to the traditional support we've had for laboratory informatics. Maturity in data science is becoming a basic tenets of running an efficient and cutting-edge clinical laboratory.

How will this kind of partnership make sure that you're using the right data instead of just collecting a lot of it?

High-quality data is a very important part of informatics and data science. That's why it is so important for clinical laboratories to collaborate with other professionals who have data science expertise. I've seen both scenarios: situations where people only have a laboratory medicine background but don't have necessary technical data skills; and those where people have tremendous data science skills but don't understand the laboratory medicine workflows or regulatory constraints. They're missing that context or subject matter experience.

We need teams of people, composed of those who understand best practices for data collection, data management, and data preparation and those who understand the clinical laboratory's workflows and regulatory considerations.

What role can national organizations play in the development of informatics pipelines?

One of the major roles of ADLM is to help educate and build not only data literacy but also technical skills in laboratory directors and trainees. This way, they are poised to lead these types of efforts that are going to become foundational to laboratory medicine.

ADLM is also making sure to publish and disseminate cutting-edge science and innovation in this area, which has been very exciting to see. The other thing ADLM does well is work on advocacy. We're making sure that members who have clinical laboratory expertise are part of larger initiatives to really help steward and optimize the use of data and its integration at a very broad and even national level for clinical care and research.

Can you describe a case where data science provided an unexpected insight?

We wanted to deploy phlebotomists more effectively within our hospital to balance their blood collection workloads, particularly in times of staffing shortages. So, we built a model that would look at factors like the number of requests in a day and the types of patients to understand the difficulty or complexity of the phlebotomy required. With that data, we figured out how we could better utilize our people to improve patient care through more timely blood collections and thus faster result availability.

Big picture, how do you see data science changing the field of lab medicine?

One area that is very promising is the question of augmenting human workflows, particularly in areas where we have a shortage of people or shortage of very specialized expertise. Are there ways we can improve access to substantial expertise, but also where we can better utilize our human resources? These kinds of solutions will enable us both to handle more samples and perform even higher quality testing more efficiently. In addition, there also are a lot of tedious or repetitive and low risk tasks that we should automate.

So, I see laboratory medicine using data science not only to provide new insights that guide care, but also to enhance the efficiency and effectiveness of laboratories themselves, both of which enable us to improve patient care.

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FOCUS ON **DATA SCIENCE**

AN INTERVIEW WITH CATHERINE MOORE, MBE, PHD, FRCPATH

Preparing for Flu Season: Pathogen Detection and Surveillance

By Jen A. Miller

FOCUS ON MOLECULAR DIAGNOSTICS

As summer turns to fall, respiratory viruses are about to be in the spotlight. The clinical laboratory plays a critical role in detecting which pathogens are circulating in the community, how those pathogens are affecting different populations, and how those patients will be tested and treated.

We spoke with Catherine Moore MBE, PhD, FRCPath, consultant clinical scientist at Public Health Wales, about what her institution does to prepare, how they handle both potential bacterial and viral infections, and how surveillance — which was disrupted by the worst of the pandemic — can play a key role in helping the community through this season.

What are the main pathogens for labs to target during flu season?
Influenza would be number one, and then SARS-CoV2. Because it's winter, we normally also target respiratory syncytial virus (RSV), which is a common cause of bronchiolitis in children. We now have immunizations available for pregnant women for RSV, as well as for the elderly.

Clinicians can also offer a new monoclonal antibody to neonates that can help protect them from RSV for up to 6 months.

In most emergency departments, they'll do rapid tests for influenza A and B, RSV, and SARS-CoV-2.

How do you prepare to test samples coming from different patient populations during seasonal epidemics of respiratory infections? Are there different approaches for immunocompetent and immunocompromised patients?
The severity of influenza, RSV, and COVID-19 are well known. However, the impact of other respiratory viruses has probably been underestimated and underresourced for many years. That includes those associated with rhinovirus, also known as the common cold; parainfluenza, human metapneumovirus, and various other respiratory infections that people get all year round. In certain populations, like those who are immunosuppressed, they can be severe.

When we look at local testing in Wales, we have a range of multiplex PCR-based molecular panels that are specific for different patient groups. If it is a patient who is normally fit and well, it would be appropriate to use an influenza A and B, RSV, and SARS-CoV-2 panel. For patients who are immunosuppressed, the clinicians could suspect rhinovirus or parainfluenza.

Following the worst of the COVID-19 pandemic, do you see a change in implementation of multiplex PCR testing in clinical settings?
Prepandemic, it was the laboratory running most of the panels. There was a little bit more expansion into emergency departments for things like influenza, but broad panels that include a lot of other respiratory infections were only just being introduced. Commercial companies were bringing out expanded panels, with ongoing studies to look at implementation in emergency departments — in particular, how they affected patient management and patient flow through hospital systems. But they weren't really being taken up because they are quite expensive.

Since we started to come out of the pandemic, we're now seeing expansion, not just in expert areas of microbiology, virology, and other areas of laboratory medicine, but directly into emergency departments. The world has definitely changed.

For the most part, multiplex PCR testing is still mostly for viral infections because the evidence base is more clear. We've been doing viral molecular testing for decades. I set up testing back in the early 2000s, and we've been expanding ever since. We have good evidence of utility and of the caveats that go with that testing. With bacteria, it's just starting to take off.

How can the public health benefit from clinical laboratories continuing to adopt multiplex PCR testing?
Outside of the four that we generally test for — influenza A and B, RSV and SARS-CoV-2 — we don't really have enough evidence about other viruses or

other pathogens. So expanding the panels and looking at clinical symptoms associated with those other viruses and pathogens can only help public health.

One of the things we struggle with most as virologists and clinicians is looking after people with viral infections, particularly in the immunosuppressed population. The more that we test and the more we understand the morbidity of these infections, the more we might drive better treatment and better prevention.

What is the role of surveillance for respiratory pathogens? Are there any learnings from the surveillance efforts that translate into the clinical setting?

Surveillance is very close to my heart. It's one thing I have been passionate about since the early 2000s: making sure the surveillance of these infections is understood, and that we incorporate as many pathogens as possible in our sentinel surveillance schemes.

Sentinel surveillance for influenza involves extensive testing to characterize circulating viruses, helping us better understand clinical presentations and the effectiveness of current vaccines. We expanded this system by including additional pathogens. We have detailed information about patients' underlying conditions, whether they are children or adults. The symptoms they present with are clearly listed, along with their immunization status. This allows us to investigate other pathogens and viruses and examine what patients are presenting with at their general practitioners.

The pandemic disruption was significant. People were encouraged not to go to primary care. It was difficult to understand how other viruses were circulating in the community. Everybody was presenting with COVID-19 at the same time, and we weren't always getting the information we were looking for.

A big concern for us is that the sequences of viruses and pathogens change all the time.

We were very keen, throughout the pandemic, to bring back our sentinel surveillance and look at novel ways of collecting that information from the community — and not just about COVID-19. In particular, we wanted surveillance of influenza because we knew it would start circulating again.

What is your view on clinical utility of smaller versus larger respiratory panels?

It depends on the patient population and on who is delivering the test. For the big four — influenza A and B, RSV and COVID-19 — there are pathways in place, and treatment options. The laboratories know very well how to deliver high-quality and appropriate testing.

Expanding outwards to rhinovirus or parainfluenza, the evidence becomes less well established. Sometimes these wider panels are being performed directly in emergency departments, but without any background or understanding of what those infections might cause, or what their treatment might be. That could lead to problems, because symptoms overlap quite a lot in some of these infections, particularly if the patients have other underlying conditions.

For those panels, clinicians are likely to engage with experts, whether that's local infectious disease teams or microbiologists, to support management of those patients with infections that aren't those big four.

Anything else on your mind as we head into fall and winter when it comes to the laboratory?

A big concern for us is that the sequences of viruses and pathogens change all the time. RNA pathogens are particularly prone to mutation. As a result, we don't always know if the test being used is still able to detect the target if it has mutated.

We experienced that problem a lot with SARS-CoV-2, and it is also relevant with influenza, RSV, and parainfluenza. The test might be working well for one particular type of virus, but next year it might not work so well. I believe we could be missing a lot of cases.

That's why surveillance is important, but also the engagement of experts who perform ongoing genomic analysis of the pathogens. The laboratory must make sure that the test is actually testing for what it says it does, because it doesn't take much for a test to stop working. I think engagement between experts and commercial companies developing these tests is essential.

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AN INTERVIEW WITH MANISH PATEL, MD, RPH, FACS, FPMRS

The Benefits of Syndromic Testing for Respiratory Infections

By Jen A. Miller

FOCUS ON MOLECULAR DIAGNOSTICS

Respiratory infections continue to be a problem coursing through healthcare. Not only is COVID-19 still active, but influenza, respiratory syncytial virus (RSV), and other pneumonia-causing conditions can lead to severe complications if not treated early and with the right medication. But testing for viral and bacterial causes of respiratory infections can be tricky, especially in vulnerable populations — and where more than one infection can hit a patient at a time.

That's especially true with RSV, which largely affects children and older adults. According to a 2023 report, RSV leads to 60,000 to 160,000 hospitalizations and 6,000 to 10,000 deaths in older adults in the U.S. each year (J Clin Virol 2023; doi: 10.1016/j.jcv.2023.105399). More than three-quarters of RSV-related deaths happen in older adults as well. Because RSV presents clinically no different than influenza or SARS-CoV-2, identifying it through testing is critical to help treat vulnerable populations.

CLN spoke to Manish Patel, MD, RPH, FACS, FPMRS, chief medical officer at Vikor Scientific, a high-complexity molecular laboratory in Charleston, South Carolina, and assistant professor of urology at the Medical University of South Carolina regarding syndromic testing for respiratory tract infections about why it's the better way to proceed, testing for coinfections, how to make testing better by addressing human error.

Patel also spoke to why it's so important to test and treat them in an outpatient setting, before they become so sick that they need to be admitted to the hospital. He also addressed why the U.S.'s previous influenza B rates may not be as high compared with other countries as it may seem.

What are the benefits of syndromic testing for respiratory tract infections?

There are lot of benefits overall to molecular technology compared with the way we typically try to identify bacterial pathogens.

Currently, when clinicians are suspicious of upper respiratory infections, many institutions rely on culture. But that's not ideal for several reasons, including poor specimen collection and simply the fact that growing a pathogen in a culture is really difficult.

What we've realized clinically from laboratory side is that if we can identify a pathogen using its own DNA and RNA, it's much more accurate. Moreover, we can identify whether there is more than one pathogen involved. This is much better for patient care overall.

When you think of culture, it is amazing to me, as a physician of more than 25 years, that we're using technology from 1882 in 2024. It doesn't make sense for culture to be the standard of care when PCR molecular testing isn't even new to this century. It's technology from 1980. We've just learned how to improve it with the aid of new technology to make it faster and more reliable.

What is the impact of syndromic respiratory testing in at-risk populations, particularly when it comes to RSV in older adults?

It is vital for any at-risk population. Older adults particularly are more likely to be admitted to the hospital and ultimately face a sepsis protocol. The CDC has emphasized that time to treat and the ability to narrow the spectrum of antibiotics as critical. The narrower the antibiotic spectrum, the better it is for the patient and for antibiotic stewardship globally.

The goal should not be treatment in the hospital setting. It should be treatment in the outpatient setting to prevent patients from going to the emergency room and to prevent them from being admitted.

Why was influenza B activity so elevated in the U.S. compared to other countries?

It's not necessarily that the U.S. had higher rates, but because the U.S. has better detection rates than other countries. Our ability to both identify and then ultimately track those patients through our data systems — many countries do not do that and do not have the ability to even follow

patients as along as we do. We're the standard bearers in a lot of these situations. There are other countries that do well with testing and tracking, though, including Japan, some European Union countries, and Great Britian.

What do laboratory managers have to take into consideration when validating their PCR workflows prior to the upcoming flu season?

From that standpoint, the laboratory needs to ensure it is identifying the right influenza virus. They also should carefully plan to manage the volume of testing and ensure their staffing and other resources are ready to maintain high quality.

In our laboratory, part of our planning and decision-making process is following closely what is happening across the globe, for example, the data coming out of Asia. This can help laboratories predict the percentage of patients in the US that might become infected and need testing.

How common are coinfections, particularly cases of both a viral and bacterial infection in one patient?

I recently gave a presentation at a scientific conference about a study where we evaluated more than 30,000 respiratory samples. We examined several parameters, including how often samples were positive for SARS-CoV-2 as well as secondary bacterial or viral pathogens, including RSV and influenza.

An alarming finding of this study was that up to 25% of samples had coinfections with bacteria, and very aggressive at that. We found *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae,* and others. I think this explains why we saw greater mortality among certain patient population during the COVID-19 pandemic.

Utilizing only a limited viral panel for high-risk populations is nearly malpractice. The clinician has no other way to reliably predict which potential coinfection could be present.

This adds to the evidence that, in my opinion, utilizing only a limited viral panel for high-risk populations is nearly malpractice. The clinician has no other way to reliably predict which potential coinfection could be present. That's the purpose of a large syndromic panel. The healthcare team often only gets one shot to get testing and treatment right before a patient ends up in critical condition.

What should a laboratory manager consider when evaluating a new syndromic testing solutions for respiratory pathogen detection?

I think it's important to consider who the vulnerable population is, what they specifically are at risk for, and what those copathogens tend to be. Finally, we also need to consider the antibiotic resistance of those pathogens. Clinical pharmacologists or infectious disease experts can use that to further narrow or taper those therapies. These are elements that I think are necessary, which is why the way we develop panels at Vikor Scientific.

Is there anything else you'd like our readers to know that can help make testing better in this realm, especially as we approach flu season?

I think one of the important things to focus on is acquiring high-quality respiratory samples. The laboratory should take the lead in teaching people proper sample collection techniques. A swab in the mouth or nasopharynx won't always get enough sample to identify RNA or DNA for sample amplification. With a high-quality sample, we can achieve a specificity of 99%. But sample collection quality is based on human skill, and human error can be reduced with proper training.

And finally, while rapid tests are also a piece of the puzzle for tackling respiratory infections, we should remember that antigen testing can have up to a 30% false negative rate, while PCR — again done appropriately — can achieve a 99% sensitivity and specificity rate.

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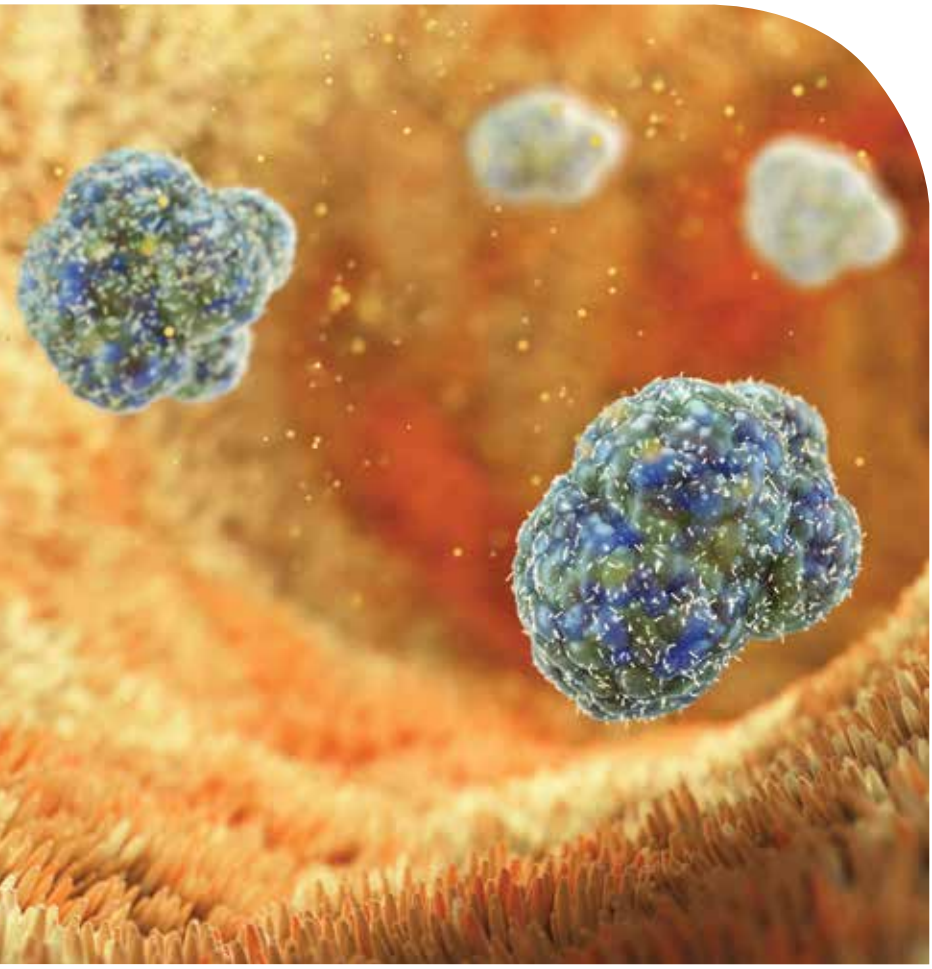
Regulatory Roundup



Cepheid point-of-care hepatitis C RNA test gets FDA authorization

The U.S. Food and Drug Administration (FDA) recently granted Cepheid marketing authorization for the Xpert HCV test and GeneXpert Xpress System, the first point-of care (POC) test for the potentially deadly hepatitis C virus (HCV).

Using a blood sample from the fingertip, the test detects HCV RNA in about an hour. The test may be performed in settings operating under a CLIA waiver, including certain substance use disorder treatment facilities, correctional facilities, syringe service programs, doctors' offices, emergency departments, and urgent care clinics. The test is indicated for adults with symptoms of risk for hepatitis C, but not for use in monitoring patients undergoing treatment or for use in screening blood, plasma, or tissue donors.

The newly authorized test allows patients to be tested and treated for HCV in a single visit, negating the need for follow-up appointments for test results and treatment. FDA officials said the test may result in hundreds of thousands more HCV patients being diagnosed and treated and less spread of the disease.

ROCHE EXPANDS ACCESS TO CERVICAL CANCER SCREENING AND RESPIRATORY DISEASE TESTING

The World Health Organization (WHO) has awarded a Roche human papilloma virus (HPV) test prequalification designation for use on the cobas 5800 System and for self-collected samples on the cobas 5800, 6800, and 8800 Systems.

The FDA has also granted the company emergency use authorization (EUA) for its cobas liat SARS-CoV-2, Influenza A/B & RSV nucleic acid test, an automated, multiplex, real-time polymerase chain reaction (RT-PCR) assay that runs on the cobas liat system.

The WHO prequalification better enables low- and middle-income countries to use Roche HPV screening solutions, including self-collection, in their national cervical cancer elimination programs, which will greatly increase access, Roche said.

It added that the EUA for the respiratory assay gives the test the potential to provide swift and precise results, expedite clinical decision-making processes, reduce unnecessary antibiotic usage, facilitate targeted treatment strategies, and ultimately enhance patient outcomes.

BIOMÉRIEUX RESPIRATORY/SORE THROAT TEST GETS FDA SPECIAL 510(K) CLEARANCE

bioMérieux's BIOFIRE SPOTFIRE Respiratory/Sore Throat (R/ST) Panel Mini has received FDA Special 510(k) clearance and a CLIA waiver, the company recently announced.

Used on the BIOFIRE SPOTFIRE system, the test is a multiplex PCR panel that detects five of the most common viral and bacterial causes of respiratory or sore throat infections in about 15 minutes. Samples can be taken from a nasopharyngeal or from a throat swab when a respiratory

Alllex / iStock

tract infection is suspected. The BIOFIRE SPOTFIRE system is a POC platform that can run either a large multiplex respiratory test with up to 15 pathogens or the five-pathogen test, allowing clinicians the flexibility to choose the right test, the company said.

The CLIA waiver is key to decentralized testing because it allows non-lab professionals to use the test, especially in urgent care centers, physician offices, local pharmacies, student health clinics, and emergency departments, bioMérieux added.

The World Health Organization and the U.S. Centers for Disease Control and Prevention have identified *C. auris* as a fungal pathogen of critical importance.

DIASORIN C. AURIS TEST GETS FDA DE NOVO AUTHORIZATION

The FDA granted de novo authorization to the Diasorin Simplexa C. *auris* Direct kit to test patients with suspected Candida auris (C. *auris*) colonization and help prevent spread in healthcare settings, Diasorin recently announced.

This real time PCR assay is used for the direct in vitro qualitative detection of C. *auris* DNA from an axilla/groin swab from patients suspected of C. *auris* colonization and detects the six C. *auris* clades that are circulating globally. Run on the LIAISON MDX, the system has a streamlined workflow that yields results in less than 2 hours, Diasorin added.

C. *auris* is challenging because patients may be asymptomatically colonized. C. *auris* colonization is a risk factor for invasive infections associated with high mortality rates and often does not respond to commonly used antifungal drugs. The World Health Organization and the U.S. Centers for Disease Control and Prevention have identified C. *auris* as a fungal pathogen of critical importance.

Diasorin officials said the authorization fills a much-needed gap in C. *auris* molecular detection and positions their company as the first molecular diagnostic vendor to commercialize a PCR test for the prevention and control of C. *auris* infection in healthcare settings.

FOUNDATION MEDICINE LIQUID BIOPSY TESTS NOW FDA APPROVED AS PROSTATE CANCER COMPANION DIAGNOSTIC

Foundation Medicine recently announced FDA approval for its FoundationOne Liquid CDx test to be used as a companion diagnostic for AKEEGA (niraparib and abiraterone acetate) from Janssen Biotech.

AKEEGA is the only FDA-approved dual-action tablet combining PARP inhibition and hormone therapy for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated metastatic castration-resistant prostate cancer, Foundation Medicine said.

BRCA1- or *BRCA2*-mutated mCRPC is an aggressive form of the disease, occurring in approximately 11% of diagnoses. The approval allows healthcare providers to leverage a minimally invasive liquid biopsy to identify additional patients with *BRCA* mutations and insufficient tumor tissue available for traditional biopsy.

FoundationOne Liquid CDx analyzes more than 300 cancer-related genes to provide genomic insights. The test has several other companion diagnostic indications across non-small cell lung cancer, prostate cancer, breast cancer, and colorectal cancer, plus a pan-tumor indication specific to NTRK1/2/3 fusions.

C. DIFFICILE TEST GETS IVDR CERTIFICATION

TECHLAB, part of the SSI Diagnostica Group, recently announced that its C. DIFF QUIK CHEK COMPLETE test has received certification under the European in vitro Diagnostic Medical Device Regulation (IVDR).

The C. DIFF QUIK CHEK COMPLETE test is a rapid membrane enzyme immunoassay designed for the simultaneous detection of *Clostridioides difficile* (C. *difficile*) glutamate dehydrogenase (GDH) antigen and toxins A and B in a single reaction well. The test provides both GDH and toxin results within approximately 30 minutes, enabling healthcare professionals to differentiate between active C. *difficile* infection and colonization in a cost-effective and clinically relevant manner, the company said.

The company added that the assay is the first combined GDH plus toxin A/B test to get IVDR certification for a combined GDH plus toxin A/B test.

Industry Playbook

Quest Diagnostics to acquire OhioHealth outreach laboratory services

Quest Diagnostics recently announced an agreement to buy select assets of OhioHealth's outreach laboratory services business.

The transaction will broaden access to cost-effective and innovative laboratory services in Ohio, according to Quest. Providers and patients will benefit from access to Quest's test menu, network of patient service sites throughout the state, broad health plan coverage, and lower out-of-pocket costs for many services, the company said.

OhioHealth Regional officials said their company has the specialization and scale to ensure its patients have continued access to high-quality lab services that, in many cases, will be more affordable for patients. They added that Quest can deliver meaningful cost savings in lab services without sacrificing quality.

After the acquisition closes, most outreach testing performed by OhioHealth will transition to the Quest Diagnostics full-service laboratory in Pittsburgh, Pennsylvania. OhioHealth will continue to wholly own and operate its hospital labs, providing high-quality laboratory services for inpatient and hospital-based outpatient care as well as anatomic pathology and oncology.

ALZPATH ANNOUNCES LICENSING AGREEMENT WITH ROCHE FOR ALZHEIMER'S TEST

ALZpath, which develops diagnostic tools for Alzheimer's disease and related dementias, has announced a strategic license agreement with Roche for use of the ALZpath pTau217 antibody to develop and commercialize an Alzheimer's disease (AD) diagnostic blood test, to be offered on the Roche Elecsys platform.

The Roche pTau217 test recently received FDA Breakthrough Device designation and will be commercialized as part of an ongoing collaboration between Roche and Eli Lilly.

pTau217 is a critical blood biomarker for detecting the presence and progression of Alzheimer's disease. Research has shown that the assay using ALZpath's pTau217 antibody provides the same accuracy and reliability as more expensive and invasive PET imaging or cerebral spinal fluid testing while being more affordable, and less invasive, ALZpath said.

Researchers advising ALZpath said that incorporating a diagnostic reagent such as the ALZpath pTau217 antibody into widely used diagnostic platforms such as the Roche Elecsys could boost Alzheimer's disease research, accelerate the evaluation of promising interventions to treat and prevent the disease, and improve the assessment and care of people with memory problems.

NOWDIAGNOSTICS SECURES $22.5 MILLION IN SERIES B FUNDING

NOWDiagnostics (NOWDx) recently announced it has raised $22.5 million in Series B financing.

Led by DigitalDx Ventures, with notable investors including the Labcorp Venture Fund and Kompass Kapital Management, this oversubscribed funding round will be used to drive the commercialization of at-home diagnostic tests, expand the pipeline of tests, and support strategic hiring initiatives, NOWDx said.

NOWDx's First To Know Syphilis over-the-counter test, now undergoing Food and Drug Administration (FDA) de novo review, would provide an at-home result in minutes. In addition to

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the syphilis test, NOWDx has more than 30 diagnostic tests in the clinical research pipeline that have the potential to provide accurate results in minutes.

The patented technology platform that powers NOWDx products is involved in 75 patents issued and pending. The company's approach allows virtually any immunological assay to be accurately performed in one step at home using a small amount of capillary blood, yielding results in minutes. Their platforms also include saliva and plasma test technologies, enabling rapid testing at home without needing a blood draw or throat swab, the company said.

In addition to the syphilis test, NOWDx has more than 30 diagnostic tests in the clinical research pipeline that have the potential to provide accurate results in minutes.

TEMPUS AI ANNOUNCES PRICING OF INITIAL PUBLIC OFFERING

Tempus AI recently announced the pricing of its initial public offering of 11,100,000 shares of its Class A common stock.

Tempus focuses on selling genomic diagnostics tests across oncology and other areas, including neuropsychiatry, radiology, and cardiology to clinicians and hospital systems. The company uses artificial intelligence (AI) to interpret medical tests.

The gross proceeds to Tempus from the offering, before deducting underwriting discounts and commissions and other offering expenses payable by Tempus, were expected to be $410.7 million.

Wall Street analysts believe Tempus's clinical and molecular data library could lead to more powerful diagnostic tools. Before going public, Tempus was on the 202 and 2021 CNBC Disruptor 50 lists, Reuters has reported.

ROCHE SUES STANFORD UNIVERSITY STARTUP OVER TRADE SECRETS

Roche recently sued Stanford University and medical technology startup Foresight Diagnostics in California federal court, alleging that Foresight improperly used Roche genetic sequencing trade secrets to develop competing cancer detection tests.

At issue is a deal that Roche made with two of Foresight's founders, who are also Stanford University professors. The professors previously helped establish Capp Medical, which Roche purchased in 2015 to obtain Capp's genomic cancer detection platform CAPP-Seq, the lawsuit says.

Roche requested an unspecified amount of monetary damages and asked the court to force Stanford and Foresight to provide patent applications that allegedly cover Roche's technology.

The lawsuit alleges that the two Stanford professors and a third in 2020 secretly cofounded Foresight, which improperly used CAPP-Seq to develop an expanded approach to capturing and analyzing circulating tumor DNA. The suit also alleges that the professors violated their Roche contract provisions about protecting confidentiality of Roche information, assigning certain inventions to Roche, and disclosing potential conflicts of interest.

A prepared Foresight statement maintains that Stanford owns the patents in dispute. It says that Foresight's founders created the technology at issue using Stanford's time and resources, under agreements with Stanford, and that Roche has known that Foresight has had exclusive rights to this intellectual property for many years. It contends that Roche's litigation is a negotiating tactic. "Foresight intends to vigorously defend this litigation and demonstrate that Roche's allegations are baseless," the statement adds.

Stanford neither made a statement about the lawsuit available nor responded to requests for comment.

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Ask The Expert

Clinical decision support for preterm hyperbilirubinemia

By Yi Xiao, PhD, DABCC, FADLM

What are clinical decision support (CDS) tools?

A: CDS tools are digital solutions designed to assist healthcare providers to improve patient outcomes, reduce medical errors, and increase compliance with standards of care. Common applications include preventing the overuse of certain tests to support laboratory stewardship and reminding healthcare providers of newly implemented workflows to ensure adherence.

How can CDS tools help evaluate preterm infants for hyperbilirubinemia?

CDS tools can automate many manual evaluation steps that may otherwise lead to inconsistent and delayed evaluations of hyperbilirubinemia.

Accurate and timely evaluation of hyperbilirubinemia is critical for preterm infants since they are at higher risk of developing kernicterus and irreversible damage to the brain. With prompt evaluation and intervention, most cases of kernicterus can be prevented. Unfortunately, unlike newborn infants 35 or more weeks of gestation, there is limited consensus on how to evaluate preterm infants for hyperbilirubinemia.

Most clinicians use medical decision levels (MDLs) based on serum total bilirubin results and a combination of factors including the patient's gestational age, age, and weight to guide the initiation of phototherapy or exchange transfusion.

Although the evaluation workflows vary among medical institutions, multiple manual steps are generally followed: 1) identify preterm infants at risk of developing hyperbilirubinemia; 2) retrieve information scattered across different databases within the laboratory information system (LIS) and electronic health record (EHR), such as the most recent bilirubin result, specimen collection date/time, gestational age, birth date/time, and the most recent weight; 3) perform the necessary calculations, such as a preterm infant's age in hours; 4) identify the corresponding MDLs to initiate phototherapy or exchange transfusion from a worksheet, nomogram, or chart, as indicated by each medical institution's policy; 5) compare the identified MDLs with the most recent bilirubin result; and 6) order phototherapy or exchange transfusion, if not already in place and not contraindicated.

This multistep manual evaluation workflow is laborious, and a 4% error rate was reported for manual hyperbilirubinemia risk stratification. Children's Hospital Los Angeles implemented a CDS tool and has significantly reduced delayed phototherapy orders. Nonetheless, CDS tools are only meant to assist clinical decision-making, not to replace clinical judgment and dictate clinical practices, as each case is unique.

What are some challenges to implementing a CDS tool to manage neonatal hyperbilirubinemia?

Early engagement of the hospital IT team is critical to implementing CDS tools with complex algorithms. Conventional LIS tools are limited, as some patient information required to evaluate hyperbilirubinemia — including gestational age, birth time, and weight — is stored in other modules of the EHR and cannot be readily used by the LIS. Support from healthcare providers is also essential.

In addition, laboratory medicine professionals, healthcare providers, and the hospital IT team must discuss many nuances. What are the manual steps to be automated and replaced? What happens when critical information is later documented or corrected? Is the automated evaluation process triggered by each new bilirubin result, or as indicated by healthcare provider? How should evaluation results be communicated? Are there other capabilities of the CDS tool that may be beneficial? Thoroughly discussing each decision is essential to ensure that healthcare providers' needs are fully addressed, and limitations are clearly understood.

Finally, teamwork is required to thoroughly evaluate the CDS tool, including multiple iterations with collaborative discussions. It would also be beneficial to track relevant quality indicators, such as the number of delayed phototherapy orders and length of stay for preterm infants with hyperbilirubinemia, in order to monitor the outcome of this quality improvement project.

Yi Xiao, PhD, DABCC, FADLM, is an assistant professor of clinical pathology at the Keck School of Medicine of University of Southern California and the assistant director of the core laboratory at Children's Hospital Los Angeles.

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