July/August 2024

CLN Clinical Laboratory News

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MACHINE LEARNING IDs miRNA SIGNATURES

93.75%

Model's accuracy for esophageal cancer miRNAs

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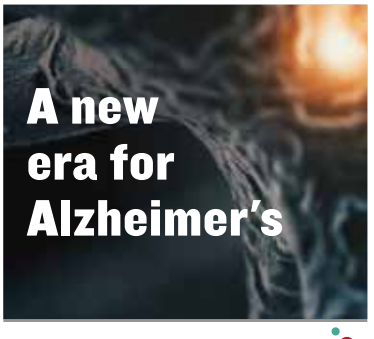

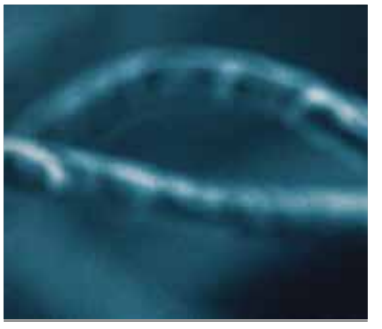

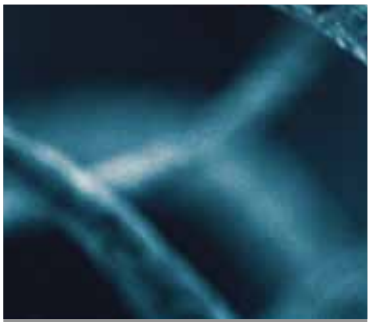

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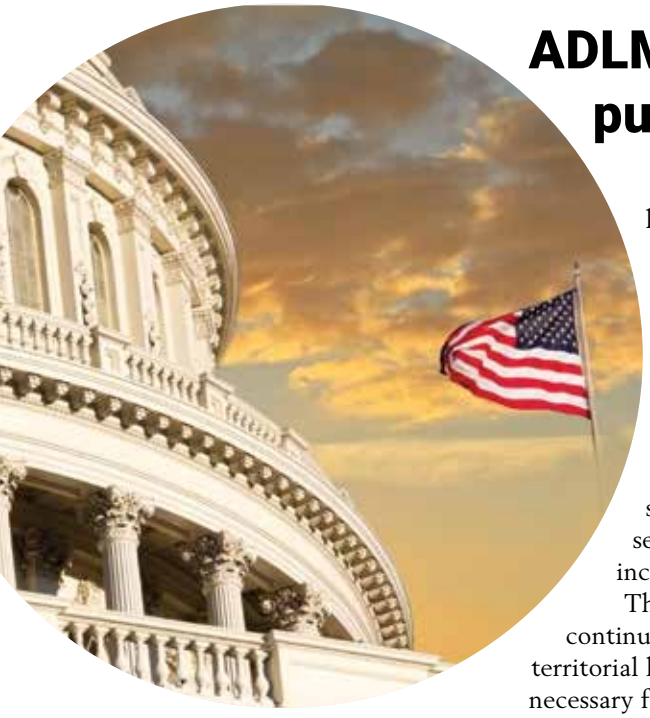

ADLM presses Congress for public health data modernization

The Association for Diagnostics & Laboratory Medicine (ADLM, formerly AACC) has joined a coalition of dozens of healthcare organizations that are urging Congress to fund public health data infrastructure revitalization efforts.

In a letter to congressional leaders, the coalition seeks at least $340 million annually for the Centers for Disease Control and Prevention's (CDC) Public Health Data Modernization initiative. The funds are earmarked for the creation and upkeep of state-of-the-art data systems and a skilled information technology workforce, both of which are vital to the nation's health security, the letter notes.

The letter emphasizes the critical role of public health data in swiftly identifying, tracking, and responding to a range of public health threats. With the speed of change in information technology, the need for updates, software patches, security vulnerability protection, and upgrades in public health data systems becomes increasingly pressing, the letter argues.

The organizations project that a 5-year investment of $7.8 billion is necessary for continuous improvement in public health infrastructure at the state, Tribal, local, and territorial levels. "Public health data is not only needed during an emergency response; it is necessary for people and communities to thrive by rapidly identifying, tracking, and responding to daily public health threats of all types — acute, chronic, and emerging," the letter states.

CMS PROJECTS NATIONAL HEALTH EXPENDITURE SURGE BY 2032

The Centers for Medicare & Medicaid Services' (CMS) Office of the Actuary has released a report that projects a considerable rise in U.S. healthcare spending through 2032. The report forecasts national health spending to grow annually by an average of 5.6%, outpacing the 4.3% predicted growth in gross domestic product (GDP). This imbalance will increase healthcare's share of GDP from 17.3% in 2022 to 19.7% by 2032.

Key contributors to this growth will be Medicare and retail prescription drug spending. CMS now expects that average annual Medicare spending growth will be 7.4% for 2023-2032. It predicts growth then a slight slowdown to 7% in 2030-2032, after the last of the baby boomers (people born between 1946 and 1964) enroll in 2029. Average annual growth in retail prescription drug spending of 6% is expected over 2023-2032. "The impact of new drug introductions, particularly for oncology, immunology, and diabetes, is expected to put upward pressure on growth across all payers," CMS said.

LEAP IN MINORITY HEALTHCARE COVERAGE TOUTED BY BIDEN ADMINISTRATION

The Department of Health and Human Services (HHS) recently released five reports on health insurance coverage that the administration says demonstrate significant advancement in healthcare coverage for minority communities. HHS called it a "direct consequence of the Affordable Care Act (ACA)."

The reports underscore a substantial reduction in the uninsured rate among several minoritized groups from 2010 to 2022. These changes in the uninsured include Black Americans, from 20.9% to 10.8%; Latinos, from 32.7% to 18%; Asian Americans and Pacific Islanders, from 16.6% to 6.2%; and Native Americans, from 32.4% to 19.9%.

"The data mirrors our steadfast commitment to making healthcare a universal right, irrespective of race or background," stated HHS Secretary Xavier Becerra.

Overall, the reports show that the national uninsured rate reached 7.7% in 2023, which is the first year the uninsured rate has been below 8% since this number has been tracked in federal surveys. That also marks a nearly 50% decrease since before the ACA.

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Is mass spectrometry ready to go from the lab to the operating room?

Hannah Brown, PhD

Intraoperative ambient ionization mass spectrometry promises to add more precision to surgical oncology.

Cancer diagnosis and prognosis increasingly relies on the analysis of molecular features from tumor biopsies. Since its first application in tissue sample analysis in 2005, ambient ionization mass spectrometry (MS) has made significant strides, and helped reshape the landscape of intraoperative molecular diagnostics.

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This article describes the recent advances in intraoperative MS with a focus on ambient ionization techniques and the challenges that need to be addressed for clinical implementation.

MOLECULAR FEATURES IMPROVE CANCER DIAGNOSIS AND TREATMENT

The predominant method for tumor diagnosis during surgery is based on a technique developed more than 150 years ago — frozen section histopathology. In addition to being time-consuming, the microscopic review of frozen sections is limited insomuch as it is primarily used only to provide an initial diagnosis of tissue biopsies, confirm the nature of the lesion, and ascertain the need for surgical resection. Nonetheless, this method leaves the diagnostic consultation incomplete and, at times, inconclusive in the absence of relevant molecular features. Noninvasive medical imaging methods, although helpful for determining surgical approach and extent of resection, do not allow for the comprehensive analysis of molecular features.

Molecular features of cancer have become significant factors for informing patient prognosis and clinical decision-making. These features often offer more accurate indicators than cellular morphology and imaging alone. Consequently, treatment approaches have shifted from a one-size-fits-all approach towards protocols that are tailored to the unique molecular profile of a patient's tumor. However, enacting this personalized approach intraoperatively requires an intraoperative assessment of molecular features, which has only recently become possible.

MS ENABLES RAPID MOLECULAR ANALYSIS

There is a clear clinical need for novel technologies that will enable rapid disease diagnosis based on molecular features, ideally from unprocessed samples. MS is a highly sensitive and powerful analytical technique capable of detecting and quantifying diagnostic molecules (specifically metabolites, lipids, and proteins) from complex matrices. Ambient ionization MS provides limits of detection in the sub-parts-per-million range on complex tissue samples. For these reasons, MS tissue analysis methods may be able to provide clinically relevant diagnostic information on biological specimens at the time of surgery. A minimum requirement for surgical relevance is that a technique provides reliable molecular data rapidly while using unprocessed samples. However, intraoperative MS faces barriers to implementation due to the time required

for sample preparation and an antiquated imperative to combine separation techniques such as gas chromatography with MS.

Mass spectrometry is a highly sensitive and powerful analytical technique capable of detecting and quantifying diagnostic molecules from complex matrices.

AMBIENT IONIZATION METHODS TAKE MS TO THE PATIENT

Ambient ionization methods overcame this barrier to implementation and are well-suited to intraoperative applications due to their ability to generate ions directly, under ambient conditions. This eliminates the need for ionization in a vacuum or for sample pretreatment or purification. The first tissue measurement completed with ambient ionization occurred in 2005 using an electrospray (desorption electrospray ionization). Since then, many ambient ionization methods have been developed, including those using an electrocautery knife, a surgical laser, and a drop of water. These methods differ in the amount of tissue being removed, analysis time, risk of cross-contamination, preanalytical factors, and surface resolution.

Despite variations in their acquisition methods, all these techniques are based on the premise that different types of tissues will exhibit distinct mass spectral profiles. Consequently, the measured profiles can be analyzed and used to differentiate between tissue types, such as distinguishing between cancerous and benign tissue, grades of cancer, and mutation status. In recent studies, researchers have used intraoperative MS methods to characterize tissue samples and differentiate between cancerous and benign material at tumor margins, both in vivo and in vitro.

For example, in brain cancer, metabolic profiling using ambient ionization has identified specific metabolites associated with different cancer types (glioma, lymphoma, meningioma), as well as the presence of prognostic isocitrate dehydrogenase mutations. In ovarian and thyroid cancer, the intensity profile of lipids within tumors has been used to distinguish cancerous margins from neighboring healthy tissue. The implementation of these methods in clinical and surgical settings has the potential to inform clinical decision-making, both intraoperatively and postoperatively, and enhance patient care by improving surgical outcomes, maximizing the extent of resection, reducing operation length, and increasing treatment efficacy.

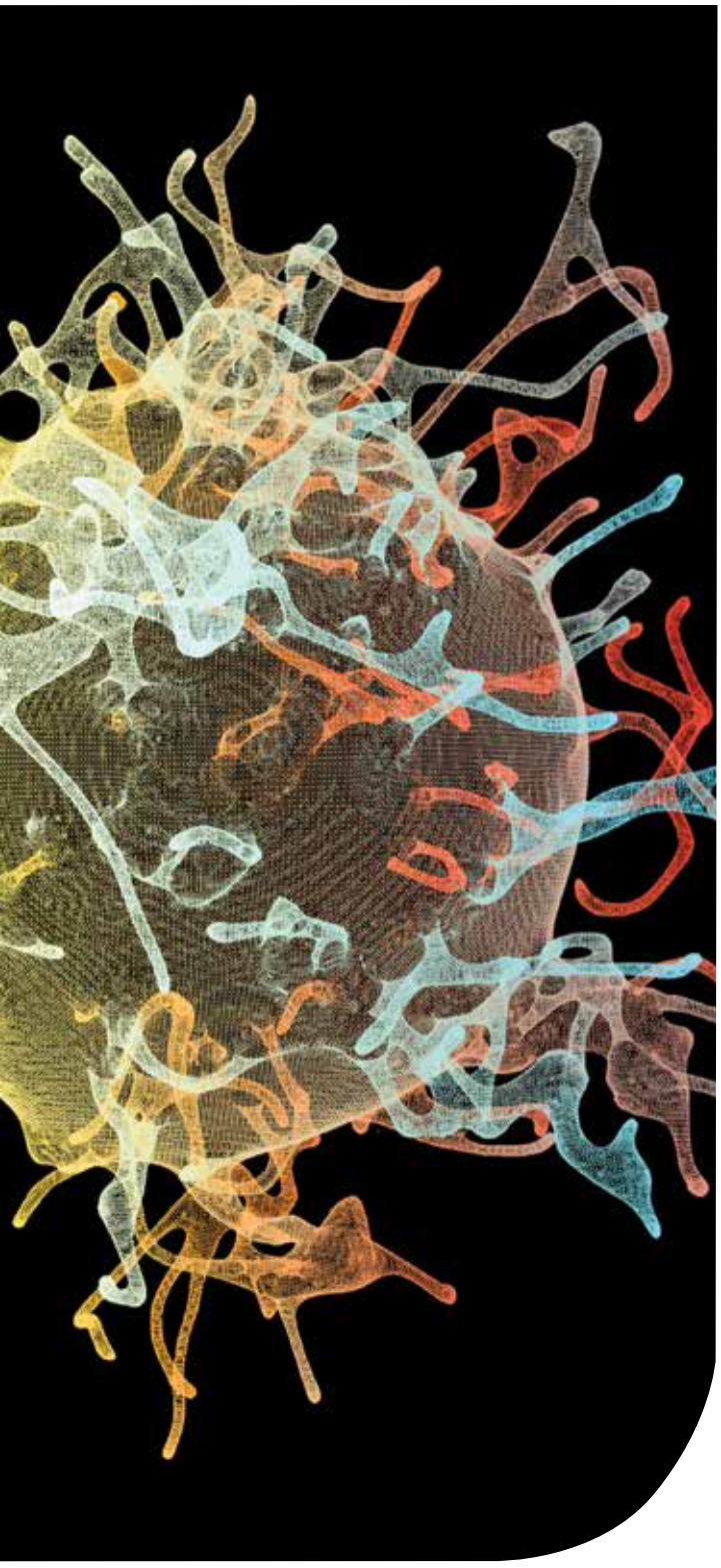
PATHWAY TO CLINICAL IMPLEMENTATION IS UNCHARTED, BUT PROMISING

The path to acceptance of ambient ionization MS as a standard medical tool is not clear. Regulatory hurdles pose challenges, with an unclear path to Food and Drug Administration approval, especially considering the new laboratory developed test rule and limited publication of multicenter studies. Additionally, for results to be acted upon intraoperatively, data processing workflows need to provide validated, actionable results in near-real time, but the regulatory path for integrated diagnostic algorithms remains to be determined. To translate these technologies to routine clinical practice, collaborations among teams with expertise in ambient ionization MS, instrumentation manufacturing, and clinical practice are critical. Medical institutions of all sizes will incorporate this technology to meet a variety of clinical needs, but only with access to commercially approved clinical and surgical instruments.

The potential of ambient ionization MS is high. Intraoperative MS has the potential to reshape the landscape of intraoperative molecular diagnostics. Its inherent strengths make it well-suited to play a significant role as a diagnostic modality that complements the standard of care by providing information on key molecular features currently unavailable intraoperatively. As we navigate the challenges and continue to innovate, the future of cancer diagnostics looks brighter and more precise.

Hannah Brown, PhD, is the clinical and forensic toxicology medical director at Hennepin Healthcare. She recently completed a clinical fellowship in clinical chemistry at Washington University in St. Louis School of Medicine.
+EMAIL: hannah.brown@hcmed.org

The Sample



Machine learning and miRNA show promise in diagnosing esophageal cancer

Recent research shows machine learning (ML)-based microRNA (miRNA) classifiers' potential for diagnosing esophageal cancer (EC) (J Appl Lab Med; doi: 10.1093/jalm/jfae037).

Often diagnosed at advanced stages, EC has high mortality rates, and current tests for the disease have limited efficacy. In response, the researchers wanted to harness miRNA's potential as a noninvasive diagnostic EC biomarker. The study aimed to determine miRNAs' diagnostic accuracy and the ability to distinguish miRNAs associated with EC from control miRNAs.

The researchers used ML software Waikato Environment for Knowledge Analysis (WEKA) and a custom-built TensorFlow Keras neural network to analyze complex biomolecular datasets of miRNAs. Three WEKA models — random forest, Hoeffding tree, and naïve Bayes — delivered promising results, with naïve Bayes reaching the highest accuracy of 93.75%. The TensorFlow Keras model achieved an average accuracy of 87.7% over five trials, a Matthews correlation coefficient (MCC) of 0.758, and an area under the curve of 0.910. When tested on independent data, TensorFlow Keras achieved even higher accuracy of 91%, with an MCC of 0.822 and an AUC of 0.896, demonstrating its ability to generalize and accurately identify miRNAs associated with EC in unseen data.

Although their study yielded an ML model that can accurately differentiate miRNAs associated with EC from unrelated miRNAs, the model might not directly apply to clinical settings where EC cases are significantly less prevalent than in the general population, the researchers noted.

They called for further studies to validate their findings and explore the full clinical potential of the approach. The researchers plan to focus on validating the model and enhancing its capabilities by incorporating a broader spectrum of noncoding RNAs and integrating more comprehensive clinical data. The data might include patient demographics and cancer stages. Testing the model in diverse, realistic, and clinical settings with datasets that reflect actual cancer prevalence rates will be crucial, the researchers noted.

GENETIC VARIANT COMMON IN BLACK INDIVIDUALS CONTRIBUTES TO CARDIOVASCULAR DISEASE

A genetic variant present in 3-4% of self-identified Black individuals in the U.S. increases the risk of heart failure and death (JAMA 2014; doi:10.1001/jama.2024.4467).

Previous research has shown that the amyloidgenic V142I variant of the transthyretin gene increases heart failure and mortality risk. The variant causes misfolding of the blood protein

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transthyretin, leading to deposits of abnormal amyloid protein in the heart and other parts of the body. In the heart, these deposits cause cardiac amyloidosis — thickening and stiffening of muscle — which can lead to heart failure.

The researchers aimed to better define the natural history of disease in V142I carriers during mid-to-late life, assess variant modifiers, and estimate cardiovascular burden in the U.S. population.

They analyzed data from a total of 23,338 self-reported Black participants initially free of heart failure in four large observational U.S. studies. Of these participants, 3.2% were V142I carriers. Participants had a mean of 15.5 years of follow-up. Outcomes were heart failure hospitalizations and all-cause mortality determined by generating 10-year hazard ratios for each age between 50 and 90. Using actuarial methods, the researchers estimated mean survival by carrier status and applied it to the 2022 U.S. population using U.S. census data.

The researchers found that V142I increased the risk for heart failure hospitalization by age 63 and the risk of death by age 72. The variant's contribution to heart failure risk increased substantially with age but was not itself increased by other known risk factors such as diabetes and hypertension. The team also showed that female and male carriers of the variant were equally at risk, contrary to some previous studies showing that men were more affected. This suggests that women are likely underdiagnosed, the researchers wrote. They estimated that individual carriers with the V142I variant live 2 to 2.5 years less than expected.

The researchers found that V142I increased the risk for heart failure hospitalization by age 63 and the risk of death by age 72.

The researchers say their data may guide discussions with patients about genetic screening and inform strategies for early targeted therapies.

CELL-FREE DNA TEST PROPOSED FOR COLORECTAL CANCER SCREENING

An experimental cell-free DNA (cfDNA) blood test may be useful for colorectal cancer screening, according to recent research (NEJM 2024; doi: 10.1056/NEJMoa2304714).

Early detection could prevent more than 90% of colorectal cancer-related deaths, but more than one-third of people eligible for screening are not up to date with screening despite multiple available tests. An easy blood test could improve screening adherence, detect disease earlier, and reduce mortality related to colorectal cancer.

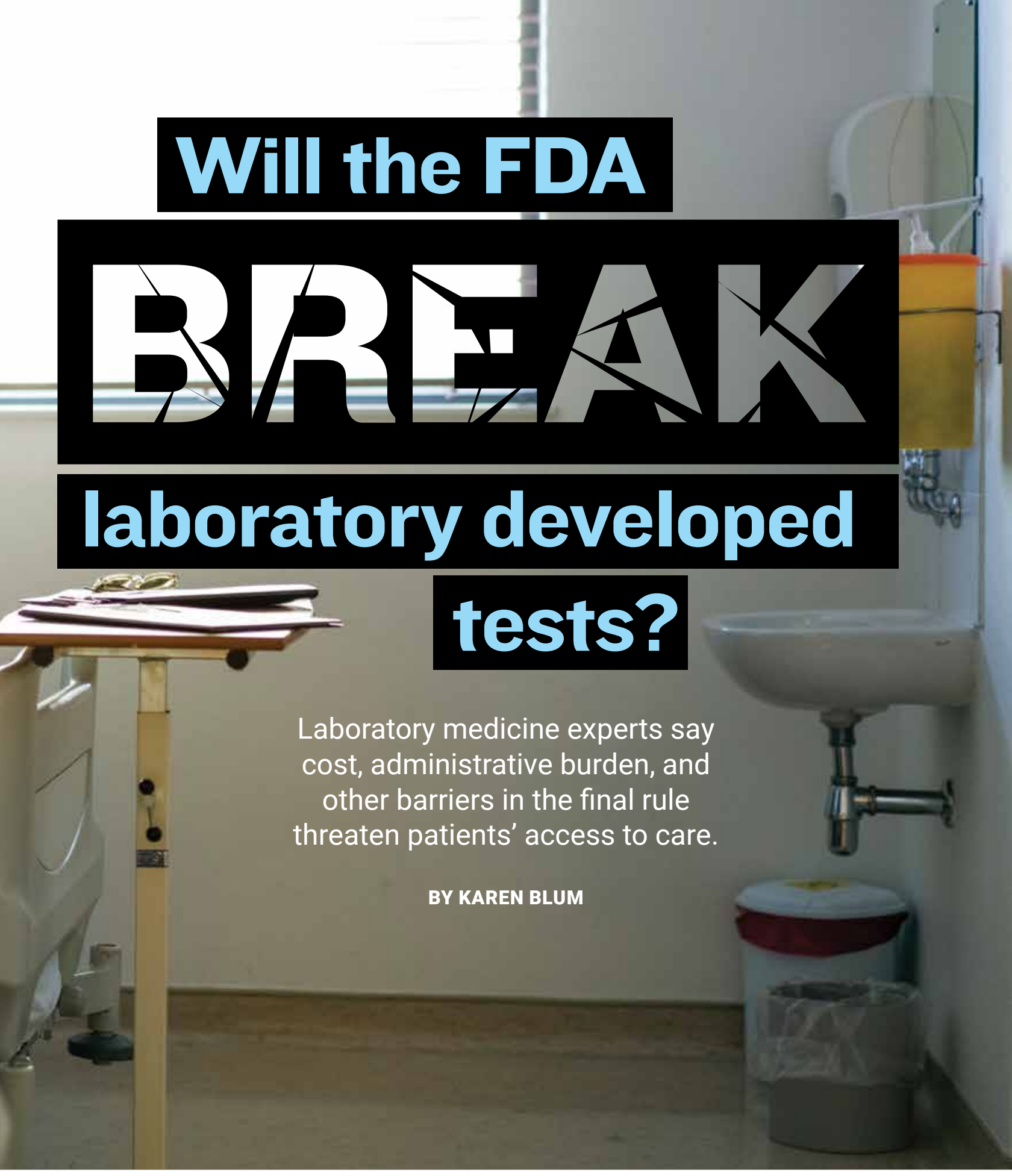
The researchers tested a cfDNA screening test in 7,861 average-risk patients ages 45 to 84. Primary outcomes were sensitivity for colorectal cancer and specificity for advanced neoplasia relative to screening colonoscopy. The secondary outcome was sensitivity for precancerous lesions.

A total of 83.1% of participants with colorectal cancer detected by colonoscopy had a positive cfDNA result and 16.9% had a negative result, for a sensitivity of 83.1% (95% CI, 72.2-90.3). Sensitivity for stage 1, 2, or 3 colorectal cancer was 97.5% (95% CI, 75.3 to 94.1). Sensitivity for advanced precancerous lesions was 13.2% (95% CI, 11.3 to 15.3).

A total of 89.6% of the participants without colorectal cancer or advanced precancerous lesions identified on colonoscopy had a negative cfDNA blood-based test, while 10.4% had a positive cfDNA blood-based test. The researchers said these results indicate a specificity for any advanced neoplasia of 89.6% (95% CI, 88.8-90.3). Specificity for negative colonoscopy (no colorectal cancer, advanced precancerous lesions, or nonadvanced precancerous lesions) was 89.9% (95% CI, 89.0-90.7).

In average-risk patients, the cfDNA test had a specificity of 83% for colorectal cancer, 90% for advanced neoplasia, and 13% for advanced precancerous lesions.

Blood-based testing offers a colorectal cancer screening alternative to the available stool-based tests and may improve screening participation and early detection of colorectal cancer, the researchers said.



Will the FDA BREAK laboratory developed tests?

Laboratory medicine experts say cost, administrative burden, and other barriers in the final rule threaten patients' access to care.

BY KAREN BLUM

Much to the dismay of many laboratorians nationwide, the Food and Drug Administration (FDA) on May 6 issued its final rule on laboratory developed tests (LDTs). The rule stakes claim to regulation of laboratory testing services as in in vitro diagnostics (IVD) devices defined by the Federal Food, Drug, and Cosmetic Act. Although the agency will not immediately require FDA clearance or approval of all LDTs, and defined several carveouts for "enforcement discretion," even tests that fall into these special categories will require new documentation, compliance systems, and reporting to the FDA that laboratories have never done.

The FDA spelled out a four-year plan to implement the changes. However, it is likely that some of the provisions may wind up altered because of at least one lawsuit challenging the FDA, the presidential election in November, or actions from Congress, experts say.

"Clinical laboratories currently have no infrastructure to do what the FDA wants us to do, and 4 years is too aggressive a timetable," said Dennis Dietzen, PhD, DABCC, FADLM, professor of pathology and immunology at Washington University School of Medicine and medical director of laboratory services at St. Louis Children's Hospital. Even when using so-called "grandfathered" tests, labs still have to comply with quality documentation records and registration and reporting of errors, he said, and some patients, particularly newborns whom he designs tests for, could face reduced access to testing or face delays: "I think we're all hopeful that this is going to get changed, delayed, or annulled in some way."

WHAT'S NEW IN THE RULE

The FDA had considered an LDT to be an in IVD intended for clinical use and designed, manufactured, and used within a single laboratory certified under CLIA to perform high-complexity testing, said Elizabeth Hillebrenner, associate director for scientific and regulatory programs at FDA's Center for Devices and Radiological Health, during a May 14 FDA webinar to explain the rule.

For years, FDA maintained enforcement discretion, she said, as LDTs were mostly performed in small volumes by laboratories serving their local communities, employed manual techniques, and were intended for use in diagnosing rare diseases. Today, labs offer IVDs as LDTs more often in high volume for large, diverse populations; increasingly rely on high-tech or complex instrumentation and software; and are used in laboratories outside a patient's healthcare setting, she said. Additionally, they are more commonly performed by independent labs, using instruments or other components not legally marketed for clinical use, and then marketed nationwide.

"As a result of these evolutions in the testing landscape, FDA has long recognized the need for a change in the agency's general enforcement discretion approach for LDTs," Hillebrenner said. "We believe this rule will better protect the public health by helping to assure the safety and effectiveness of IVDs offered as LDTs while also accounting for other public health considerations, such as patient access and reliance."

The rule, published May 6 and officially taking effect July 5, requires laboratories to comply with a litany of requirements over a four-year "phase out" period, explained Jonathan Genzen, MD, PhD, chief medical officer and senior director of government affairs at ARUP Laboratories, in a May 23 webinar hosted by ARUP (See chart, page 14).

In one year — by May 6, 2025 — laboratories need to comply with stage 1 requirements, including medical device reporting, requirements related to device correction and removal from the market, and maintaining files of complaints about assays.

By May 6, 2026, laboratories need to comply with stage 2 requirements for LDTs including registration and listing, labeling, and investigational use.

"Labeling is something that I would urge laboratories to start reading about early on to make sure that they can comply within that two-year timeframe," Genzen said. "There's a lot of important information in those documents and labs would need to compile that information according to FDA requirements. And if your LDTs are being used in investigational studies by other individuals, there may be additional requirements that the laboratory

"Clinical laboratories currently have no infrastructure to do what the FDA wants us to do." — Dennis Dietzen

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must now follow, described in the Code of Federal Regulations."

Labeling also includes information on unique device identifiers (UDIs) — requirements specifically related to labeling that help laboratorians trace back each individual component or reagent, he added. "This is going to be very challenging for laboratories that are not physically manufacturing kits but assembling these items as test systems. That's why I recommend people start studying labeling early on."

By May 6, 2027, laboratories need to comply with stage 3 quality system requirements other than complaint files. "This is also a big deal," Genzen said, and another area that labs should look into early "because there are significant requirements related to how you do your design work related to LDTs and how you document information that is probably different than the way that you are documenting information currently."

By November 6, 2027 (stage 4) and May 6, 2028 (stage 5), laboratories need to submit certain assays for premarket review. Stage 4 relates to high-risk IVDs requiring premarket authorizations, and stage 5 relates to moderate- and low-risk IVDs that would require the 510K or de novo review or clearance.

There are several areas in which the FDA said it intends to continue enforcement discretion, Genzen and Hillebrenner said: "1976-type" LDTs, or manual tests that involve no automated preparation or interpretation, such as immunohistochemistry tests or tests that use staining antibodies and general purpose reagents for cytology, hematology, and bacterial infections; human leukocyte antigen tests specifically for transplant; forensic tests intended solely for law enforcement/forensic purposes; and LDTs developed and performed within Veterans Administration hospitals and the Department of Defense.

Exclusions also generally will apply to the following: LDTs approved by the New York State Department of Health's Clinical Laboratory Evaluation Program; LDTs marketed prior to May 6 that either have not been modified or modified in certain limited ways; nonmolecular antisera LDTs for rare red blood cell antigens; and LDTs developed and performed by a laboratory integrated within a healthcare system for an unmet need of patients receiving care within the same healthcare facility

This last exception is an area hospital laboratories will carefully need to scrutinize, Genzen said. For example, FDA does not consider "unmet need" to apply to patients being treated at an affiliated hospital with a different corporate ownership than the laboratory. The policy also is limited to LDTs ordered by a healthcare practitioner on the staff or who has credentials and privileges at a facility owned and operated by the same healthcare system employing the laboratory director and performing the LDT. "They've created a very restrictive definition of unmet needs that actually is not going to be applicable in many settings," he cautioned.

As detailed as the rule is, there are still many unanswered questions, such as what to do about tests scheduled to be released before the stages set in, Genzen told *CLN*: "We will need much more specific information."

"I'm concerned about the impact on diagnostic innovation going forward, that the ... financial burden of introducing new tests will increase significantly."
— Jonathan Genzen

LABORATORIES QUESTION FDA'S DECISION — AND FILE SUIT

ADLM has outspokenly opposed this rule since a draft was released in October 2023, advocating for the FDA to withdraw their proposed rule and work with the laboratory community, patients, and Congress to update CLIA standards, which since 1988 have been the mechanism for regulating LDTs.

"ADLM agrees that increases in the number and complexity of LDTs may necessitate a review of the regulations governing these critically important clinical testing services … [but] is concerned that extending FDA oversight to LDTs will duplicate the existing regulatory structure, diverting limited laboratory resources from the provision of care to new, unnecessary administrative requirements," ADLM president Octavia Peck Palmer, PhD, FADLM, said in written testimony before the House Energy and Commerce Subcommittee on Health in March 2024.

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What does the final rule mean for my laboratory?

Requirement and relevant section from Title 21 in the Code of Federal Regulations	Implementation stage	Date	1976-Type	HLA for Transplant	Forensic	VHA/DoD	NY CLEP	Unmet Need	Currently Marketed	Rare RBC Antigens	New LDT	Minor Mod. to Curr. Mark.	Signif. Mod. to Curr. Mark.	Mod. Other's 510(k)	Mod. Other's PMA
MDR, Correction, Removal (§ 803 and § 806)	1	May 6, 2025	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Complaint Files (§ 820.198)	1	May 6, 2025	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Registration (§ 807)	2	May 6, 2026	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Listing (§ 807)	2	May 6, 2026	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Labeling (§ 809.10)	2	May 6, 2026	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Investigational Device (§ 812)	2	May 6, 2026	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Design Controls (§ 820.30)	3	May 6, 2027	No	No	No	No	Yes	No	No	No	Yes	No*	Yes	Yes	Yes
Purchasing Controls (including supplier controls) (§ 820.50)	3	May 6, 2027	No	No	No	No	Yes	No	No	No	Yes	No*	Yes	Yes	Yes
Acceptance Activities (receiving, in-process, and finished device acceptance) (§ 820.80 and § 820.86)	3	May 6, 2027	No	No	No	No	Yes	No	No	No	Yes	No*	Yes	Yes	Yes
CAPA (§ 820.100)	3	May 6, 2027	No	No	No	No	Yes	No	No	No	Yes	No*	Yes	Yes	Yes
Records (part 820, subpart M)	3	May 6, 2027	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Premarket Review (high risk); PMA	4	Nov 6, 2027	No	No	No	No	No	No	No	No	Yes	No	Yes	No	Yes
Premarket Review (mod/low risk); 510k and De Novo	5	May 6, 2028	No	No	No	No	No	No	No	No	Yes	No	Yes	No	N/A (PMA)

Chart courtesy of Jonathan Genzen, MD, PhD, ARUP Laboratories.

*Pending clarification.

"The FDA states that laboratories that develop LDTs are medical device manufacturers and must be subject to the same requirements," Peck Palmer said. "The agency assumes that hospitals, small community testing facilities, and other providers can afford the technical and administrative staff necessary to perform the studies, file the submissions, provide supplemental information, and continue an ongoing dialogue with the FDA to gain agency clearance or approval of an LDT. We are concerned that the costs associated with this duplicative regulatory structure will be significant for many healthcare facilities, forcing them to discontinue or scale back these services."

Other laboratorians have expressed alarm, too.

Dietzen said the unmet need clause may be helpful for laboratories like his that build tests when no FDA-approved alternative exists, Dietzen said, "But the way that we have to build these is going to be drastically different than the way we do it today under CLIA." The FDA has thrown additional requirements on top of those from CLIA, he added, "and in some cases, they are likely to be duplicative or maybe even contrary to one another."

"I'm concerned about the impact on diagnostic innovation going forward, that the … financial burden of introducing new tests will increase significantly," Genzen said. The FDA acknowledged in their regulatory impact analysis and final rule preamble that this may disproportionately affect smaller labs, he said: "Those are really important settings."

Many of the negative impacts will not appear until the second year or later after the rule's release, when the requirements hit and labs will decide whether to discontinue or outsource some testing, he added.

While some question the FDA's right to oversee LDTs, the agency did cite legal cases in their claim for this authority, said James Boiani, JD, an attorney with Epstein Becker Green in Washington, D.C. However, this has not ever been

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decided by courts, he noted, "so it's certainly open to challenge."

The American Clinical Laboratory Association (ACLA) and its member company, HealthTrackRx, already took action, filing a lawsuit on May 29 in the U.S. District Court for the Eastern District of Texas against the FDA to challenge its authority. Named as codefendants are the Department of Health and Human Services, HHS Secretary Xavier Becerra, and FDA Commissioner Robert Califf. ACLA has worked collaboratively with Congress, FDA, and others on legislation to establish "an appropriate regulatory framework for diagnostics," according to an ACLA news release announcing the suit. "Rather than continue that dialogue, FDA chose instead to act unilaterally and impose an ill-fitting device regime on laboratory testing services."

"If it is not vacated, FDA's unprecedented final rule will have devastating and far-reaching consequences not only for the nation's clinical laboratories, but also for the nation's entire healthcare system, including the millions of vulnerable patients who depend on the essential clinical testing services that laboratories provide," the complaint states. It includes declarations from Genzen as well as executives from Labcorp, Quest Diagnostics, and Mayo Clinic Laboratories.

It's likely that either additional laboratories will sue or Congress will somehow get involved, potentially as part of FDA's periodic negotiations for funding for its medical device user fee program, Boiani said. "There are going to be changes and revisions and challenges, probably in the courts and also on Capitol Hill, as this works its way forward to implementation."

There's a very high chance that this is not going to play out exactly as written, said Bruce Quinn, MD, PhD, a diagnostic consultant with Bruce Quinn & Associates, for several reasons. One, there are limited staff at the FDA and in the industry trained on proper regulatory submissions, and gathering many times that number will take time. This or additional potential lawsuits could tie up progression of the rule for at least a year or two. And, with the November presidential election on the horizon, a potential change in administration could upend things as well.

WHAT LABORATORIES CAN DO NOW

Meanwhile, as a first step, start assessing what the impact of the rule will be on your laboratory, Boiani advised. See what the new regulations will require and try to map out how it's going to impact your operations, so you have a sense of what sort of investments you may need to make if the rule goes forward, and whether it's worth challenging, he said. Consider the costs of the quality system and adverse event reporting requirements, registration fees, and whether you need any additional licenses from your state, as well as any Sunshine Act reporting payments to physicians.

Genzen concurred: "I strongly recommend people use this time to increase their own understanding of quality system requirements, labeling requirements, and even investigational use requirements if they have clinical services that are using their tests for research or investigational purposes."

Additionally, Boiani said, follow the guidances issued by the FDA and submit comments if you see a problem. The agency did adjust some pieces from the proposed to the final rule based on comments. "FDA has people with experience in the industry, but labs that are living this day to day are going to know the practical problems with what might be proposed," he said.

Some laboratories will go to one of two extremes, Quinn said. They'll ignore the rule completely, "which might seem rational, because something will probably happen. The other extreme would be devoting half of your cash flow trying to hire people and meet these rules. I really don't know what the answer is."

Meanwhile, "All of us are going to have to sit tight and watch how this plays out," Dietzen said.

FDA intends to hold additional webinars on specific aspects of the final rule, targeted enforcement discretion policies, and other matters applicable to IVDs including LDTs, Hillebrenner said. ADLM launched a series of webinars on LDTs available on www.myadlm.org.

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RESOURCES:

- **ADLM webinars:**
www.myadlm.org/advocacy-and-outreach/congressional-briefings

- **FDA Laboratory Developed Tests website:**
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- **Federal Register final rule:**
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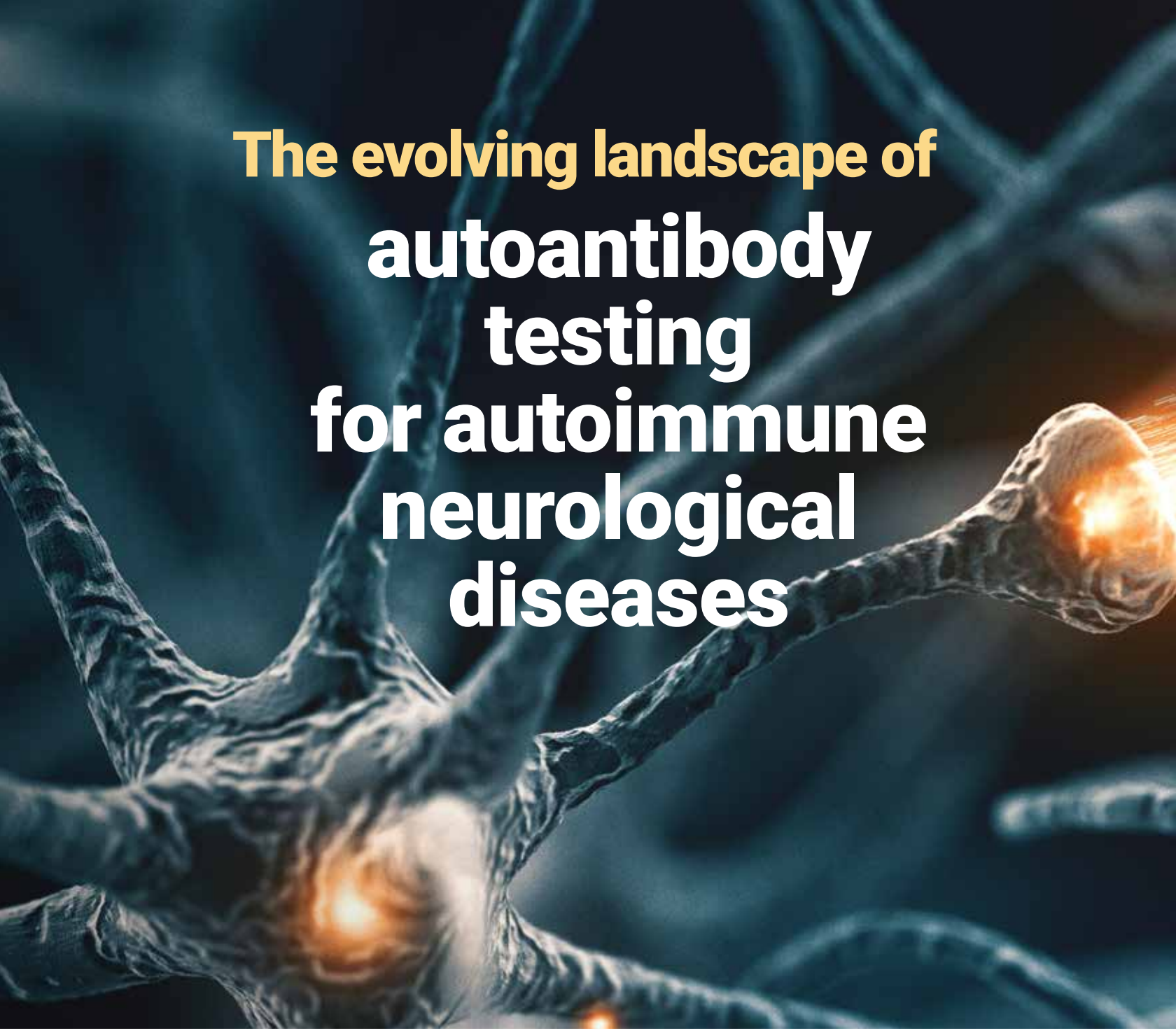

The evolving landscape of autoantibody testing for autoimmune neurological diseases

Clinical laboratories must keep up with current literature and monitor utilization carefully as new antibodies are discovered.

Autoimmune neurology is a subspecialty of neurology that focuses on the interaction between the immune system and the nervous system. These autoimmune neurological disorders occur when the immune system misfires against components of the nervous system, leading to a range of diverse neurological symptoms and conditions. The immune system's impact on the nervous system can manifest in numerous ways, affecting the central nervous system, spinal cord, peripheral nerves, and neuromuscular junction.

The challenge with autoimmune neurological disorders is that they often mimic more common underlying etiologies, making them difficult to diagnose in a timely manner. Yet prompt treatment often is critical, with significant impact on patient morbidity and mortality.

BY JACK L. WU, PHD, MLS(ASCP)CM AND JOHN R. MILLS, PHD, DABCC, FADLM

The diagnosis requires clinicians to consider the clinical presentation, neurological examination, imaging and electrodiagnostic testing, as well as laboratory investigation. The diagnostic criteria for autoimmune neurological disorders frequently include identifying underlying neural-specific antibodies in patient's serum or cerebrospinal fluid (CSF). These antibodies are critical biomarkers that help establish the diagnosis.

The field of autoimmune neurology is ever-changing. In the last several years there have been new paraneoplastic neurological syndrome (PNS) criteria (*1*), calls for updates to autoimmune encephalitis diagnostic criteria (*2*), newly discovered antibodies and corresponding tests, and a move towards phenotype-specific antibody evaluations. This article explains the current biomarkers and assays available, and how clinical laboratories should select and interpret them to ensure the best patient care possible.

TRACKING A GROWING LIST OF BIOMARKERS

Accelerated discovery of new autoantibodies and their nervous system targets has led to an expanding list of clinically relevant antibody biomarkers. These biomarkers are critical as their detection can fulfill diagnostic

criteria, rule out certain diagnoses, aid in the search for malignancy and provide treatment guidance.

Dozens of new antibody assays are now offered clinically — distributed across a variety of phenotype-specific antibody evaluations or profiles. One of the largest autoimmune neurology antibody panels currently available includes measurement of thirty reportable antibodies (Mayo Clinic Laboratories; Autoimmune Movement Disorder, Evaluation). Discovery of new antibodies has significantly accelerated over the last 20 years, with more than one novel antibody being discovered per year thanks to new methodologies for antigen identification, translational research efforts to identify and characterize unique staining patterns in tissue observed on indirect immunofluorescence assays (IFA), and lastly, expansion of in vitro diagnostics companies into the field of autoimmune neurology.

Accelerated discovery of new autoantibodies and their nervous system targets has led to an expanding list of clinically relevant antibody biomarkers.

In addition to new antibody discoveries, researchers have elucidated the antigen identities of previously recognized tissue IFA patterns in recent years. Immunoprecipitation-mass spectrometry (IP-MS) has been used to identify several antigen targets which were previously only known by their unique staining pattern on tissue IFA. For instance, MAP1B was confirmed as the antigen target of the Purkinje cell antibody-type 2 (PCA-2) pattern, an IgG biomarker of PNS with small-cell lung carcinoma (SCLC) (*3*, *4*).

Similarly, DACH1 was recently identified as the antigen for the antineuronal antibody-type 3 (ANNA-3) pattern (*5*). Another antigen discovery technique with good yield has been phage display immunoprecipitation sequencing (PhIP-Seq), which uses a library of phage particles presenting peptides covering the whole human proteome or targeted subsets of the proteome. In 2019, researchers reported the identification of KLHL11 antibodies using PhIP-Seq on samples from twelve male patients who presented with similar neurological features near the time of a diagnosis of seminoma (*6*). Since then, KLHL11 antibodies have been offered as biomarkers for paraneoplastic autoimmune encephalitis associated with testicular cancers (*7*). Another recent study utilized protein microarrays for novel antigen/antibody discovery in autoimmune neurological diseases. The authors demonstrated that the protein microarrays were useful for detecting antibodies targeting intracellular antigens, but also detected antibodies that target cell surface antigens that were missed by PhIP-Seq (*8*).

Besides offering new antibody tests, laboratories must keep up with current literature assessing the clinical relevance and diagnostic value of historically offered antibody biomarkers. Previously described antibody biomarkers may prove to have inferior clinical utility and eventually must be retired in favor of other superior biomarkers.

For example, historically, laboratories tested for striational antibodies (StrAbs) in patients with myasthenia gravis (MG). A recent retrospective study spanning 6 years of testing concluded that, despite a statistically significant paraneoplastic association, StrAbs were neither specific nor sensitive in predicting malignancy or neurologic phenotypes (*9*), limiting their clinical utility.

Similarly, laboratories previously included N-type voltage-gated calcium channel (VGCC) antibodies as part of PNS antibody evaluations, but evidence from multiple studies suggested that they provide limited clinical value in the context of other superior prognostic antibody biomarkers, such as SOX1 antibodies, as predictors of malignancy (*10*, *11*). Both N-type VGCC and Striational antibodies have been removed from the disease-specific evaluations to improve the positive predictive value of these panels (*9*, *11*).

The discovery of clinically relevant antibody biomarkers will require laboratories to develop and implement novel tests. They will also need to implement ongoing improvements in testing methodologies and evolution of disease-specific antibody evaluations. Currently, most neural-specific autoantibody tests are brought to market as laboratory-developed tests.

APPROPRIATE UTILIZATION OF ANTIBODY TESTS

Test misutilization continues to be a concern in the field of autoimmune neurology. This is exacerbated by the complexity and cost of this testing. Individual antibody tests are generally not available as

standalone tests, with some exceptions, due to the heterogenous clinical presentations associated with a given antibody and the inability to associate a specific clinical presentation to a specific antibody in most cases. Because of this, ordering single antibody tests has low yield in most situations.

To overcome these limitations, laboratories have grouped antibodies based on associated clinical phenotypes. While ordering single antibody tests may be more cost-effective initially and provide shorter turnaround times, this practice is less efficient given the lack of a one-phenotype-one-antibody relationship. Using a single or limited testing panel will require additional testing in most cases, making this more expensive and time inefficient.

Another risk of individual orderable antibody testing is that critical antibodies will be missed due to lack of physician awareness. This is particularly problematic in the rapidly evolving field of autoimmune neurology as several new biomarkers become available each year. Rather, expert-designed antibody profiles provide testing for multiple antibodies centered around the clinical phenotype. These so-called phenotype-specific panels often include more than 10 unique antibody targets unique to a given clinical presentation.

At the same time, these larger antibody panels can be more expensive and have longer turnaround times compared with single orderable antibody test. Furthermore, the likelihood of a false positive result increases as more tests are performed, and this is exacerbated by the inclusion of targets with lower disease-specificity, such as StrAbs mentioned earlier (*12*). However, the need to accurately diagnose and differentiate rapidly developing diseases that are treatable, or to predict paraneoplastic malignancy, outweighs the limitations of panel testing, as early detection improves patient outcomes (*13*).

Most phenotype-specific neural antibody panels contain overlapping analytes due to overlapping antibody-phenotype associations (e.g., GABA-B receptor encephalitis may present with both rapidly progressing dementia as well as ataxia). Therefore, a detailed clinical evaluation with targeted panel testing is most appropriate. However, it is common for several concurrent panels with overlapping antibodies or testing to be requested with days or weeks of each other. In most cases, this redundant testing is inappropriate. Most reference laboratories will attempt to identify these potential errors, the process for detecting this misutilization is inefficient.

A recent study investigated the ordering practice for suspected autoimmune encephalitis and paraneoplastic disorders at a tertiary referral medical center (*14*). This study found that there was significant and unnecessary redundant panel testing ordered in ~10% of cases. Of these, there were very few instances where an additional antibody was discovered or where clinical management was positively affected, indicating that the practice has limited clinical utility. Familiarization with components of antibody testing panels is critical to eliminate redundant testing. Send-out laboratories may consider building mechanisms to detect and review redundant ordering to ensure clinical appropriateness.

Another common issue leading to poor test utilization is ordering neural antibody evaluations in patients with a low pre-test probability. Several algorithms have been developed to establish pre-test diagnosis probability and guide test ordering. The Antibody-Prevalence-in-Epilepsy (APE)/Antibody-Prevalence-in-Epilepsy-and-Encephalopathy (APE2) score can be used to predict the likelihood of neural-specific autoantibodies in autoimmune epilepsy cases (*15*), or in patients with cognitive dysfunction (*16*). The possibility of necrotizing autoimmune myopathy (NAM) can be predicted using an immune-mediated necrotizing myopathy (IMNM) calculator *(17)*. Institutions that have implemented these tools have reported reductions in inappropriate test ordering.

Lastly, to improve the overall diagnostic accuracy of panel testing, it is recommended that both serum and CSF samples be tested simultaneously in most cases of autoimmune encephalitis. Most antibody evaluations are available in formats for both serum and CSF, with few exceptions. The sensitivity or specificity for different antibodies vary according to the specimen type (See table online: www.myadlm.org/cln). Since, in most cases, positivity for a specific antibody cannot be predicted based on the clinical phenotype, the approach of testing both specimens ensure optimal clinical test performance.

For some antibodies, such as those targeting N-methyl-D-aspartate receptor (NMDAR) and GFAP antibodies, testing in CSF is more sensitive and specific. For others, such as LGI1 and CASPR2 antibodies, testing serum is more sensitive (18–20). When comparing the results from paired serum and CSF samples, the clinical specificity of GFAP antibody positivity for meningoencephalomyelitis was greater than 95% in CSF compared with less than 10% when positive in serum only (21). For some antibody targets, such as GABAB receptor and NMDAR, isolated positivity in serum is associated with a higher

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risk of false positivity. Laboratorians should take extra precautions when interpreting discordant results from different specimen types, especially when patients have atypical clinical presentations.

CHOOSING THE MOST APPROPRIATE NEURAL ANTIBODY DETECTION APPROACH

There are five major analytical techniques universally applied to detection of neural antibodies. These include tissue-based indirect immunofluorescence (IIF) or immunohistochemistry (IHC), recombinant cell-based assays (CBA), immunoblotting, ELISA, and radioimmunoprecipitation assays. In some cases, there are strong supportive peer-reviewed studies to support the use of specific testing methodologies for specific neural antibodies. However, for many neural antibodies, there have not been systematic studies addressing method-specific clinical performance (See table online for recommended testing methods per antibody).

Neural antibody biomarkers can target either extracellular (cell surface) or intracellular antigens. Antibodies targeting intracellular antigens are typically thought to be indirectly involved in the disease. These antibodies often have high affinity to nonconformational epitopes. Furthermore, they target single protein antigens rather than antigen complexes. These antibodies can often be detected using methods that do not maintain the antigen in its native conformation (e.g., IIF, immunoblot or ELISA). Examples of this include antibodies against the cytoplasmic protein Yo/PCA-1 or antibodies against the nuclear/cytoplasmic protein Hu/ANNA-1. These antibodies are most commonly measured utilizing IIF assays and confirmed with line immunoblot assays (LIA) or ELISA, where the antigen is at least partially denatured.

In contrast, clinically relevant antibodies against the NDMAR are directly involved in disease pathogenesis, where they bind and modulate the receptors off the cell surface. NMDAR antibodies cannot be readily detected by methods such as LIA or ELISA that utilize denatured protein subunits of the receptor. Instead, laboratories use CBAs used where the antigen is expressed recombinantly in human cells. This approach has proven to be the most sensitive and specific method for detecting NMDAR antibodies.

Testing methodologies should be considered based on the biological and physiological nature of the antibodies as well as their clinical use, such as screening vs. confirmation tests (*22*). Antibodies against collapsin response-mediator protein-5 (CRMP5), also called CV2, are onconeural antibodies associated with SCLC and thymoma (*23*, *24*). A study showed that 7.5% of seropositive samples identified by immunohistochemistry on rat brain tissue were missed by two widely used commercial LIAs, but positive on CBA (*25*).

Additionally, clinical laboratories should not depend solely on LIA for CRMP5 antibody testing nor use these tests as screening tests. A standard procedure with screening using tissue-based IFA followed by confirmation with a specific assay is recommended for CRMP5 antibody testing in most situations (*22*). In general, it is not optimal to use LIAs as the sole methodology for detection of neural antibodies for the reasons outlined above for CRMP5.

Most clinically relevant neural autoantibodies are of the IgG isotype. However, depending on the antigen, the clinically relevant antibodies can favor one or more of the IgG subclasses. Generally, anti-human pan-IgG is used as the secondary antibody in most assays, but using a subclass-specific secondary antibody can increase test specificity or provide additional clinical information in some situations (*26*, *27*). NF155 is paranodal protein that forms a protein complex with contactin-1 and CASPR1 to ensure the integrity of myelin in the nodes and paranodes. Studies have shown that detecting the IgG4 subclass of NF155 antibodies most strongly associates with suboptimal response to intravenous immunoglobulin (IVIG) therapy. NF155 IgG4 positive patients also have unique clinical and electrodiagnostic signatures, and favorable long-term outcomes when compared with NF155 cases with isolated IgM or antibodies of other IgG subtypes (*28*).

LABORATORY STANDARDIZATION AND QUALITY ASSURANCE

Most testing for antibodies related to autoimmune neurology occurs in a handful of large national reference laboratories and occasionally smaller specialty laboratories. The methods used, the composition of antibodies included in various panels, the testing algorithms followed, the provided interpretations, and the degree of consultation available all vary dramatically across laboratories.

Neural antibody biomarkers can target either extracellular or intracellular antigens.

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Therefore, although each of these laboratories offer an "autoimmune encephalopathy" antibody evaluation, there are significant differences between them.

Understanding the differences across laboratories has become more difficult in the last several years as the number of available antibody biomarkers increased, as well as the number of laboratories offering these antibody panels. Several studies have dealt with this problem.

To assess cross-laboratory agreement in neural antibody testing in Italian laboratories, an external quality assessment program was organized in 2018 (*29*). This study found partial or large interlaboratory disagreement across commercial and in-house tests for detecting antibodies against AQP4, MOG, and gangliosides. Even for laboratories using the same commercial kits, such as a commercial ELISA for myelin associated glycoprotein (MAG) antibodies, the researchers detected significant differences in results, indicating cross-laboratory difference in either performance or interpretation of the test.

Another international multicenter study of testing methodologies for MOG antibody suggested that live CBA showed excellent agreement (96%) across testing sites for high titer and negative samples, followed by fixed-CBA (90%), while ELISA showed no concordance with CBAs for detecting MOG-IgG (*30*). However, the agreement for borderline positive and negative samples were suboptimal across similar CBA assays (*30*). These studies highlight the need to improve the standardization of neural antibody testing across laboratories.

Part of the problem relates to the fact that these antibodies are rare, and given the limited number of laboratories performing the testing, there have not been standard reference material or external proficiency testing (PT) programs that readily allow laboratories to compare to their peers. To fulfill regulatory requirements, most laboratories resort to alternative assessment of performance (AAP) with internal blinded testing. Much of the autoantibody testing performed for autoimmune neurological disorders still depends on manual and subjective interpretation of indirect tissue IFA and microscopy-based CBAs. These assays are thus highly dependent on the experience of the individual interpreting the results under the microscope.

To fulfill regulatory requirements, most laboratories resort to alternative assessment of performance with internal blinded testing.

To further evolve and improve the field, there is a need to establish expert-led consensus criteria for the interpretation of tissue IFA and CBAs. This includes best practices for the use of testing algorithms, results interpretation, development of shared reference materials, movement away from subjective testing platforms where possible, and further effort to define the differences in testing methodologies.

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THE START OF A NEW ERA FOR Alzheimer's testing

What labs need to know about the promise and potential pitfalls of emerging blood-based tests for this condition.

BY GRACE BROWNE

There has long been a need for a better way of diagnosing Alzheimer's disease. The traditional route to diagnosis typically involves a pen-and-paper memory test and interviews with people close to the individual, which is not exactly misdiagnosis-proof.

Only a small minority of patients receive objective clinical tests that confirm the disease: PET scans of the brain that reveal amyloid plaques and spinal taps that measure amyloid proteins in cerebrospinal fluid. However, the former is costly, while the latter is an invasive procedure.

A new type of testing looks increasingly promising: blood testing. These tests work by measuring the presence of certain proteins in the blood associated with Alzheimer's disease. The advantages include a lower cost than brain scans and a less invasive approach than spinal taps. With new advancements come new challenges, though, and clinical labs need to be ready to help healthcare providers understand the capabilities and limitations of these tests.

NEW TESTS AND TREATMENTS COULD WORK HAND IN HAND

Researchers have been working on blood tests for Alzheimer's for a long time, "but it hasn't been until somewhat recently that there have been some successes analytically to make that happen," said Mari DeMarco, PhD, a clinical associate professor at the University of British Columbia's department of pathology and laboratory medicine and a clinical chemist at Providence Health Care. "So all of a sudden, it's become an opportunity."

So far, research is promising. The results of a 2024 study suggested that a blood test could detect Alzheimer's disease as accurately as standard spinal taps.

Aside from the gap in the market for cheaper, more accessible forms of testing, the need for a new approach to testing was also accelerated by the recent landmark development and approval of new drugs that treat the disease. These drugs work by targeting amyloid-beta (Aβ) pathology and have been shown to slow — though not halt — disease progression.

With the introduction of treatments for Alzheimer's, the number of patients who need to be tested for it has skyrocketed. A blood test could enable many more people to get a faster diagnosis and initiate treatment at the right time, which is crucial because the drugs work best at slowing the progression of the disease when it is still in its early stages and symptoms are mild. That's where the current gold standard methods for diagnosing the disease fall short — many patients may receive a diagnosis at a point in their disease progression when the treatments are no longer helpful.

"I think the whole idea of maybe moving treatment of amyloid early also spurred the development of having a blood-based test that can detect amyloid early in asymptomatic patients," said Danni Li, PhD, an investigator in the Advanced Research and Diagnostic Laboratory at the University of Minnesota.

Another reason the new treatments spur on the need for blood-based testing is the safety concerns associated with the drugs. During the clinical trials, a handful of patients died as a result of side effects, particularly brain swelling and hemorrhage. "Having a biomarker that's predictive of that would be very helpful for monitoring patients on therapy," DeMarco said. At the moment, patients are monitored using MRIs, which is "quite costly and cumbersome to the patient to have to go into repeat imaging," she added.

A blood test could also monitor how well new treatments work. And another major boon of accurate blood tests is that they could help to drive clinical research forward. A simpler, cheaper mode of testing makes it easier to sign participants up for a clinical trial, DeMarco said. "These types of discussions need to happen with patients as part of pre-test counseling."

"We need increased transparency on diagnostic performance data from the clinical laboratories offering the test." — Alicia Algeciras-Schimnich

NOT ALL BIOMARKERS ARE CREATED EQUAL

The surge in biomarker research has led to calls to update the diagnostic criteria for the disease, and the Alzheimer's Association is working on doing just that. The association's draft guidelines promote the hypothesis that Alzheimer's disease should be defined as a biological disease rather than based on a clinical syndrome. The idea is that someone could receive a diagnosis based on a positive test for amyloid — picked up by, say, a blood test — as opposed to the onset of cognitive decline.

Already, a handful of blood tests have made their way into the clinic, with many more following behind. However, despite the excitement over the advancements in blood-based testing, quality between tests tends to vary. Different tests look for different biomarkers, with some bolstered by more robust data than others. With such a big target population — more than 6 million people in the United States have Alzheimer's disease — it's important to ensure they are not used inappropriately.

Currently, the most promising blood-based biomarker is p-tau217, according to Alicia Algeciras-Schimnich, PhD, professor of laboratory medicine and pathology and co-director of the Clinical Immunoassay Laboratory at Mayo Clinic. It's a surrogate measure of Aβ accumulation in the brain and is the biomarker measured by the Mayo Clinic Laboratories test. While

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no blood-based tests have received Food and Drug Administration (FDA) approval — currently, all are available as laboratory developed tests — p-tau217 assays from Roche Diagnostics and Quanterix have received breakthrough status from the FDA, which expedites agency review of the assays.

Other tests, such as C2N Diagnostics, measure the Aβ42/40 ratio, which can be used to assess whether amyloid plaques have begun accumulating in the brain. This test also has received breakthrough status. Another company, Labcorp, has launched a test that measures three blood biomarkers: amyloid plaques, tau tangles, and neurodegeneration.

But while some biomarkers have a strong evidence base behind them, not all assays perform the same. "That's something that is probably not apparent to a clinician ordering the test," Algeciras-Schimnich said. "We need increased transparency on diagnostic performance data from the clinical laboratories offering the test. This data needs to be based on the assay they offered and the intended use population."

ENSURING APPROPRIATE UTILIZATION

Right now, it is recommended that the tests only be used in specialized dementia clinics. However, if the goal is to eventually use these tests for early diagnosis, these products need to be evaluated in broader patient populations, DeMarco said. "We know they have different performance metrics if you move from a high prevalence population to a lower prevalence population." There's also a concern that these tests could be used in patient populations for which the accuracy has not been evaluated, such as young, healthy adults. One day, if the data support it, these tests could be used for these patients to predict whether someone with no symptoms will eventually develop Alzheimer's. But the research is not there yet.

Li, however, is confident that these tests will be used in the correct context with education. "I think we need to educate providers so that those blood-based tests will be appropriately used in the context of asymptomatic individuals," she said.

There's a concern that because blood tests are so simple to administer, they will be used without due diligence. "You can imagine the ease of access [means] it tends to shift from appropriate utilization to what would now be considered inappropriate utilization," DeMarco said. For instance, an asymptomatic individual in a primary care setting receiving a blood test as opposed to a symptomatic individual in a specialist setting. There are questions about what a positive test could mean for employment and insurance, too.

The rise of blood tests also brings up some ethical quandaries. There's the question of whether clinicians should test asymptomatic individuals at all. For a diagnosis as devastating as Alzheimer's disease — a condition with no cure — for some, more information is not always better. Say you get a positive result for a blood-based biomarker test. "What's the follow up?" DeMarco said. "These types of discussions need to happen with patients as part of pre-test counseling."

The need for blood tests for Alzheimer's disease is clearly there. But it's crucial that these tests are validated and used in the appropriate setting. "I'm enthusiastic, but also cognizant of some of these things we need to work out before we have more widespread usage," DeMarco said.

To learn more about this topic, come to the ADLM 2024 session "Alzheimer's disease and the new therapeutic age" in Chicago on Wednesday, July 31. This session will cover the rapidly shifting therapeutic landscape for this condition and the rise of biomarker testing.

Grace Browne is a freelance journalist and a fellow with the Health Innovation Journalism Fellowship through the International Center for Journalists. She lives in London.

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"I think we need to educate providers so that those blood-based tests will be appropriately used in the context of asymptomatic individuals."
— Danni Li

Product Spotlight

Flex Testing Puts You in Control of Target Selection and Cost

Novel model aligns with diagnostic stewardship goals and shifting reimbursement landscape

BY CHRIS GARDNER

For clinical laboratory testing, flexibility and customization are essential for ensuring that all patients get the most appropriate test for their specific situation. Meeting the goals of diagnostic stewardship requires moving beyond a "one size fits all" approach to testing — but in an era of labor shortages and rising healthcare costs, that can seem like an insurmountable challenge.

Today, labs are faced with this dilemma for respiratory infection testing: Either run a full syndromic panel or run a series of more targeted assays until a result comes back positive. Using a syndromic panel has the advantages of a single workflow and a more comprehensive approach that is likely to reveal the answer quickly, but it is very expensive and includes targets that are not recommended by clinical guidelines for all patients. Running targeted assays can better align with clinical testing guidelines, but this requires multiple workflows and can take far too long to return results, risking the inappropriate use of antimicrobial treatments or the wrong course of therapy.

Now, there is a better option — one that combines the best of both worlds to ensure that labs can achieve their diagnostic stewardship goals. The automated, sample-to-answer LIAISON PLEX® System and the LIAISON PLEX® Respiratory *Flex* Assay from Diasorin offer the customization and flexibility needed for the most optimal respiratory testing.

The LIAISON PLEX Respiratory *Flex* Assay is based on a unique Flex testing approach that enables users to perform a full syndromic panel or select, report and pay for results as if they were running targeted panels. With each patient sample, labratorians choose from a syndromic panel of 14 viral and 5 bacterial targets, paying based on the number of targets selected. But if all selected targets come back negative, users can select additional targets and report more results—without rerunning the panel or performing additional tests. New targets are simply selected in the software for processing, with results reported immediately. Costs are based on how many targets from the overall syndromic panel are reported. Custom mini panels can be defined ahead of time by the lab and run for certain patient demographics, or targets can be chosen ad hoc as needed.

With the LIAISON PLEX Respiratory *Flex* Assay, clinical laboratories receive the benefits of having access to results from a full syndromic panel without the downsides of higher costs and over-testing. This approach will help reduce the inappropriate use of antimicrobial treatments by getting actionable answers to physicians more quickly.

Shaping the future

of laboratory medicine at ADLM 2024 in Chicago

ADLM 2024 (formerly the AACC Annual Scientific Meeting & Clinical Lab Expo) is heating up alongside summer in the northern hemisphere. The event, scheduled for July 28 through Aug. 1, promises groundbreaking research, cutting-edge technology in the Clinical Lab Expo, and thought-provoking discussions in hundreds of educational sessions. It's not just a conference; it's a beacon of innovation in laboratory medicine.

BY JEN A. MILLER

Behind the success of ADLM 2024 is the demanding work of the ADLM Annual Meeting Organizing Committee (AMOC). Comprised of 12 volunteers, the AMOC works diligently to make each year's meeting a must-attend education and networking event.

CLN spoke to Mark Marzinke, PhD, DABCC, FADLM, AMOC Chair and professor of pathology and medicine at Johns Hopkins University, for his perspective on why it is a must-attend this year.

What are you looking forward to most about ADLM 2024?

It's really going to highlight the breadth of clinical laboratory medicine in multiple facets and is inclusive of really understanding practical approaches to the provision of care via clinical laboratory medicine. I'm also really excited to get a better understanding of what's innovative and will impact our field in the 5-10 years to come.

How have changes in laboratory medicine affected the content of the meeting?

There have been a number of changes in our field that have impacted laboratory medicine, and you'll see that reflected in the meeting in three main ways: greater intersection between laboratory medicine disciplines; integration of automation into the clinical microbiology space; and the increased

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leveraging and utilization of data analytics, including large language model artificial intelligence and data visualization.

Another topic will be how the clinical laboratory community can respond to the evolving landscape of laboratory developed tests, particularly considering the recent Food and Drug Administration final ruling that will go into effect in May 2027.

Was there something specific you wanted to achieve as chair of the Annual Meeting Organizing Committee?

This is a shift for us. We celebrated our 75th anniversary as AACC last year, and this is the first conference under our new name, ADLM. As such, this scientific meeting really does need to reflect the landscape of laboratory medicine. When developing the scientific program, we wanted to ensure that there were topics and science that are practical, and that are translational and forward thinking. Our slogan for this conference is "bold move." A bold move is not just in the renaming of our organization. A bold move reflects the trajectory of the profession and the role of clinical laboratorians when it comes to delivering high-quality healthcare.

ADLM 2024 Pathways

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BIOMARKER DISCOVERY

The Nexus of Innovation: How Laboratory Medicine Supports Cellular and Gene Therapy Advancements

Emerging Diagnostics to Differentiate Type 1 From Type 2 Myocardial Infarction and Acute Non-Ischemic Myocardial Injury

Acute Kidney Injury Biomarkers: Ready for Primetime?

Alzheimer's Disease and the New Therapeutic Age

New Diagnostic Laboratory Assessments in Polycystic Ovary Syndrome

Preeclampsia in the Unites States: Clinical Details, Best Practices in Laboratory Medicine, and Impact of Foundational Support

DATA SCIENCE

Visualizing Laboratory Data: The Good, the Bad, and the Ugly

Bad, Better, Best: Putting Data Visualizations to the Test

Operationalizing AI in Lab Medicine: Approaches for Effective Machine Learning Integration and Deployment

Getting Started with Data Analytics: Indirect Reference Intervals as a Case Study

Ensuring Equity and Fairness in Machine Learning*

The Use of Intelligent Algorithms and AI in Pathology: Applications and Apprehensions

MANAGEMENT AND LEADERSHIP

The Fee-for-Service Payment System for Lab Tests: A Challenge for Labs, Patients, Physicians, and Insurers

Community Engagement, Research, and Healthcare: Laboratory Medicine's Lead Role in Ensure Health Equity*

Moving Beyond Sensitivity and Specificity: Showing the Value of Lab Medicine Through Outcome Measures

Improv and the Art of Medicine: Adaptable Skills for an Uncertain World

Speaking their Language: Communicating to Hospital Leadership the Essential Role of the Laboratory in Value-Based Care

Effective Communication with C-Suite Executives: A Chief of Operations and a Department Chair Perspective

What else can attendees expect from ADLM 2024?

Historically, the annual scientific meeting is a way to connect with colleagues. It's also a way to leverage the latest and greatest technology at our clinical laboratory exposition, which is the largest in the northern hemisphere. ADLM 2024 paves a way for attendees to build bridges, both personally and professionally, and to learn about what can be applied to your home institution or to your home field. This is a meeting that is complimentary and synergistic with the diversity of roles that clinical laboratorians have in their day-to-day lives. That's something I've always found valuable in our annual meetings. Attendees will always leave with not just added knowledge but added tools to implement in their laboratories at home.

Register, explore, and plan your meeting at meeting.myadlm.org

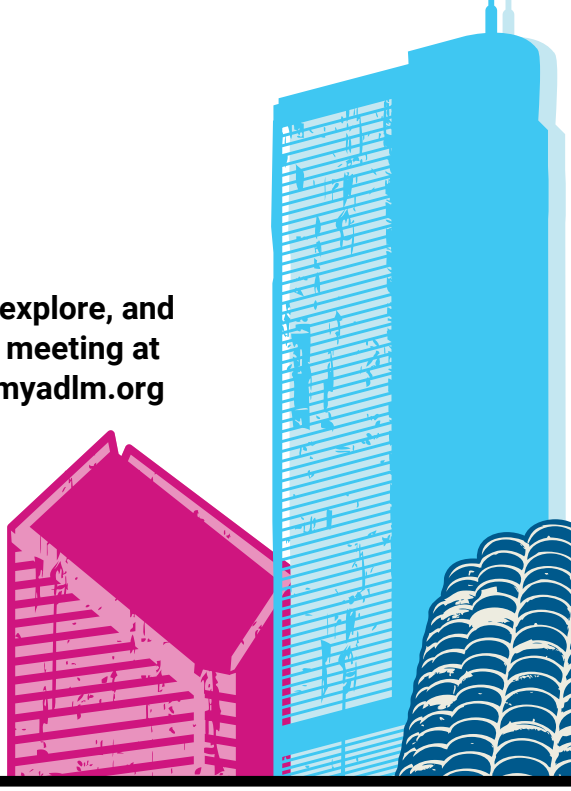
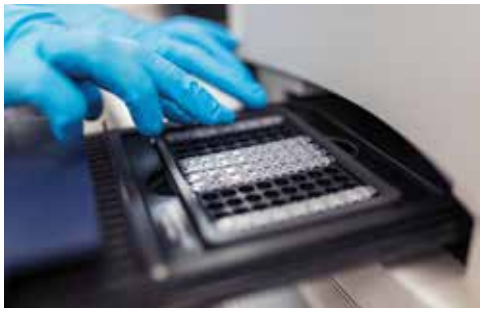


Chart your course through the meeting using these expert-curated tracks from the scientific program.



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MICRO & MOLECULAR DIAGNOSTICS

Next Generation Sequencing for Laboratorians: Understanding the Essentials

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Microbes Meet Machines: Total Laboratory Automation in Clinical Microbiology

Navigating Constitutional Genomic Disorders Throughout the Exome

Changing the Sexually Transmitted Infection Control Paradigm: Novel Diagnostics and Treatment Strategies

Current and Future State of Metagenomics for Infectious Diseases Testing

NEAR PATIENT TESTING: POINT-OF-CARE TO CRITICAL CARE TESTING

Solving Problems and Resolving Challenges in Point-of-Care Testing

Accelerating Point-of-Need Diagnostics to Meet the Growing Demand for Acute and Advanced Care at Home

Advances and Limitations of Consumer-Initiated Laboratory Testing

Pathogen Detection, Machine Learning, or Host Biomarkers: Can Any of These Technologies Help Address the Challenge of Sepsis?

Metabolic Emergencies in the Pediatric Patient: Laboratory Differentiation of Inborn Errors of Metabolism and Acute Drug Exposure

Point-of-Care Testing Challenges in Traditional and Non-Traditional Settings

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Responding to the Threat of Xylazine and Drug Supply Adulteration: Clinical Testing Strategies and Empowering Point-of-Service Community Drug Checking

Unexpected Toxicology Results as Real Time Opportunities for Collaboration

Clinical Toxicology in the Courtroom: How to Serve as an Expert Witness

The Toxicological Problem Accumulating Inside of Us All: Breaking Down the Uses, Abuses, and Growing Public Health Concerns over PFAs

AN INTERVIEW WITH MICHAEL JORDAN, MD, MPH, FIDSA

HIV Drug Resistance Surveillance and Guidelines in Low and Middle-Income Countries

FOCUS ON MOLECULAR DIAGNOSTICS

By Jen A. Miller

Dolutegravir (DTG), an integrase inhibitor used in combination with tenofovir and lamivudine, is a powerful treatment for HIV and has been the World Health Organization's (WHO) preferred first- and second-line antiretroviral (ART) since 2018. This recommendation was based on evidence showing that DTG is highly effective in blocking HIV replication leading to high levels of viral suppression, is easier to take and has fewer side effects compared to other antiretroviral (ARV) drugs. DTG also has demonstrated a substantially lower risk of selecting for drug resistance compared with other drugs.

By July 2023, 91% of 127 low- and middle-income countries (LMIC) reporting data to WHO had adopted DTG-based ART, according to the WHO.

Recent surveillance data show population levels of acquired HIV drug resistance to DTG ranging from 3.9% to 8.6% and reaching levels as high as 19.6% in one heavily treatment-experienced cohort. Overall, available data — especially from LMIC — remain limited, and more data from standardized surveillance and well-characterized cohorts are needed.

Michael Jordan, MD, MPH, FIDSA is associate professor of medicine and public health and community medicine at Tufts University. He's also a consultant to the WHO and cochairs the WHO HIV Drug Resistance (HIVDR) Surveillance and Monitoring Working Group. *CLN* spoke to him about why, while these numbers require further study, drug resistance might not be as high as recent studies might indicate.

What is the WHO's current guidance and rationale for HIVDR individual-level patient testing?

WHO does not recommend individual patient HIVDR testing to guide regimen selection. The reason for this current recommendation is multi-factorial. One is that with integrase inhibitors, we see very high levels of population-level viral suppression, often greater than 95%. That kind of viral suppression at a population level is something we didn't see with prior nonnucleoside reverse transcriptase inhibitors (NNRTI)-based regimens. The high levels of population-level viral suppression achieved with DTG-based ART is a game changer and viral suppression is drug resistance prevention.

Drug resistance testing is also expensive — in some countries a drug resistance test can be more expensive than an entire year of treatment for an individual. At present, with the low cost of the fixed dose combination of tenofovir, lamivudine, dolutegravir (TLD) and even the comparably higher cost of other regimens, such as protease inhibitors, drug resistance testing is not generally likely to be cost-effective in most settings. Clear cost benefit and cost-effectiveness analyses are needed.

What trade-offs were considered by the WHO for HIVDR testing in resource-limited settings?

First and foremost, we look at the impact of drug resistance testing on treatment outcomes when ART is delivered following a public health approach. Does using the result of that test for clinical management lead to better treatment outcomes? The second thing we look at is the cost-effectiveness of that test. A third consideration would be capacity. If this test were to be recommended, could it be implemented, and would the results be of high quality and provided in a timely manner to guide patient management decisions? Given what we know from clinical trials about DTG used in combination with tenofovir and lamivudine, the vast majority of people are likely to achieve viral load suppression with optimal adherence, even if some NRTI drug resistance mutations are present. Simply put, TLD is highly potent and effective — this is why we are seeing high population-levels of HIV viral suppression, often ranging from 90% to 95% in countries reporting data to WHO.

With respect to HIV drug resistance testing in people receiving TLD who do not have viral load suppression, we need to consider adherence to treatment. Currently, data suggest that the vast majority of people in LMIC taking DTG-containing regimens with

detectable virus are likely not optimally adherent to treatment. We need better ways of measuring patient and population-level adherence and better ways to support adherence. Optimal adherence to treatment and drug resistance prevention go hand in hand.

How does the WHO surveillance and monitoring working group treat new findings showing resistance?

To put this in perspective, let's think about the data that we had available 5–10 years ago when most people were receiving NNRTI-based regimes (e.g., efavirenz or nevirapine-containing ART). The first point to note is that viral suppression in patients receiving ART was lower than what we see today. In the NNRTI era we saw 70–90% viral suppression. We're now seeing levels of viral suppression at or above 90–95% among people receiving DTG-based ART.

Moreover, unlike in the NNRTI era when most people failing ART had NNRTI drug resistance associated mutations, in the DTG era we see vastly lower levels of DTG drug resistance associated mutations. As I mentioned, currently available data suggests that the majority of people who are failing DTG-containing regimens are doing so because of sub-optimal adherence.

Surveys reported in WHO's 2024 HIV drug resistance report found 3.9%–8.6% DTG resistance among people with viral nonsuppression. If these same people had been receiving NNRTI-based therapy, we would see around 70% –90% of the approximately 20–23% of people without viral suppression having NNRTI drug resistance. That means the absolute number of people who have acquired DTG resistance is significantly smaller than was the case when NNRTI regimens were used.

One of the challenges we have with integrase inhibitors, including DTG, is we're still learning about the clinical relevance of some DTG-associated drug resistance mutations. Some of them probably matter more than others.

What are the risks posed by this new epidemiological evidence to achieving the UNAIDS 2030 Fast Track Targets of 95-95-95?

At present, I don't see great risks. I think there's every likelihood that we can achieve the global 95-95-95 elimination goals for HIV, but we really need to maximize adherence to treatment and pay attention to the quality-of-service delivery (this means maximizing retention in care, preventing drug stockouts or drug shortages that may impact adherence to treatment, and scaling up viral load testing and use of viral load test results to inform patient management). We also need to ensure that we expand access to HIV testing and deploy HIV prevention strategies like pre-exposure prophylaxis (PrEP). Concerns about HIVDR should never be a barrier to the scale up of treatment of prevention of HIV.

We also need routine, standardized surveillance of HIV drug resistance to inform national and global HIV regimen guidelines. If we look at clinical trial data, we saw levels of DTG drug resistance in ARV drug-naive people that were less than 1%. In real life, we're seeing something closer to 4–9%. This difference could be because in clinical trials, people were followed very closely, adherence was monitored and supported, and participants' regimens were switched quickly if they experienced virological failure. As HIV incidence in LMIC declines, this means that more and more people are not ARV drug naïve. Many people in LMIC have also started and stopped treatment in the past and/or were treatment experienced at the time of the switch from NNRTI-based to DTG-based ART and may have had unsuppressed viral loads at time of switch. This is the real-world situation and helps to underscore the need for data from observational cohorts and from standardized and routinely implemented surveillance.

We continue to look for signals of DTG resistance, and at this point, there is no need for alarm. That's not to say we can neglect people living with HIV who have DTG resistance and whose regimens are failing them, and we do need to think about what the optimal treatment is for people in whom DTG-based therapy is failing.

It is surprising to learn that people may still achieve viral load suppression when some level of DTG resistance is present. Do we understand why this is true? Was this true with NNRTIs?

There remains an important research gap.

Note to readers:

Thermo Fisher is working with global health access organizations to make HIV drug resistance testing available and affordable to all in low- and middle-income countries. To learn more about the company's global health equity program, visit www.thermofisher.com/us/en/home/clinical/public-health/global-health-equity.html

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AN INTERVIEW WITH NATASHA DAVIES, MD

An HIV clinician's perspective with resistance to dolutegravir among pregnant women

By Jen A. Miller

FOCUS ON MOLECULAR DIAGNOSTICS

Scientists hoped that the HIV treatment dolutegravir (DTG) would be a nearly resistance-proof solution when it was rolled out in South Africa in 2020. And although it has been more successful than other HIV treatments, there are reports of surprising resistance, ranging from 3.9%–8.6% — even as high as 19.6%.

Clinical Laboratory News spoke to Natasha Davies, MD, an HIV specialist, and senior clinician at Anova Health Institute in South Africa about the problem. She works primarily with pregnant and breast-feeding women whose HIV viral loads are unsuppressed or have advanced HIV. She sits on the national third-line treatment/drug resistance committee.

How do you respond to suspected HIV drug resistance?

With pregnant women that I manage, the decision needs to be made quickly, because we're worried about exposure of the infant in utero and during delivery. If the patient has two viral loads over 1,000 copies/ml within a month of each other, is reporting full adherence, and her history indicates past unsuppressed viral loads, I request an antiretroviral drug resistance test to genotype the virus.

With the general adult population, we only order resistance tests if the patient has been on DTG-based regimens for more than 2 years, has had multiple high viral loads, and we have effectively addressed adherence issues.

How do you confirm adherence?

That's the hardest part. Patients are often nervous about disclosing adherence problems because they expect a negative provider response. We lack a good objective measure to confirm adherence, except relying on patients' self-reports and following South African guidelines which suggest clinicians check clinic attendance records and pharmacy refill information. Research data shows both methods can be useful. However, in the real world, some patients religiously attend their clinical visits, pick up their medications, but don't take their pills as prescribed.

Really, the only reliable way to measure adherence is with drug-level testing, either using the relatively new Tenofovir urine tests or therapeutic drug monitoring. Unfortunately, in South Africa we don't yet have easy access to these objective measures.

What are the factors contributing to the emergence of drug resistance to DTG in patients with HIV?

In high-income countries with smaller programs, resistance to DTG was uncommon. Because of reports from these programs, when DTG came to South Africa in 2020, we were very excited; however, by 2021, we were already seeing early resistance cases.

In high-income countries, when an individual experiences viral rebound, a multidisciplinary team provides guidance to enhance adherence. This approach aims to ensure better outcomes for patients facing viral rebound. In contrast, lower-resource settings often deal with patients who experience prolonged viral nonsuppression due to inconsistent drug pressure. Fluctuating adherence levels contribute to the replication of the virus along the mutation pathways, leading to emergent drug resistance

Another critical consideration arose with the transition of our patients to the tenofovir, lamivudine, and dolutegravir (TLD) regimen. In 2020, upon gaining access to DTG, we faced the challenge of ensuring patients achieved viral suppression before switching medications. However, this cautious approach inadvertently slowed down the adoption of TLD.

Subsequently, three clinical trials demonstrated favorable outcomes when patients with background resistance to nucleotide reverse transcriptase inhibitors and unsuppressed viral loads were switched to TLD. These study results were extrapolated to a large-scale program serving five million people, where patients do not receive the same high level of adherence support, and some continue to grapple with long-standing adherence issues

Based on these findings, South Africa shifted policy, allowing

nearly all patients to transition to TLD, irrespective of their current viral load or antiretroviral therapy (ART). The only exceptions were patients who had been on a protease inhibitor regimen for more than two years, exhibited high viral loads, and had addressed adherence challenges. In retrospect, it appears that this broad approach may not have been optimal for certain cohorts.

How does DTG resistance impact the effectiveness of HIV treatment?

We initially anticipated that DTG would serve as a bridge for patients with fluctuating adherence while we dealt with their adherence challenges. However, recent observations indicate that even a few months of suboptimal adherence in treatment-experienced patients can lead to the development of DTG resistance.

Thankfully, for ART-naïve patients who initiate TLD as their first-ever regimen, resistance remains uncommon unless they have encountered issues related to tuberculosis and perhaps failed to receive the appropriate double-dosed DTG.

In cases where a patient becomes resistant to DTG, the next step involves transitioning to darunavir — a medication that is more difficult to administer. Notably, patients with prior protease inhibitor exposure (a relatively common scenario) may exhibit cross-resistance from lopinavir to darunavir. If these patients develop resistance to DTG and switch to darunavir, its efficacy might be compromised if administered once daily. We must look after these patients carefully to safeguard their future treatment options.

What are the current strategies employed by physicians to manage dolutegravir-resistant cases?

The current South African guidelines set a high bar for resistance testing. Patients must meet four criteria: have been on TLD for at least two years; failed a previous regimen; have at least two viral loads over 1,000 copies/ml; and their clinician must objectively confirm that they have more than 80% adherence.

The challenge with this approach is that some primary healthcare clinicians work in high-volume sites with more than 10,000 patients enrolled on ART, perhaps seeing 40 to 50 patients a day. To confirm that a patient meets all four of those criteria is very challenging. The provider also needs approval to request a resistance test. Some provinces haven't even put that process in place yet.

In my clinical practice, I encountered six pregnant women with confirmed dolutegravir resistance. Interestingly, none of them met all four criteria outlined in the guidelines. Despite this, I made the decision to perform resistance testing due to the critical implications for maternal and infant health.

Notably, emerging data from laboratories suggest a significant decline in the number of requested resistance tests following the implementation of the current guidelines. These guidelines, while setting a rigorous standard, have inadvertently led clinicians to conduct fewer resistance tests, potentially resulting in underdiagnosis of DTG resistance in South Africa.

Are there any promising advancements in HIV drug resistance and dolutegravir?

For me as a clinician, drug level testing is the most promising advancement. Being able to perform drug level monitoring gives clinicians an advantage. We can differentiate between non-adherent patients with high viral load and adherent patients with high viral load, so we know who needs resistance testing.

Drug resistance testing works very well. What we need as clinicians is a better way of quickly identifying those who need the test so we're not wasting limited resources.

How can healthcare providers and patients collaborate to prevent or minimize DTG resistance?

Personally, I develop a rapport with my patients that helps to build trust so that they can feel comfortable telling me when adherence is the issue. Many patients hesitate to confide in their clinician when they struggle with medication adherence. Without trust — without open, honest, and supportive conversations — it can be a frustrating process to work out whether a patient is adherent or not.

From the patient's viewpoint, optimal adherence is key in preventing resistance. Yet, it hinges on how we, as providers, and the systems we operate within, empower patients to maintain consistency over a lifetime.

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AN INTERVIEW WITH PATRICK MATHIAS, MD, PHD

Why informatics is crucial to preparing for the next pandemic

By Jen A. Miller

The ability to sort, collect, and analyze data was a key factor in how some healthcare systems were able to mobilize effectively during the worst of the COVID-19 pandemic. The University of Washington was one of the fastest in the country to expand testing for COVID-19, partially because of the informatics resources they had prior to the pandemic.

Although COVID-19 has faded, it's still circulating — and H5N1 bird flu looms on the horizon. We asked Patrick Mathias, MD, PhD, vice chair of clinical operations and associate medical director of the informatics division at the University of Washington School of Medicine, about how his institution was able to mount such a quick response, and what they learned for the next time a pandemic comes knocking.

How can informatics help laboratory medicine prepare for the next pandemic?

COVID taught us that we need broader awareness of different threats to our public health. We need a more robust infrastructure for collecting data and monitoring infectious diseases and potential pandemics. We also need more connected systems to make sure that our different data sources are plugged into the larger public health infrastructure.

This is all key in continuing to work with our public health colleagues, as we did during the COVID-19 pandemic, to ensure we're monitoring new pathogens, like H5N1 and other variants of influenza.

During the pandemic, my institution pulled together a multidisciplinary group across departments and worked closely with county and city officials to think about how we could make our processes more efficient. We asked, how can we scale up our testing? How can we understand the various information systems in play? And how can we connect them by writing software to pull different tools together to get patient test results efficiently and to get those results to our public health authority?

We learned that informatics expertise is critical. We had to do a lot in the laboratory to get data to flow from point A to point B to point C as efficiently as possible. We also worked on continuous improvement methods, which aren't explicitly informatics but do tie into analytic infrastructure.

We were able to have the laboratory handle tens to hundreds of times its normal volume of testing. A lot of that relied on having the right information systems and the right infrastructure to build tools on the fly and connect systems together using the data that we were collecting, and then also share that data with our colleagues.

How can labs use data science to improve readiness for events like this?

There are three main ways. The first is knowing our existing information systems, including how they work and communicate with one another. We need to have complete understanding of those pieces so we know what we could change relatively quickly. Informatics is not necessarily something where you can hire someone from the outside to fix your problems. You need to know where you're starting from, have comfort with the current state of things, have a team of experts, and link them together.

The second is having data so we can react, and using it to understand how we can optimize operations. For example, there were times during the worst of the pandemic when we were low on supplies, like reagents and pipette tips. We had to scale up and track these things. We had what my chair, Geoffrey Baird, MD, PhD, called a "Noah's ark strategy" for our instrumentation where we bought two of everything, and we had to shift on the fly, from day to day, based on what we had. We developed more rigorous inventory management techniques so we could know, at any given time, what supply we had on hand,

FOCUS ON **DATA SCIENCE**

and what our burn rate was. We developed dashboards so we could have day-to-day awareness of supply and know where we could make changes so we wouldn't completely run out.

The third way is that, over time, we developed some in-house capabilities to write software. Many of the problems we had to solve were not overly complicated, like needing to get data from this instrument and reformat it to put it into that instrument or through that interface. We were able to utilize cloud capabilities and write software to connect everything to all the places it needed to be connected to.

What are some lessons your group learned that would make it easier to deal with the next emergent disease? What worked well? What were the barriers you had to overcome?

During the worst of the pandemic, a lot of our historical barriers shifted significantly. We were really freed up and given license to do what we needed to scale up our operation. We had lots of groups from different places all over the university — in addition to outside entities – pitching in to help move things along. Having a collective goal helped us align.

But since then, there's been some falling back. Large disruptions can shake people loose a little bit to consider how to operate in a better, more efficient way. But that is harder when the institution is no longer in that mode of responding to an emergency.

In general, how would you describe the opportunities for lab medicine professionals to use informatics more in their institutions?

Often, people are attracted to working in laboratories because we have very predicable work. You need to make sure you're following the same script every time.

Understanding information systems, workflow, and how staff operates — all those things can really help make improvements within the laboratory, not just being more efficient but in developing new ways to ensure patient safety and think about the value that we provide to our colleagues.

That's true even with what seem like small ideas, like mapping a process or tackling turnaround times and how many samples are making their way from point A to point B during a given time. By asking questions about these basic processes, and by fostering collaboration between laboratory directors and staff, we can make those processes better.

Outside the laboratory, we have opportunities to improve the value of the results we provide. I'm particularly passionate about data analytics and data science and how we can apply data to improve patient care at a population scale.

For instance, how do we modify our electronic health records so we can nudge our colleagues to use the best laboratory test for a particular scenario? We also can improve patient safety by flagging things that might be less apparent to a healthcare provider, such as identifying and calling out common laboratory test interferences. Individual incidents of those kinds of cases might seem rare, but when you add them up, it happens to quite a few patients.

How do you recommend people get started with informatics and data science?

There are certifications and courses for those who are interested in informatics but don't want to become board certified in it. These include courses from the American Medical Informatics Association and Association of Pathology Informatics, as well as educational resources from the Association for Diagnostics & Laboratory Medicine (ADLM, formerly AACC). The ADLM Data Analytics Steering Committee is also preparing a certificate program.

What are the most exciting developments around informatics in lab medicine for the near and medium-term future?

You can't go too far in this space without bumping into something around artificial intelligence (AI) or machine learning (ML). While there's been some hype around AI or ML for the last 10 or so years, there are now actual applications for those techniques in the laboratory in addition to broad applications around medicine.

I'm excited about stretching and pushing that boundary of what humans can do a little further by using some of these techniques. That way, we can provide better outcomes for patients in the laboratory. We can also identify trends and problems that we may never have recognized before.

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PLUGS Patient-centered Laboratory Utilization Guidance Services

BY BROOKE A. GAGNER,MS, HTL(ASCP)CM, BRENDA L. TOMANEK, MLS(ASCP), AND MICHELLE STOFFEL, MD, PHD

Stewards of the future: Engaging trainees in laboratory utilization initiatives

LABORATORY STEWARDSHIP FOCUS

Laboratory stewardship is a strategic approach to achieving the optimal test utilization practices for high-quality yet resource-efficient healthcare. Training the next generation of laboratory testing stewards is crucial for sustaining appropriate utilization practices and ensuring that stewardship principles will evolve in alignment with emerging testing methods and technologies. While gaining medical and technical knowledge during training is critical, lab education systems should also expose trainees to the "when" behind testing, along with the "why" and "how."

All laboratorians-in-training need exposure to stewardship principles

Teaching the principles of appropriate utilization is a practical way to bridge the gap between medical knowledge and laboratory practice. For example, learning that a hemoglobin A1C reflects the approximate 120-day lifespan of a red blood cell can help reinforce the learner's understanding of physiology and the rationale for performing the test (*1*). Additionally, optimizing test utilization allows trainees to experience the logistical processes of clinical ordering in a way they otherwise might not get to experience within the lab.

Any laboratorian can champion stewardship initiatives. To that end, individuals in training for a variety of laboratory roles can have stewardship principles incorporated into their pre-job or on-the-job training. An example for phlebotomist trainees could be a basic introduction to stewardship concepts that includes the importance of collecting specimens at the intended time. The training could highlight the fact that if drug monitoring tests are drawn too early or too late, it can lead to inaccurate results and a wasted draw.

Training also can include case studies to demonstrate that having a questioning attitude at the bench or bedside can lead to utilization improvements. For example, a technologist may notice that a platelet count is ordered on a subset of patients who had a platelet count upon admission. The investigation may lead to the discovery that the order set used for this patient population has a platelet precheck to establish a baseline. Improvements can then be made to uncheck the default platelet order in the order set to promote only ordering if there is no current platelet result. Incorporating stewardship training for new hires thus lays a foundation for continuous improvement related to the use of healthcare resources.

Three examples to engage trainees in stewardship work immediately

Laboratories may wonder, "How can we get trainees involved in stewardship work in the short term, even if we don't have an established laboratory stewardship committee?" Every laboratory will have new staff onboarding and may implement a combination of structured and informal training such as training guides, job shadowing, or quiz modules. The training period for any role is an ideal opportunity to incorporate stewardship principles and provide an avenue for feedback when new trainees identify opportunities to improve utilization.

For example, training materials might include introductory concepts around appropriate utilization, such as calling out that certain tests like high-sensitivity troponin may have an intended ordering interval that aligns with systemwide algorithms. High-sensitivity troponin may default to "STAT" priority and may need to be repeated within a specified time interval, like 2 hours. However, troponin should not be repeated sooner than clinically intended because doing so may not give the clinician the needed clinical information.

Example 1: Workflow documentation for stewardship improvements

Inefficient workflow often leads to inappropriate test utilization, but the root cause of the issue may be hidden within complex processes. For example, clinical users may order an acute test too frequently due to concern that reordering will be missed because of a lack of needed clinical decision support, such as order sets to guide standardized ordering. There also may be a

completely different reason, such as barriers to canceling unwanted tests that are already ordered. Mapping out the current state process can prevent implementing stewardship interventions aimed at inaccurate root causes of poor utilization.

Trainees are ideal individuals to engage in this work for several reasons. First, mapping the workflow helps the trainee learn the culture and background of the system. Second, trainees have fresh insights and can often suggest great ideas for improvement. Third, workflow mapping is a valuable skill for trainees to learn and can be used in many other career areas.

Example 2: Stewardship-related data analysis

Engaging trainees in stewardship data analysis provides opportunities for a broad range of collaborative interactions. Trainees can be coupled with senior faculty, clinicians, and even operational leaders when engaged in stewardship projects, and they can provide capacity for the healthcare teams by owning segments of the data analysis. Trainees also can use stewardship-related data analysis as a basis for establishing their skills and credibility as laboratory professionals. An example of how stewardship projects can build data presentation skills is for trainees to submit abstracts to conferences and copublish with faculty in medical journals.

When working with trainees on mining data for utilization insights, it is fundamental to ensure that the data accurately models the specific stewardship activity. Thus, having a little of the "right" data is more important than accessing large amounts of nonmeaningful data. It is also important to discuss examples where limitations to the data may exist due to the design of the laboratory information system (LIS). An example of a data limitation in anatomic pathology utilization work could be having negative immunohistochemistry (IHC) control slides categorized in the LIS as IHC antibodies, which could inflate IHC antibody utilization data if these slides were not excluded. Once trainees understand the power of selecting the correct data and specific data curation methodologies, they will gain insights into the power of data-driven decision making and problem solving that can lay the foundation for a lifetime of informed practice.

Example 3: Laboratory stewardship communications

Every laboratory stewardship initiative will require communication with stakeholders, whether it is understanding the needs around utilization or announcing that a change has been made that affects clinical ordering. Trainees can be involved in creating and disseminating these communications. For example, if a new order set to support appropriate infectious disease testing is being implemented, trainees could help identify the specific clinical stakeholders who would benefit from communication about the new tool, such as internal medicine physicians, and draft communication to distribute to rounding teams. Participating in interdisciplinary communications requires learning how to think about the needs of clinical stakeholders and patients and offers an additional way to broaden clinical perspectives outside the lab.

How lab stewardship fosters leadership skills for trainees

Laboratory stewardship work involves change management by design, and the decisions and priorities discussed during stewardship work can serve as a model for consensus-building in a trainee's future practice. For example, if a trainee can participate in a multidisciplinary decision to insource a genomic test to the hospital lab rather than sending it to a reference lab, they may listen to laboratory and clinical leaders' respective viewpoints, observe collaboration strategies, and experience conflict resolution. Similarly, learning how to prioritize limited resources while balancing high-quality care is another important leadership skill that stewardship work can build in trainees.

In summary, equipping lab trainees with stewardship principles in the learning environment helps build confidence in providing appropriate and sustainable patient care in their future careers.

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BY MONIQUE TRINH, MHA, PMP AND
ALLISON CHAMBLISS, PHD, DABCC, FADLM

How a Program Manager Aligns Quality Improvement, Laboratory Stewardship, and Equity, Diversity, and Inclusion in Pathology and Laboratory Medicine

LABORATORY STEWARDSHIP FOCUS

Our Department of Pathology & Laboratory Medicine at the University of California, Los Angeles (UCLA) is committed to optimizing patient outcomes. In support of this mission, our department has invested in several programs to enhance our clinical services: quality improvement (QI), laboratory stewardship (LS), and equity, diversity, and inclusion (EDI). Although each program has its own distinct initiatives, they each share the overarching goals of the quintuple aim for healthcare improvement: 1) improving population health, 2) enhancing the care experience, 3) reducing costs, 4) addressing clinician burnout, and 5) advancing health equity (*Figure 1*) (*1*).

To optimally align our QI, LS, and EDI activities, and to promote collaboration among them, our department hired a program manager to support all three programs. A program manager is a strategic project-management professional who oversees and coordinates projects and strategic initiatives across an organization or department. This article illustrates how clinical laboratories and health systems can incorporate program managers to promote collaboration, innovation, and patient-centered healthcare.

What background and education does a program manager typically have?

Program managers in healthcare can have a variety of backgrounds and typically have both an undergraduate and master's degree. Our program manager, Monique, obtained a bachelor's degree in environmental science before beginning her healthcare career with patient-facing roles as a medical assistant and receptionist. She then obtained a certificate in accounting and moved up the ranks in clinical finance positions at UCLA, first in obstetrics & gynecology and then in pediatrics. These roles equipped her with a deep understanding of the operations of an academic medical center and fueled her passion for enhancing systems and processes. She then transitioned to her current role as a program manager for pathology & laboratory medicine as she was one year into a two-year Master of Healthcare Administration program in health policy and management.

Although academic qualifications are essential, Monique's success also hinges on her mastery of soft skills such as leadership, communication, and problem-solving. These abilities enable her to effectively navigate the complex landscape of healthcare program management, fostering collaboration and driving innovation across QI, LS, and EDI initiatives.

What does a day in the life of a program manager look like?

As a program manager supporting QI, LS and EDI, Monique oversees various strategic initiatives and projects focused on continuous quality improvement, value-based healthcare, and advancing health equity. Each program has its own committees and dedicated faculty and staff cochairs, with whom Monique works closely. Supporting these programs and their numerous individual projects and priorities requires strong organizational skills, attention to detail, and a collaborative approach.

Each day requires her to wear a different hat depending on the task at hand. Monique's previous experiences equipped her with a diverse skill set, allowing her to serve as a strategist, marketer, project manager, finance analyst, data analyst, programmer, or operations analyst. On any given day, Monique may:

- Lead meetings (scheduling, agendas, meeting minutes, action items)
- Develop strategies and manage project plans (Reports to define project backgrounds, problem statements, proposed actions, data metrics)
- Support laboratory personnel in retrieving and analyzing data (laboratory, clinical, financial) and developing dashboards
- Create visual content to share

project status updates and successes, or to promote relevant events (slide decks, website design, posters, flyers)

How can a common program manager for QI, LS, and EDI has aligned these priority areas?
The alignment of the QI, LS, and EDI programs has strengthened collaborations both within and outside of our department. For the LS program, expertise and advice from the QI group have allowed us to optimize the approach and structure of our stewardship initiatives.

Collaboration with the EDI group has empowered us to promote equity, diversity, and inclusion both in how we structure stewardship project groups and in how we take a patient-centered approach when designing stewardship interventions. As an example, one of our most successful stewardship initiatives to date focuses on reference laboratory test utilization. Monique organized and delegated a review by faculty subject matter experts of tests historically sent through "miscellaneous" (nondiscrete) test orders in the electronic health record (EHR) to evaluate test appropriateness and to select the most optimal tests and reference labs. We then built 45 (and counting) new discrete tests into the EHR, and Monique designed an automated email tool to send targeted provider notifications about the newly built tests. Through this project, we have been standardizing our reference lab test offerings across our health system and improving access to the most appropriate, high-quality, and cost-effective tests, regardless of the patient's location.

How can institutions justify program managers for these areas?
It's important to acknowledge potential challenges to hiring program managers. These might include concerns about resource allocation or the perceived need for additional layers of management. However, we believe that by demonstrating the tangible benefits and return on investment associated with program managers, coupled with effective communication of their role in driving organizational success, these concerns can be addressed effectively.

Our QI, LS, and EDI programs have been successful due to the extraordinary support of our department chair, dedicated faculty and staff cochairs, and high-level visibility across our health system. For LS, in addition to a department-driven laboratory stewardship committee, we have a Laboratory Stewardship Oversight Committee (LSOC) composed of key health system leaders (3). Monique leads a quarterly LSOC meeting in which we share with these leaders our latest stewardship successes and challenges and seek feedback about active areas of priority for the health system. Quantifying and sharing successes in this way has led us to continuously iterate and expand our initiatives with support from the highest levels.

Our QI, LS, and EDI programs have each developed so successfully over the past few years that we recently hired a second program manager to support them. With our program management capacities now increased, we are seeking to expand our efforts to incorporate trainee education and involvement in projects and to share our successes externally via conference abstracts and publications. Further, we are integrating our program managers into our Laboratory Medicine Informatics division to optimally incorporate data analytics and clinical decision support design, etc. to support our LS initiatives. Overall, our program managers will ensure strategic alignment, cross-functional coordination, and outcomes realization in support of our missions of improving patient and population health.

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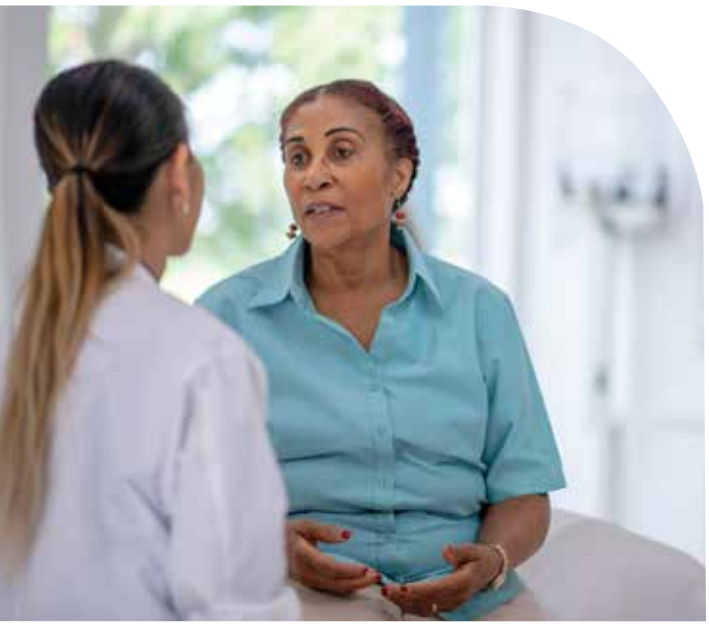
Regulatory Roundup



FDA approves HPV self-collection solution

The Food and Drug Administration has approved Roche's human papillomavirus (HPV) self-collection solution, making it one of the first available in the United States, according to the company.

The HPV self-collection solution is approved for use with Roche's cobas HPV test. This test runs on the cobas 4800 and the fully automated cobas 5800/6800/8800 systems, which provide up to 96 results in about 3 hours.

The solution, which is intended for use in healthcare systems, allows the patient to collect their own vaginal sample without a pelvic exam. The healthcare provider then sends the sample to the lab.

Roche hopes that this solution will increase access to HPV screening at a time when more than half of all U.S. cervical cancer patients are insufficiently screened. Each year in the U.S., more than 13,000 patients are diagnosed with cervical cancer and approximately 4,000 die from this preventable disease, caused by HPV infection.

PILLAR BIOSCIENCES RECEIVES FDA APPROVAL TO INCLUDE SOLID TUMOR PROFILING IN PANEL

The Food and Drug Administration has approved Pillar Biosciences' premarket approval supplement application for its oncoReveal CDx pancancer solid tumor test.

The approval expands the indication of oncoReveal Dx from EGFR and KRAS therapy selection in non-small cell lung cancer and colorectal cancer to include general solid tumor profiling.

The test has a fully automated workflow any clinical laboratory can perform, with a sample-to-report time of as little as 48 hours. Approved for use on the Illumina MiSeq Dx System for tumor profiling and therapy selection, the test includes actionable targets on most common solid cancer types and covers 22 clinically relevant genes in one multiplex reaction.

NONINVASIVE COLORECTAL SCREENING TEST RECEIVES FDA APPROVAL

Geneoscopy recently announced Food and Drug Administration approval for its ColoSense noninvasive colorectal cancer (CRC) screening test in adults aged 45 years of age or older who are at typical average risk for developing the disease.

ColoSense is the first noninvasive CRC screening test to provide a dynamic view of disease activity by using RNA biomarkers, according to Geneoscopy. The company chose to target RNA biomarkers with this test because these markers are not subject to age-related methylation patterns, which can lead to test performance variability across different age groups.

The ColoSense CRC-PREVENT study of more than 1,800 average risk individuals ages 45 and older demonstrated 93% sensitivity for detecting CRC and 45% sensitivity for detecting advanced adenomas (AA). In a subgroup of individuals aged 45–49, the test showed 100% sensitivity in detecting CRC and 44% sensitivity for AA.

Geneoscopy plans to launch the test with Labcorp either in late 2024 or early 2025.

FDA CLEARANCE EXPANDS USE OF BLOOD SAMPLES WITH HEMOSONICS CARTRIDGE

HemoSonics has earned 510(k) clearance from the Food and Drug Administration (FDA) for expanded use of arterial blood samples with its Quantra QStat Cartridge, which runs on the Quantra Hemostasis Analyzer.

HemoSonics' QStat Cartridge first received 510(k) clearance from the FDA in 2022 for use with venous whole blood samples. The more recent clearance enables hospitals to further standardize and operationalize viscoelastic testing with an arterial and venous indication for both HemoSonics' QStat Cartridge and the QPlus Cartridge.

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2024

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The world of critical and point-of-care testing (CPOCT) is driven by the need for accurate, rapid diagnosis that is integrated into healthcare systems. To meet this need, new and emerging CPOCT technologies are continually advancing the field with an increasing global adoption in many healthcare settings.

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The Quantra System enables decisions on management of bleeding patients and medically appropriate therapy amidst recent shortages of blood. It provides comprehensive whole-blood coagulation analysis at the point of care or in laboratory-based settings, typically in less than 15 minutes. The system is cleared for use in cardiac, trauma, liver, and major orthopedic surgeries.

QIAGEN GETS FDA OK FOR RESPIRATORY TESTING PANEL

The Food and Drug Administration has granted 510(k) clearance to Qiagen for its QIAstat-Dx Respiratory Panel Plus syndromic test.

The panel covers 21 viral and bacterial targets and is designed to support clinical decision-making in diagnosing upper respiratory infections. The panel gives results in about 1 hour, with less than 1 minute of hands-on time. Cycle threshold values and amplification curves are easy to view, according to the company.

The company currently also has a gastrointestinal panel under FDA review along with a meningitis/encephalitis panel.

FDA GREENLIGHTS DIASORIN RESPIRATORY PANEL

Diasorin has received Food and Drug Administration clearance for the NxTAG Respiratory Pathogen Panel (RPP) v2. This panel covers many pathogens commonly associated with respiratory infections and has added SARS-CoV-2 to its mix of 19 viral and 2 bacterial targets. The updated panel also provides enhanced target performance to increase inclusivity and specificity, while improving usability of the product with easier-to-identify plate seals.

These product updates integrate with existing features, allowing for testing of up to 96 specimens in a single run. Designed to run on Magpix systems, the NxTAG panel also complements the recently cleared Liaison Plex Respiratory Flex panel. The two syndromic solutions respectively address the need for high throughput batch testing and on-demand random access, the company said.

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Industry Playbook

Genomenon partners with Pharming to advance APDS diagnosis

Genomenon and the Pharming Group have partnered to make variant data on the *PIK3CD* and *PIK3R1* genes available to genetic testing labs and clinicians worldwide, Pharming announced recently.

Genomenon data will enable accurate molecular diagnoses and support precise medical management of activated PI3K delta syndrome (APDS), a rare primary immunodeficiency. The partnership also will improve resolution variants of uncertain significance and advance Genomenon's mission to curate the human genome, Pharming said.

APDS was first characterized in 2013. It can lead to abnormal development and function of immune cells, immunodeficiency, and immune dysregulation. Although APDS severity varies, individuals with the disorder can develop recurrent, severe infections, bronchiectasis, lymphoproliferation, and even lymphoma. Currently, patients typically experience a median 7-year diagnostic delay.

The partnership will help Pharming provide clinicians and genetic testing laboratories access to comprehensive *PIK3CD* and *PIK3R1* variant data through Genomenon's Mastermind platform. Mastermind offers variant landscapes of all published variants in association with activated APDS. Variants are summarized and classified using molecular pathology guidelines from the American College of Medical Genetics and Association for Molecular Pathology.

Pharming said the partnership will help labs and clinicians ensure patients with APDS receive earlier, more accurate molecular diagnoses, and ultimately, appropriate medical management.

Genomenon officials said the partnership has the potential to enhance validation, diagnostic developments, and patient identification for precision medicine.

COLLABORATION FOCUSES ON NGS LIBRARY PREPARATION

Beckman Coulter Life Sciences recently announced a collaborative partnership with Watchmaker Genomics to deliver robust, reliable automated liquid handling solutions that enable labs to streamline operations and generate consistent results.

As part of the agreement, the two companies will codevelop methods for next-generation sequencing (NGS) library preparation, using Watchmaker's portfolio of rapid and highly sensitive DNA and RNA solutions on the Biomek i7 Dual Hybrid Liquid Handler from Beckman Coulter Life Sciences.

One of the first outputs of this collaboration will be an RNA library preparation method that enables walkaway automated processing of up to 96 libraries in under 8 hours. The method will use the Watchmaker RNA Library Prep Kit with Polaris Depletion and support clinically relevant samples. These include formalin-fixed and paraffin-embedded samples, as well as samples with input amounts as low as 1 ng.

Watchmaker officials said that the collaboration will ultimately save users time and operational bandwidth while improving data quality. Beckman Coulter said the partnership advances its mission to harness the benefits of automation to accelerate research discoveries, including for NGS, sample management, drug discovery, functional screening, synthetic biology, and proteomics.

BIO-TECHNE ANNOUNCES NEW DISTRIBUTION AGREEMENT WITH THERMO FISHER SCIENTIFIC

The global life sciences company Bio-Techne Corporation recently

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ADLM Association for Diagnostics & Laboratory Medicine™
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announced plans to enter a strategic distribution agreement in Europe with Thermo Fisher Scientific.

Under the agreement, Thermo Fisher will distribute Bio-Techne's products — including antibodies, proteins, immunoassay kits, reagents, and enzymes — to labs and research institutions across Europe. Bio-Techne said the products are designed to accelerate research and improve outcomes in cell and gene therapy, immunology, and neuroscience.

Bio-Techne officials said the agreement will enhance its ability to provide customers with the latest technologies and expertise while Thermo Fisher hopes to further empower scientists with tools to drive discoveries and advances in healthcare.

IMMY ACQUIRES OLM DIAGNOSTICS

IMMY recently announced acquisition of United Kingdom-based OLM Diagnostics.

IMMY specializes in fungal diagnostics and OLM works in molecular diagnostics with a focus on including PCR assays for underserved medical areas.

Through the acquisition, the companies aim to improve and better customize customer service for patients.

IMMY officials said the acquisition expands their company's product portfolio and commitment to empowering laboratorians and clinicians with cutting-edge tools for precise identification of fungal disease.

U.S. COURT APPROVES INVITAE SALE TO LABCORP

Labcorp and Invitae have announced U.S. Bankruptcy Court approval of a bid by Labcorp to acquire Invitae assets, the companies announced recently.

Labcorp noted the advanced genomics-based testing solutions in Invitae's network will complement its genetic screening, diagnostics, and specialty testing.

Labcorp noted the advanced genomics-based testing solutions in Invitae's network will complement its genetic screening, diagnostics, and specialty testing. Invitae called the court approval of the sale a positive step in its restructuring process.

Both companies said they expected the transaction to bolster Labcorp's genetic specialty testing capabilities, especially in oncology and rare diseases. The deal also is expected to strengthen Labcorp's ability to use genetic data to enhance and support clinical trials and treatment regimens, the companies said.

The companies anticipate the sale will be completed in the third quarter of 2024, subject to customary closing conditions and applicable regulatory approvals.

ARBOR BIOTECHNOLOGIES ACQUIRES SERENDIPITY BIOSCIENCES

Arbor Biotechnologies recently announced acquisition of Serendipity Biosciences, a private company focused on unique gene-editing technologies.

Serendipity's assets include editing technologies such as Fanzor and Isr-B. They complement and expand Arbor's existing editing capabilities and may result in new therapeutic applications for Arbor's portfolio of genomic medicines, the company said.

The technologies build on CRISPR-Cas approaches by harnessing next-generation components to enhance Arbor's reverse transcriptase editing, as well as insertion of exons or entire genes in vivo through unique cutting properties. Other expected improvements include expanded genomic targeting and enabling delivery through adeno-associated virus vectors and other size-constrained delivery vehicles, Arbor officials said.

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Ask The Expert

An intro to AAV9 antibody tests

By Jingcai Wang, MD, PhD, CC(NRCC), MLS(ASCP) SH

Recombinant adeno-associated virus (AAV) vectors are most commonly used as a delivery system for in vivo gene therapies. Of all the AAV subtypes, AAV9 is one of the most studied and widely used in clinical trials.

One limitation of these treatments is that pre-existing antibodies against AAVs can bind to the capsid of an AAV-based gene therapy, potentially reducing its benefits or even causing adverse events. Consequently, AAV9 antibody tests are used to prescreen gene therapy candidates to identify those who might not be suitable for AAV9-based therapies. These tests are also used to monitor ongoing treatment, to guide dosage adjustments, and to personalize treatment plans.

What are the different types of AAV9 antibody tests?

A: The primary types include multiplex assays, neutralizing antibody assays, and total antibody testing.

Multiplex assays simultaneously detect antibodies against multiple AAV serotypes, including AAV9, saving time and providing a comprehensive immunological profile. This is useful for screening and understanding cross-reactivity among different AAV vectors.

Neutralizing antibody tests measure the ability of antibodies to inhibit the AAV9 vector, offering insights into the potential efficacy of gene therapy.

In contrast, ELISA-based total AAV9 antibody tests provide a comprehensive view of all AAV9 antibodies, including both neutralizing and non-neutralizing types, aiding in the evaluation of a patient's overall response and gene therapy candidate prescreening.

What should labs consider when choosing an AAV9 antibody test?

First and foremost, labs must determine which method is most appropriate based on their technical capabilities and requirements.

Titer cutoff is another criterion to consider. AAV9 antibody tests semi-quantify antibody titers by sequentially diluting the serum or plasma until an endpoint titer is reached. The greater the dilution, the higher the antibody levels. For example, a dilution or endpoint titer of 1:400 indicates a higher antibody concentration than an endpoint titer of 1:200. The chosen titer cutoff can differ between assays. Variations in titer cutoff may also arise within the same assay depending on how the test is optimized. It is therefore crucial to standardize assay conditions when choosing an AAV9 antibody test.

Additionally, sensitivity and specificity are crucial factors in selecting an AAV9 antibody test. In particular, the test should be sensitive enough to detect low levels of antibodies, especially for the purpose of prescreening patients who may have minimal pre-existing immunity.

What should labs consider when validating AAV9 antibody tests?

Variations in assay conditions, reagents, and equipment can impact the comparability of data across different studies and clinical trials. Addressing these challenges requires rigorous assay development, thorough validation, and interdisciplinary collaboration.

Labs should develop comprehensive protocols detailing AAV9 antibody testing procedures, including sample preparation, assay methodologies, and data analysis. These protocols should be standardized to ensure consistent execution across different operators and test batches. Assay parameters such as antibody dilution and incubation time should be optimized to enhance sensitivity and specificity. Additionally, labs should evaluate the analytic performance characteristics of a test to ensure that they adhere to predefined quality criteria.

ELISA assays in particular come with additional considerations. These tests detect antibodies in serum or plasma samples using the AAV capsid protein as an antigen. The concentration of this capsid protein directly influences these assays' sensitivity and specificity, making it crucial that this parameter be standardized across labs. Using an appropriate capsid concentration through accurate capsid titration ensures that there's a sufficient amount of antigen for antibody binding, thereby maximizing the signal-to-noise ratio and enabling reliable detection even at low antibody levels.

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