November/December 2026

CLN Clinical Laboratory News

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MAKING TB TESTING MORE ACCESSIBLE

51.1%

The reduction in cartridges used for molecular TB testing when sputum is pooled.

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The hidden debate over newborn screening









Pursuing personalized reference intervals







How to launch a lab developed test







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Federal Insider



Proposed CLIA changes would weaken standards for high-complexity lab leadership

A new proposed rule from the Centers for Medicare and Medicaid Services (CMS) would reduce the minimum qualifications needed to direct laboratories that perform the most advanced and essential laboratory testing. According to CMS, changes would provide flexibility, reduce regulatory burden, and help with workforce shortages. But several provisions would remove independent safeguards that determine whether laboratory directors have the knowledge and competence required to oversee complex testing that millions of patients depend on every day.

The rule, CMS-3478-P, would not only update personnel provisions but also would recommend broad changes to CLIA. The personnel provisions in particular raise serious concerns for laboratory professionals and the patients they serve. CMS proposes eliminating the requirement that doctoral scientists directing high-complexity laboratories hold a Department of Health and Human Services (HHS)-approved board certification. Under the proposal, a doctoral scientist could qualify with either 1 year of experience directing or supervising high-complexity testing or 20 continuing education (CE) hours covering laboratory director responsibilities.

However, board certification for laboratory directors proves much more than the fact that someone has spent time in a supervisory position. Importantly, it provides an independent assessment of specialized knowledge and competence across laboratory medicine. Experience remains important, but it does not, in itself, show that a candidate has mastered the breadth of knowledge required to direct a high-complexity laboratory.

Laboratory directors' expertise is especially important as medicine is transformed by artificial intelligence (AI). ADLM has urged policymakers to ensure that emerging AI tools remain subject to the same professional expertise, quality systems, validation, and monitoring standards that apply to laboratory testing. Effective oversight requires qualified laboratory professionals who understand laboratory methods, data, validation, and sources of error. As AI becomes more deeply integrated into laboratory medicine, maintaining that expertise becomes more important.

ADLM is advocating for CMS to retain the HHS-approved board-certification requirement for doctoral high-complexity laboratory directors and reconsider the proposed experience and CE alternatives. Modernizing CLIA should strengthen the law's ability to protect patients as laboratory medicine changes; it should not undermine standards for those entrusted to lead its most complex work.

ADLM HOLDS CONGRESSIONAL BRIEFING ON ETHICAL AND EFFECTIVE USE OF HEALTHCARE AI

On October 13, the Association for Diagnostics & Laboratory Medicine held a congressional briefing on Capitol Hill to discuss the policy changes needed to ensure that healthcare artificial intelligence (AI) is used judiciously and ethically and benefits all patients, especially children.

AI is becoming an integral part of American healthcare. At the briefing, moderator Dennis J. Dietzen, PhD, chair of pathology and laboratory medicine at Phoenix Children's Hospital, discussed how this revolutionary new technology is rapidly changing how

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healthcare organizations manage their operations, analyze data, and diagnose disease. Because clinical laboratories generate approximately 80% of the data used to inform medical decisions, laboratory medicine is at the center of efforts to harness AI to improve patient care.

Although these developments hold much promise, there is still much to be done. Congress needs to put in place a regulatory framework that ensures healthcare AI is used safely and responsibly, while maximizing its benefits and limiting its potential shortcomings.

The briefing featured leading experts in laboratory medicine, including speakers Sarah Wheeler, PhD, clinical pathology medical director at the University of Pittsburgh Medical Center Children's Hospital of Pittsburgh, and Stephen Master, MD, PhD, vice chair for innovation in the department of pathology and laboratory medicine at Children's Hospital of Philadelphia.

Wheeler discussed the differences between rule-based AI, which follows an explicit set of rules written by humans, versus generative AI, and the challenges that arise from the different outputs that generative AI gives.

AI needs more than just lab results to function well, Wheeler said. It needs the expertise of laboratory professionals who are adequately provided with the context behind those results.

Master discussed examples of variables that can influence the accuracy of AI healthcare tools in laboratory medicine. One variable is the instrument or manufacturer used to generate test results. Many labs still produce different results depending on the instrument and manufacturer. This can influence how AI healthcare tools report test results.

Another variable is the demographic data that an AI algorithm was trained with. If it was trained with data from adult patients, can it adequately address the test results of pediatric patients? Given these and many more variables, laboratories need transparency from developers on the data used to train AI healthcare tools.

● THE SENATE PASSES HEALTH CARE CYBERSECURITY AND RESILIENCE ACT

The Senate passed the Health Care Cybersecurity and Resilience Act of 2026 on September 30 by unanimous consent. This bipartisan bill aims to improve coordination between the Department of Health and Human Services (HHS) and the Cybersecurity and Infrastructure Security Agency to strengthen responses to cyberattacks in healthcare.

Clinical laboratories operate within the healthcare data ecosystem that this legislation is trying to safeguard; they handle protected health information and rely on digital systems to process and communicate test results. The bill's cybersecurity requirements and provisions therefore have direct implications for clinical labs, where a breach or system disruption can affect both patient data and laboratory operations.

If made law, the bill would require entities regulated by the Health Insurance Portability and Accountability Act (HIPAA) to make significant investments in cybersecurity infrastructure, including implementing multifactor authentication, encryption, penetration testing, and alignment with national frameworks, such as the National Institute of Standards and Technology Risk Management Framework. These obligations would call for a thorough review of existing compliance programs.

The bill would also implement a deadline for HHS — 1 year after the legislation becomes law — to promulgate regulations that implement the safe harbor for "recognized security practices." Originally enacted in January 2021 as an amendment to the Health Information Technology for Economic and Clinical Health Act, the safe harbor provision requires HHS to consider whether a HIPAA-regulated entity implemented recognized security practices for at least the prior 12 months when determining fines, the length and disposition of audits, and other remedies for HIPAA violations.

The bill would also require annual reporting by HHS to Congress on its consideration of recognized security practices in HIPAA enforcement. For organizations proactively implementing recognized security practices, the safe harbor could potentially mitigate penalties in the event of an HHS investigation, audit, or cybersecurity incident.

Although the bill must still clear additional legislative hurdles before becoming law, its bipartisan advancement out of committee signals that HIPAA-regulated entities could benefit from proactively assessing gaps in their current cybersecurity posture, breach notification procedures, and incident response plans now, rather than waiting for final enactment of the law.

When automated urinalysis needs manual sediment microscopy review

BY JINGCAI WANG, MD, PHD, DABCC, NRCC, ASCP, FADLM



Jingcai Wang, MD, PhD, DABCC, NRCC, ASCP, FADLM

Automation has transformed urinalysis by improving throughput, standardizing particle counts, and reducing reliance on labor-intensive manual microscopy. However, even high-performing automated systems have blind spots. The practical question, therefore, is not whether manual urine sediment examination still matters, but when does it add meaningful clinical value?

Current guidance favors a selective approach. Laboratories should establish predefined criteria for microscopic review after automated particle analysis. Review criteria should reflect the analytical performance of the specific analyzer, the patient population, and clinical needs (*1*, *2*). Because analyzer performance differs, review rules should be validated locally rather than adopted from another laboratory.

Know the analyzer's blind spots

Automated systems are useful for standardized enumeration of common particles such as red blood cells (RBCs) and white blood cells (WBCs) (*1*, *3*), but limitations become more important when detailed morphology is required. Dysmorphic RBCs, acanthocytes, pathologic casts, renal tubular epithelial cells, atypical cells, unusual crystals, and other difficult-to-classify particles may require visual confirmation (*1*, *2*).

A 2025 comparison with reference microscopy found that automated systems had sensitivities below 50% for pathologic casts, lipiduria, and renal tubular epithelial cells and 62.3% for dysmorphic RBCs (*4*). In the multicenter ADORE study, the two higher-performing systems for pathologic-cast detection had sensitivities of 58.6% and 69.6%, and 90% of samples required manual on-screen review to achieve acceptable performance for dysmorphic RBC and cast detection (*5*). Selected published performance data are summarized in Figure 1.

Performance also varies by technology and particle type. The UF-5000 flow cytometry analyzer performed better than digital-imaging systems for bacteriuria and mucus threads but less well for crystals (*3*). Cast and crystal detection also varied across platforms and cutoff settings (*6*). Unusual organisms and morphologies can challenge automated classification; published yeast-like and mold-like cases illustrate why findings that do not match expected morphology deserve closer review (*7*, *8*).



Figure 1.

What should trigger review?

A practical algorithm should focus on findings for which review could change reporting or interpretation. Common triggers include instrument flags or uncertain classifications, chemistry-particle discordance, and suspicion of clinically important morphology. Examples include pathologic or unclassified casts, dysmorphic RBCs, nonsquamous epithelial cells, yeast, unusual crystals, unidentified particles, substantial dipstick blood with few RBCs, positive leukocyte esterase with few WBCs, or marked turbidity without corresponding particles.

Dipstick thresholds can help prioritize review but should not serve as the sole safeguard. In 503 predominantly nephrology specimens,

protein ≥1+ or blood ≥2+ identified nephropathy-associated sediment findings with 71.2% sensitivity and 73.9% specificity (*9*). These thresholds can enrich specimens for review but would miss important findings if used alone.

When reviewing automated findings, it's important to keep in mind that image review and manual sediment microscopy are not interchangeable. Image review may correct classification errors but cannot recover particles that were not adequately captured by the analyzer. If image review does not resolve a misclassification or if clinically important elements are suspected but were not imaged, manual sediment microscopy should be performed next.

Additionally, discordance does not necessarily indicate analyzer failure. A heme-positive dipstick with few or no intact RBCs may reflect hemoglobin, myoglobin, or RBC lysis. Automated systems may also underestimate hematuria in glomerular disease (*10*). The goal is to resolve the discrepancy before reporting an internally inconsistent urinalysis.

Clinical setting and specimen quality

Review thresholds may reasonably be lower when clinically important renal disease is suspected, including acute kidney injury or renal transplant dysfunction. It may also be appropriate to bypass automated screening and go straight to expert sediment microscopy when detailed morphology is the clinical question (*1, 2, 11*).

Dysmorphic RBCs should be interpreted with proteinuria, renal function, pathologic casts, and clinical findings rather than in isolation (*12*). In 131 patients undergoing kidney biopsy, renal tubular epithelial cells and urinary lipids were associated with clinically relevant histologic lesions (*13*).

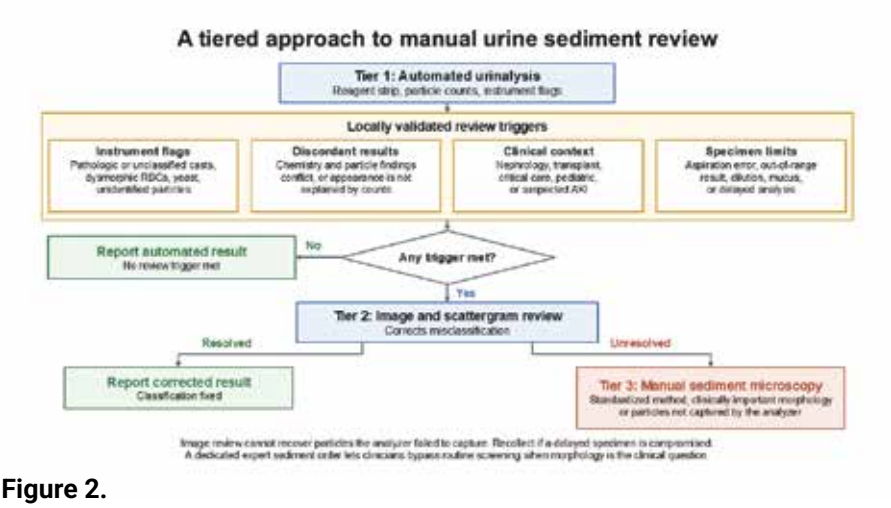


Figure 2.

Specimen quality also matters. Delayed analysis and specimens with abundant mucus, crystals, debris, or other artifacts can compromise sediment evaluation. Cells and casts may deteriorate over time; when specimen integrity is poor, recollection may be preferable to interpreting a compromised sample (*1, 11, 12*). Clinical and Laboratory Standards Institute guideline PRE05 provides guidance on urine collection, handling, transport, and specimen quality (*14*).

Use a tiered approach

Not every abnormal automated result needs manual microscopy. A tiered process preserves efficiency while directing expertise where it matters most (Figure 2). Automated analysis should handle particles it measures reliably. Instrument images and scattergrams can resolve straightforward classification questions. Manual sediment microscopy should be reserved for unresolved findings, clinically important morphology, or discordance that cannot otherwise be explained.

Manual microscopy must also be standardized. Specimen mixing, centrifugation, sediment concentration and resuspension, examined volume, microscopy technique, terminology, and reporting units can all introduce variability (*1, 2, 11*). Competency assessment should include low-frequency, high-consequence findings rather than only common RBCs and WBCs.

The best review rule is not "microscopy for every abnormal urinalysis." The best rule is a locally validated safety net built around the analyzer's known limitations, chemistry-particle concordance, specimen quality, and clinical context. The goal is not to examine more specimens manually, but to identify those in which expert microscopy can make a difference.

To view the article's references, visit myadlm.org/cln.

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The Sample



Progress made toward reference system for apolipoproteins

A reference measurement procedure (RMP) and immunoassay-based measurement procedures (MPs) have comparable selectivity for apolipoprotein A-I (ApoA-I) and apolipoprotein B (ApoB), a recent study shows (Clin Chem 2026; doi.org/10.1093/clinchem/hvag063).

The study was part of an International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) effort to develop a novel reference measurement system for seven clinically relevant apolipoproteins, including ApoA-I and ApoB. Plans for the system include a multiplex mass spectrometry-based RMP and commutable secondary reference materials (RMs), the study authors wrote.

The researchers used 30 clinical samples to study agreement between the RMP and eight immunoassay-based MPs. They also investigated the commutability of eight candidate RMs, which consisted of frozen serum pools, and the existing World Health Organization (WHO)-IFCC standards SP1-01 and SP3-08 for the measurement of blood lipids that serve as critical markers for cardiovascular disease risk.

The study found good correlation between the RMP and immunoassay-based MPs for ApoA-I and ApoB. For ApoA-I, the difference in nonselectivity (DIN) was sufficiently small in relation to the desirable or minimum analytical performance specifications (APSs) based on biological variation for all MP comparisons. These findings indicate that despite their different measurement principles, the liquid chromatography-mass spectrometry (LC-MS)–based RMP and the immunoassay-based MPs have a similar selectivity for ApoA-I, the researchers wrote. For ApoB, DINs were larger, but they were still sufficiently small in relation to the minimum APS for six of the eight MP comparisons. In all, seven candidate RMs showed good commutability, while SP1-01 and one candidate RM showed potential noncommutability for one method comparison.

Although the study shows some level of agreement among most of the MPs for ApoA-I and ApoB with traceability to the current WHO-IFCC standards, significant differences remain among the immunoassay-based MPs currently used in clinical laboratories. The availability of a new reference measurement system with an LC-MS–based RMP and commutable secondary RMs, combined with a system to monitor the correct implementation of traceability, will help improve the situation, the researchers wrote.

THE CASE FOR DIAGNOSTIC TESTING AFTER ATYPICAL CFDNA RESULTS

Diagnostic testing clarifies atypical cell-free DNA (cfDNA) screening results and detects clinically relevant abnormalities in the fetus and the mother, a new study concludes (Genet Med 2026; doi: 10.1016/j.gim.2026.102713).

The impact of atypical screening findings on pregnancy outcomes has not yet been studied on a large scale. To address this gap, researchers from a single large reference laboratory aimed to determine the diagnostic yield of invasive diagnostic testing

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after atypical cfDNA screening and to describe the genetic abnormalities underlying atypical cfDNA results.

The researchers matched 10 years of fluorescence in situ hybridization (FISH), karyotype, and chromosomal microarray analysis (CMA) testing performed on prenatal, newborn, and/or maternal samples to previous cfDNA screenings with atypical results, generating 204 index cases.

Of these 204 index cases, 102 had a diagnostic finding. Eighty-seven diagnostic findings were related to the atypical cfDNA screen. Fifty-five abnormal results were pathogenic, 18 were variants of uncertain significance, and eight were likely benign. Copy number variation (CNV) was the most common finding, occurring in 38 cases, followed by aneuploidy in 37 cases, and chromosome arrangements in 20. The researchers detected uniparental disomy (UPD) in five cases and suspected consanguinity in three. These two smallest categories may be underrepresented because UPD and consanguinity cannot be detected by chromosome analysis or FISH, the researchers noted.

In 99 of the 204 index cases, an atypical cfDNA report was available to review, and in 96 of the cases, information was provided regarding the atypical finding on the test requisition form or through calls to the healthcare provider. Details in the cfDNA report that indicate the chromosome involved, the origin of the finding, and the type of abnormality detected can inform follow-up testing. For example, cfDNA results that appear to be a CNV rather than whole-chromosome aneuploidy should prioritize CMA over chromosome analysis, the study authors wrote.

The researchers urged cfDNA laboratories to provide details on the suspected abnormality origin and type because this information guides downstream testing.

In 2024, only 54% of people diagnosed with tuberculosis received a recommended rapid molecular diagnostic test, according to WHO.

POOLED TESTING MAY EXPAND ACCESS TO MOLECULAR TESTING FOR TB

Pooled sputum testing halves the number of cartridges needed to make tuberculosis (TB) diagnoses, according to recent research. This finding suggests that pooled testing could expand access to World Health Organization (WHO)-recommended rapid molecular TB tests using existing laboratory capacity (Lancet Glob Health 2026; doi: 10.1016/j.langlo.2026.104051).

In 2024, only 54% of people diagnosed with TB received a recommended rapid molecular diagnostic test, according to WHO. To explore a potential strategy for narrowing this gap, the researchers evaluated the performance of pooled TB testing in a prospective, observational, multicenter diagnostic accuracy study.

They enrolled individuals with presumptive TB through facility-based case finding in district hospitals and primary health centers in Bangladesh, Brazil, Cameroon, Kenya, Malawi, Nigeria, and Vietnam. The researchers tested sputum individually on Xpert MTB/RIF Ultra (Xpert Ultra) and in pools of two, three, or four specimens on Xpert Ultra. Culture was the microbiological reference standard. The researchers estimated the sensitivity and specificity of pooled testing versus culture, positive percent agreement (PPA) versus individual Xpert Ultra, and cartridge savings. Results were available for 95.2% of participants from 3,666 pools, including 3,195 pools of four.

Using culture as the reference standard, sensitivity of pooled testing versus individual Xpert Ultra was 84.9% versus 88%, and specificity was 98.3% versus 97.7%. PPA was 90.1%, and it remained above 96% for high, medium, and low individual Xpert Ultra semiquantitative grades, but lower for very low and trace grades.

Pooled testing used 7,028 cartridges versus 14,362 for individual testing, a 51.1% reduction.

Scaling up of this approach could facilitate expanded access to molecular testing in low to moderate tuberculosis positivity settings without the need for additional infrastructure, the researchers wrote.

They added that their study is the first to estimate the diagnostic accuracy of sputum pooling for tuberculosis against culture as a microbiological reference standard, rather than measuring agreement with individual Xpert alone.

NEWBORN SCREENING FACES A PRIVACY CROSSROADS



Disputes over the storage and secondary use of dried blood spots have stalled long-term congressional reauthorization of this lifesaving program and intensified calls for greater transparency.

BY KAREN BLUM

Since the 1960s, newborn screening for rare diseases such as phenylketonuria and other genetic conditions has been made possible by dried blood spots — samples obtained by pricking babies' heels and collecting blood drops on filter paper cards that are then sent primarily to public health laboratories. It's been an effective method that identifies about 6,700 babies born with rare conditions each year, according to the National Organization for Rare Disorders (NORD; Int J Neonatal Screen 2023;9:23).

But in the past 2 decades, long-term storage and use of residual dried blood spots have become embroiled in lawsuits, and in one case, were even used to identify a parent accused of a crime. Because of the privacy concerns that these issues have raised, Congress has not officially reauthorized ongoing funding for newborn screening programs since 2014. Although the programs have continued to receive funding each year, the lack of formal reauthorization means that funding could be reduced or eliminated at any time.

BIG VARIATIONS IN STATE POLICIES FOR STORAGE

Most states now test for the majority of 30-plus conditions included in the Recommended Uniform Screening Panel (RUSP) for newborns. If conditions are identified, clinicians contact the parents. After that, policies on storage — and whether consent is needed for future research — vary widely by state.

"There are as many policies for retention as there are states," said Dennis Dietzen, PhD, DABCC, chair of pathology and laboratory medicine at Phoenix Children's Hospital. Some more conservative states allow storage for 3–6 months, enough to cover the newborn screening window to ensure patients are properly identified and followed up with before the spots are destroyed, he said. Other states have intermediate policies and store dried blood spots from 1–5 years. Tennessee, for example, stores for up to 2 years and doesn't permit the spots to be used for research.

Another handful of states, including California and Massachusetts, never destroy their spots. Once any diseases are identified and the families are notified, the spots typically are stored without identifying information for future quality assurance or analytic purposes, Dietzen said. In some cases, they are stored with a code that could be tracked back to a patient if needed.

Blood spots are retained by laboratories for various reasons. Labs could keep the cards short-term in case a result appears skewed and needs a retest, to uphold in-house validation and quality efforts to remain compliant with CLIA requirements, and to monitor competency among testing personnel.

But dried blood spots also hold value long-term. "Blood spots can be very stable, especially when we're talking about the markers we're looking for in newborn screening, such as amino acids, that basically dry into that paper pretty well. They can be kept in the cabinet for a pretty long period of time — months to years," said Danyel Tacker, PhD, DABCC, FADLM, medical director of clinical chemistry and mass spectrometry at West Virginia University Hospital in Morgantown, West Virginia.

When spots are maintained long term, laboratories can use them to validate new testing methods or to test for newly characterized diseases. They also provide a rich resource for population studies on various disorders, Dietzen said.

THE RISK OF REIDENTIFICATION

Typically, spots are stored with just minimal information such as gender and birth date, Tacker said. Other means for laboratories to maintain privacy include assigning a dummy ID to a card and maintaining the original information elsewhere. Laboratories are all governed by CLIA regulations, which require them to protect patient information and maintain confidentiality.

"We have built-in guidelines, checklists, and all sorts of systems to make sure that we are protecting private health information as much as possible," Tacker said. "There are some concerns publicly about bad actors coming in and buying data and then selling it again. Those are valid concerns. But I can tell you that the people that are in newborn screening labs are definitely not in it for a profit scheme. Usually, these laboratories are operating on a pretty slim to negative margin, and they're doing it strictly for clinical care."

Reidentification of samples could be possible if a disease is ultra rare and there is one patient a lab has been monitoring long-term, Tacker said. "You would basically know who that person is if you got a specific result back."

Additionally, technological advancements have improved the ability to reidentify deidentified samples. "The genomic data we dig into now gets paired with fundamental chemistry in a way that we didn't do, say, 20 years ago," Tacker said. "Twenty years ago, we were looking at single changes to DNA and saying, 'Is it there? Yes or no?' Now we can do whole genome sequencing and we can find variants of a gene that are pretty signature. When we attach that to a general profile or a region, it could trace to a patient or family. That's something that we really need to have open

Previous page and right: MassiStock / iStock



discussions about in our community [and ask,] what are we going to do about this?"

It used to be thought of as "really far-fetched" that dried blood spots might be reidentified, Dietzen said. "But I think that we have to consider the risk as real. Is it low? Heck yeah. But it is real."

One of the first concerns people think about from these spots being identified is the ability to qualify for health insurance coverage, Tacker said. Although the Affordable Care Act stated that insurers could not refuse coverage or charge more because of preexisting conditions, "there are constant challenges to that stance," she said. Yet many patients with diseases diagnosed early can live relatively stable, full lifespans, even if their conditions require lifetime management.

Another potential concern is what should happen if the spots are used for research that leads to some sort of commercial application or windfall profit for a company. Should the original owners of the samples be entitled to a cut? It's something that opponents of long-term storage and secondary use for research point out as risky, Dietzen said. "There are legal reasons, forensic reasons, insurance reasons, medical reasons — all kinds of reasons why you don't want dried blood spots to be reidentified."

"I THINK THAT WE HAVE TO CONSIDER THE RISK [OF DRIED BLOOD SPOTS BEING REIDENTIFIED] AS REAL. IS IT LOW? HECK YEAH. BUT IT IS REAL."

BUILDING TRUST THROUGH EDUCATION

Over the past couple of decades, families in Texas, Minnesota, Michigan, and New Jersey have filed lawsuits over continued storage and use of these spots for research without obtaining consent. These cases have made it to the state supreme courts or higher. Officials in Texas and Minnesota had to destroy millions of samples following 2009 rulings. However, as of 2025, the Sixth Circuit court ruled that Michigan's handling of blood spots did not violate parents' constitutional rights. Meanwhile, a federal judge last year rejected some New Jersey parents' claims that the state's practice of retaining samples violates their constitutional rights. As of October 2025, those parents filed an amended complaint.

The original complaints in New Jersey arose following a 2022 incident in which state police subpoenaed a 9-year-old child's stored blood spot to link the father to and charge him with sexual assaults from 1996 and 2003.

"The real issue is not so much privacy as public expectations," said Ellen Wright Clayton, JD, MD, professor of pediatrics, health policy, and law at Vanderbilt University in Nashville, Tennessee. She noted a need for more clarity

in the public domain. People expect health-related information to be private, but their expectations are unfounded, she said. Although the primary purpose of the newborn spot collection is to identify children in need of medical care, there are other uses that are possible.

However, Clayton added, "In this very skeptical age, programs need to be worried about whether they are going to compromise their public health function by allowing samples to be used for research."

Stanley Lo, PhD, professor of pathology and laboratory medicine at the Medical College of Wisconsin in Milwaukee, agreed. "We as practitioners need to be better at providing information to the general public about what newborn screening does and how it works, including what happens to dried blood spots and what they may be used for." Even medical residents he teaches don't necessarily know.

"A lot of people believe that parents are the owners of those dried blood spots, and states need to establish strong policies to help maintain that the spots won't be abused in any way," he said. "It comes down to education. You should get consent and say this is what we're going to do and why. My guess is that most people, once they understand what's going on, would be amenable."

THE REAUTHORIZATION IMPASSE

Why has this been a stumbling block for congressional reauthorization? Tacker admitted that laboratory professionals are mystified by this. "If you want to benefit a population, you would think newborns with metabolic disorders that are inherited or sporadic would be a key thing to fund. It's also not a very expensive program, so we're honestly a little flabbergasted about the idea that this would not be renewed," she said.

"IT COMES DOWN TO EDUCATION. YOU SHOULD GET CONSENT AND SAY THIS IS WHAT WE'RE GOING TO DO AND WHY."

Currently, Congress is doing a year-to-year reauthorization for the program, Dietzen said. The crux of the argument is what's considered identifiable, and what sort of research might increase the risk of reidentification. "It's a question that I think is best answered in a project-by-project way, where an institutional review board has to assess those risks and determine if there's substantial risk to disclosing the identity of those individuals," he said.

"I think there's a balance between what's right to do nationally, and continuing to provide independence at the state level," Lo said. "Congress is concerned that [the possibility of reidentification] violates the freedom of individuals, so I think they want to make sure that gets resolved before they move on to approve funding."

Privacy concerns over genetic information span beyond blood spots to commercial retail businesses that specialize in genealogy, such as the now-bankrupt 23andMe, Tacker noted.

"There's a whole arm of laboratory testing now that is fully commercial and fully bought into by the population. And I don't know that people give it very much thought when they swab their cheeks to find out what their heritage is," Tacker said. "There's all this information floating around, and startup labs doing all sorts of stuff. But if they're not doing clinical testing, it's strictly a boutique operation. They aren't held to the same kind of standards that we are in healthcare. The population needs to be concerned about how data are handled."

Compounding the issue, public perception of medicine and science "has taken a beating" over the last 3–5 years, Dietzen said. "When folks see scientists making an argument for unfettered use of these things without consent, I think that feeds this conspiracy that we're all up to no good, and that there are motives other than the health of the children of this country. That's unfortunate."

Sound laboratory policies could range from allowing secondary research for everything or restricting it to certain uses. But a lot will hearken back to the language in the original consent form signed by parents (if there was one) and what that allows, which differs by state, Dietzen said. In states that permit long-term storage, the children whose spots are stored age into adulthood and may themselves need to consent to research use.

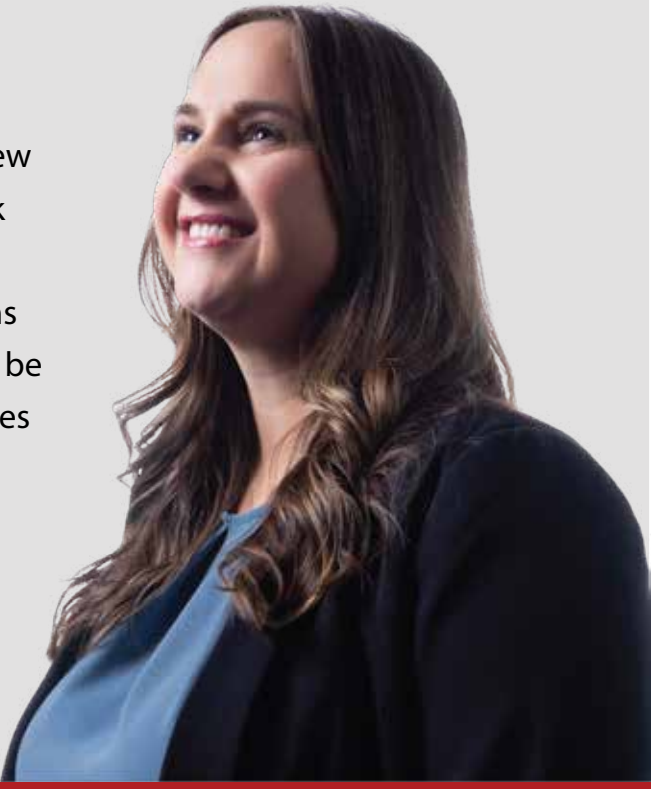
"Dried blood spots are an amazing tool that has saved the lives of many children and allowed children with what were previously fatal disorders to live normal, healthy lifespans both cognitively and physically," Dietzen said. "There's no question [that dried blood spots] are valuable, and we should treat them as the valuable resource that they are."

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“I have been a member of ADLM for the last few years. It has really helped me grow a network in the point-of-care realm specifically. I have created really great, passionate collaborations with coordinators across the nation. I cannot be any more grateful to ADLM for the experiences that I’ve had.

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Long discussed but not yet implemented in routine care, personalized reference intervals are gaining renewed attention as advances make individualized laboratory interpretation more feasible.



ONE SIZE DOESN'T FIT ALL

BY GRACE BROWNE

When a patient visits the doctor to have a blood test, their blood sample is drawn and sent to the lab, and a few results come back: cholesterol, glucose, a white blood cell count. Next to each number on the report sits a reference interval — a range that helps the doctor judge whether the result counts as normal or not. If the number falls inside the interval, it goes without further inspection. If it falls outside, it may prompt a second look, a follow-up test, or a diagnosis.

For decades, this has been the basic logic behind how blood tests are read. Reference intervals are used to interpret a patient's laboratory test results, which in turn are used for the diagnosis and monitoring of diseases, as well as to guide treatment. Typically, reference intervals are derived from a sample of an overall healthy population. But the heterogeneity of the human population means that they are not one-size-fits-all. What represents a normal range for one person may not be the same for the next. To improve on this, population reference intervals may be partitioned based on factors such as sex and age. But still, the broad brush nature of the data lacks the nuance needed to work for every individual.

That means that for some specific markers, a patient's measurement result may fall within the population-based reference interval but still represent an abnormal result for that particular person. For instance, a patient's white blood cell count could fall within the "normal" range, but their measurement could still carry increased risk for that specific individual. On the other hand, a patient may get a result that lands outside the typical population-based reference interval, but that is actually normal and healthy for that individual.

For decades, experts have pointed to the usefulness of reference intervals that are based on an individual's own repeated measurement results that were taken when they were healthy. The idea is that their intervals would then reflect their own physiology, rather than the general population, and would be specific for them.

This is not a wholly novel concept. "People in the '70s actually proposed personalized reference intervals," said John Higgins, MD, professor of systems biology at Harvard Medical School and a pathologist at Massachusetts General Hospital. "It's not a new idea by any means, but there are some reasons why it's becoming more interesting." One of the biggest is that there are a lot more laboratory data available these days, meaning more historical information on people, which makes it easier to devise these more personalized intervals. Recent advancements in medicine are allowing for more and more personalized medicine in general.

Yet despite decades of interest and a growing recognition of their potential advantages, personalized reference intervals remain largely absent from routine clinical practice. No laboratories have implemented them on a broad scale. The reasons are complex, ranging from scientific and operational challenges to questions about how clinicians would use and interpret personalized results. As researchers continue to explore their promise, they are also working to determine where these intervals could have the greatest impact and what evidence is needed to bring them into everyday care.

WHERE THINGS CURRENTLY STAND

There have been some areas where this work has progressed more than others; hemoglobin is one. Between different healthy people, hemoglobin levels vary widely, but for any one person, the level tends to stay remarkably stable over time. That means a result that's still "normal" by population standards could represent a meaningful shift for an individual, said Aasne K. Aarsand, MD, PhD, director of the Norwegian Organization for Quality Improvement of Laboratory Examinations, and a consultant medical biochemist in the Norwegian Porphyria Centre, Haukeland University Hospital.

Elsewhere, the work has been much slower. And the widespread use of population-based reference intervals comes with various cons. "You can think of a population reference interval as really just saying, here's what healthy looks like. It's very well designed to pick up abnormalities, so it captures health if you're in the middle, but not outside of it," said Brody Foy, DPhil, assistant professor at the University of Washington department of laboratory medicine and pathology.

Personalized reference intervals also could be helpful not only for detecting a deviation from health, but also in the other direction. Foy and Higgins have done some work to show that personalized reference intervals can help people who are returning to good health figure out what their healthy state looks like with more accuracy, which in turn can help them determine whether they're really heading towards their healthy baseline. "Even for really sick patients in the hospital, in the intensive care unit, knowing what their healthy baseline really looks like can help physicians figure out when somebody is on a good

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recovery trajectory and when they're deviating," Higgins said.

A DATA-FUELED SHIFT

There is a major reason why now is the time to start thinking about personalized reference intervals: We have access to more health data than ever, particularly in higher-income countries. A major step forward on the path has been the introduction of electronic health records (EHRs), Foy said, which have only become the norm in the last 5–10 years. These records mean that much of a patient's medical history, including test results, is stored in a centrally located, easily accessible database.

One technological innovation in particular could speed up the implementation of personalized reference intervals: Artificial intelligence (AI) could be used to integrate relevant individual-specific information from EHRs, refine the selection of appropriate historical data, and potentially improve the robustness and clinical relevance of personalized reference interval estimation.

At the same time, although Higgins acknowledges that AI could be used to analyze existing data in a helpful way, he thinks pretty basic calculations would help, too. "I don't think there's evidence we need fancy methods, and to some degree the simpler methods are preferable, because then they can be used everywhere and people can learn how to use them in different environments," he said.

HURDLES ON THE ROAD TO ADOPTION

The implementation of personalized reference intervals will depend on a number of factors. First, there must be robust, appropriately designed clinical studies that can demonstrate that personalized reference intervals have benefits over population-based reference intervals. These studies have to show that personalized reference intervals not only provide more accurate results, but that they also offer earlier or more accurate detection of certain diseases and improve patient outcomes, as well as being cost-effective. A convincing study would need to show that flagging a result outside a patient's own reference interval actually corresponds to a clinically significant event.

The other hurdle that personalized reference intervals face is how the clinic will handle them. "Before laboratories implement personalized reference intervals," Aarsand said, "clinicians need to know what they mean and how they should handle them."

To convince clinicians, "we should inform them about the limitations of population-based reference intervals: why they may not be sufficient to interpret all individuals' results, and why we need personalized reference intervals," said Abdurrahman Coşkun, MD, a professor of clinical biochemistry at Acibadem University in Istanbul, Turkey, who is also currently affiliated with Knappschaft Kliniken University Hospital Bochum, at Ruhr University Bochum in Germany.

The ongoing work is that, even if you can construct a personalized reference interval, you then have to come up with the evidence for how it can be used best alongside existing standards. "Say you have a personal benchmark for a patient, you still have to work out how best to use it for targeted decisions, and build the evidence that it will actually improve care," Foy said.

Thus far, these studies have been



limited. As more get underway, Coşkun and Aarsand recommend that they should focus on well-understood, commonly requested tests for widespread diseases and conditions. This could include lipid profiles for cardiovascular disease, complete blood counts for hematological disorders, and glucose and HbA1c for diabetes. Because these tests are routinely and repeatedly requested in clinical practice, it's more likely that there will be longitudinal measurement data available for a major proportion of individuals in EHRs, Coşkun and Aarsand said.

Still, barriers remain. To acquire the amount of data needed, it will require repeated testing over a substantial time period when the patient is in a healthy state. In reality, this has limited practicality. "If I could wave a magic wand and say everyone gets a test every six months while they're healthy, with no hassle to them and no cost to the lab, and we have that data and can have this rolling benchmark, that would of course be great," Foy said. "But it's utterly impractical."

Although patients usually seek out a clinic visit only when they require treatment, personalized reference intervals would require patients to routinely visit the clinic when they are in a healthy or clinically stable state. Part of Foy and Higgins' work is building methods that can isolate what is likely to be the healthy part of a patient's prior testing, so that it can be used to create a benchmark.

A more realistic route would be to estimate a patient's personalized reference interval based on their longitudinal laboratory data already available in their EHR. Three repeated measurements would be necessary at the very least, Coşkun and Aarsand said, though five would be preferable.

Another big question remains: There's a big difference between what is deemed "normal" and what is deemed "healthy," and that differentiation is really hard to untangle, Foy said. That means when you're trying to construct a benchmark, whether at the population or the personal level, you have to decide what that benchmark is actually supposed to be.

There are also some concerns that come along with personalized reference intervals. When taking a narrower personalized interval, if a patient's results go outside the bounds of it, that could raise an alarm, which could be a false positive if it is in fact normal variation. "Having lots of alarms and lots of flags would probably not be helpful — it's about finding the important signals," Aarsand said.

"But since there hasn't been any widespread implementation, and there are so many reasons to expect benefits, I think we should give it a try and find out how many false positives actually occur and whether they can be mitigated if necessary," Higgins said.

Coşkun is optimistic that personalized reference intervals are on the way. "There's gradually increasing interest, and I'm sure that in the near future it will be necessary, because for personalized medicine, we know the bottleneck is the population-based reference interval data," he said. "[To get there,] we need many more papers published on personalized reference intervals, scientific activities, and maybe workshops to disseminate this information in the laboratory community."

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A Q&A WITH DANYEL TACKER, PhD

Implementing LDTs effectively

By Jen A. Miller

FOCUS ON MOLECULAR DIAGNOSTICS

Laboratory developed tests (LDTs) can be game changers: They allow laboratories to create tests tailored to their patient populations, and they can save labs time and money by eliminating the need to send tests out. But they also come with risks, especially in a changing regulatory world.

CLN spoke with Danyel Tacker, PhD, clinical professor of pathology and medical director of special chemistry and mass spectrometry laboratories at West Virginia Hospital and J.W. Ruby Memorial Hospital, about how to use LDTs to innovate and adapt while staying within regulatory lines.

What differentiates labs that successfully launch LDTs from those that struggle?

In a nutshell, it comes down to careful planning. To launch an LDT effectively, you need to engage with the clinicians who will be using the test and develop a quality assurance system that detects real errors. You must know the method's intricacies and be able to detect drift. If you plan well, you will have systems in place that will give you confidence in the performance of the test.

What typically triggers your lab to consider developing an LDT instead of adopting a commercially available assay?

With commercial assays, sometimes there are aspects of the performance criteria that don't quite meet the needs of the population we're trying to serve. I'll use an example from my colleague Amy Pyle-Eilola, PhD, DABCC, FADLM, director of clinical chemistry at Nationwide Children's Hospital. She had to use Food and Drug Administration (FDA)-approved urine drug toxicology screens in a pediatric population, whose urine is more dilute than older patients' urine. This can lead to false-negative results in a group for whom any incidence of drugs is potentially clinically relevant.

If an FDA-approved test isn't engineered to suit your purpose, it's up to you to build one or modify an existing test. In Dr. Pyle-Eilola's case, she modified the cutoff threshold to improve the test's sensitivity among pediatric patients. Any presence of a drug was her first signal to do more digging. Then she'd send for a more extensive analysis in a mass spectrometer.

My lab's development of a test to confirm toxicology results onsite instead of sending them to a reference laboratory was driven by cost concerns — but we knew we needed to have the onsite capabilities and knowledge to do mass spectrometry testing to pull it off. We did a "toe dip" first, starting with alcohol biomarkers on a limited panel. When we saw that, yes, we were doing a good job with building this method around it, we then built opioid and tetrahydrocannabinol (THC) tests.

It can also be helpful to take input from the clinical team. When we engaged with behavioral medicine, they said they would like us to add tramadol to the opioid panel and asked if the THC test could distinguish between delta-8 THC and delta-9 THC.

What does your feasibility assessment look like before you commit resources to an LDT?

We go so far as to build the program we intend to use. If it's in mass spectrometry, we will tune standards, ask how we're going to calibrate the test, and then build a calibration method. We will simulate a clinical scenario and assess what kind of quality assurance is needed and what operational conversations we'll need to have.

For example, with our opioid test, our first results were a mess. In the development phase, we realized we were going to have to add an enzymatic digestion step to cut glucose moieties off the drugs. It took us 6 months just to present a validation plan to the clinical director.

You may need to pour thousands of dollars and hundreds of hours into that development phase. Or, if it's a modification or something smaller like adding a filtration step, you might only have to devote tens of hours and a few hundred dollars of materials to get off the ground.

With some tests, we've gotten to the point where we realized right away that feasibility was a big no with what we have onsite right now. The hospital administration was disappointed, and we told them that this is why our lab needs space, staff, and equipment. When the "no" comes,

and your institution is surprised by it, it's a good time to emphasize, "Well, you've supported us really well so far, and now that support must continue so we can expand."

What are the biggest implementation challenges you've faced? Have any caused the lab to scrap the contemplated LDT?

We've had to extensively educate our administration about the different methods for tests and feasibility. For example, if they request that we do a test for lead, we must explain that, although we have mass spectrometry in our lab, we'd need a different kind of mass spectrometer to perform that analysis.

For every possible LDT, we must consider: Do we have the space? The cash? Do we have the means to sustain it? Do we need new equipment?

There are also concerns about regulatory pressures. For example, we were building the delta-8 check for our THC test during the last round of policy discussions about LDT oversight. We did it as a qualitative yes/no test for whether delta-8 was present. The hospital really wanted that to be a quantitative test, but we were facing an uncertain regulatory structure. We didn't even know if our baseline method modification would be approved.

While we're generally good at taking our cues from a regulatory standpoint, labs are heading into a dangerous environment right now.

If we find out a user is trying to inappropriately alter a method in terms of clinical interpretation, we might put a halt on a launch and say, "Hold on, that's not what we talked about. What are you telling people this thing can do?

Some teams are afraid to go into that territory. They're worried, for instance, that they could do clinical harm, so they would rather leave the situation as it is.

How would you advise a health system on integrating LDTs alongside commercially available assays?

Consider alternative collection techniques. This is something we faced with COVID. The FDA kits had those "tickle your brain" type swabs. Labs looked into swabbing the mouth and developing self-collection techniques so they didn't have to put nurses in tents outside. They thought through how they might modify the FDA-approved kit.

Also think about how labs can complement broader efforts. For example, with the recent measles outbreak, many labs did not have collection techniques because the disease had been eliminated. But now that unvaccinated people are spreading measles in their communities, local testing options would be great.

Sending all those tests to the state lab or the Centers for Disease Control and Prevention would flood them. So creating that "hub and spoke" model, where local labs can develop and offer tests would help a lot, like it did with COVID.

How do you monitor a live LDT's performance and decide when to revalidate?

Any time you're going to change a test, you may have to go back to the drawing board on validation. I have an example that isn't even an LDT. It's an FDA test with a new generation of reagents for our primary chemistry analyzers. Right after go-live, providers started getting a bunch of elevated results.

We discovered that gold-top tubes (for serum) did not show an elevation in the outreach population, but the green-top tubes (for plasma) did. So we switched the outpatient population over to serum.

How does your lab balance innovation with concern over potential future FDA oversight?

Through careful consideration. We mapped every LDT we had and did a brief risk matrix. What are the pros and cons? What is the turnaround time if we can't do this test? Would turning off an LDT delay decision-making in the hospital units?

Maybe you can rank and prioritize tests that are critical for care, and balance your fears by streamlining the number of tests or developing contingency plans.

What advice would you give to a lab preparing to launch its first modern molecular LDT?

Get familiar with the guidelines from your accrediting agency. Look into the questions you will be required to answer before an inspector is in front of you. Ask yourself: How am I going to respond?

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A Q&A WITH HUNTER BEST, PhD, FACMG

The ABCs of LDTs

By Jen A. Miller

FOCUS ON MOLECULAR DIAGNOSTICS

Creating laboratory developed tests (LDTs) is always a challenge, especially in molecular diagnostics. As advances in genomics fuel precision medicine, today's clinicians encounter an almost infinite array of scenarios with their patients. That means that LDTs — and the lab professionals who design them — must be able to meet the challenge.

CLN spoke with Hunter Best, PhD, FACMG, about how to decide which tests to develop, the importance of having a range of patient samples for validation, and how bioinformatics is pushing the field forward. Best is the vice president of molecular operations and a medical director of molecular genetics and genomics at ARUP Laboratories and a professor of clinical pathology at the University of Utah School of Medicine.

What distinguishes labs that successfully launch LDTs from those that struggle?

Laboratories that excel in developing LDTs — especially reference labs like ARUP — succeed because people trust the validity of the tests. We try to validate our tests on every clinical scenario we're likely to encounter, so we've earned that trust.

Smaller laboratories may have samples, but they don't always have the same resources that reference laboratories do. They may come across clinical cases they weren't prepared to see. That doesn't mean they don't know how to handle them; it just means their validations are not always as all-encompassing as the ones that happen at larger labs. That can be a challenge.

How do you define the intended clinical use of a new LDT before development begins?

With a lot of the LDTs that we've developed, clinical targets were already identified, whole genome sequencing notwithstanding. We knew the clinical populations for which testing should be used, and we designed an assay to interrogate those specific regions of the genome, whether they exist within cancer cells or patients' inherited genetic material.

However, what we can't control as a reference lab is how clinicians end up ordering LDTs. Our website has recommendations explaining the best use case for each test, but providers ultimately decide how LDTs are used. ARUP is an academic institution, so we try to educate clinicians to make sure they are ordering appropriately.

What are the biggest technical challenges you encounter during assay configuration and optimization?

Gathering samples and ensuring we're covering all relevant clinical situations is what typically takes the longest time. It's an extensive process. We have tests for which we've been actively accumulating samples for more than a year before we're even ready to start the validation process. Also, we don't usually use the same samples for development and validation — which means we need to have sample sets available for both.

Successful tests must address many or all of the scenarios clinicians are likely to see. Sometimes labs will rush to onboard a test and skip some relevant scenarios in the process. I think that's what spurred the Food and Drug Administration's (FDA's) concern about LDTs in the first place.

I don't necessarily disagree with the essence of what the FDA was trying to do, but they were painting with a really broad brush. Not all LDTs are equivalent, and not all labs are equivalent. The way that startups do things is very different from how labs that have been established for decades do them.

How do you design analytical validation studies for complex molecular LDTs?

The short answer is "very carefully." We look at all the genomic regions that surround the targets we're interested in, and we design around them. If we can't do that, we don't include those targets on an assay.

A lot of factors go into the design. For example, are we looking at germline sequences or regions that exist in only a subset of cells, like in an oncology specimen? The answer to that question helps determine how we go about designing. Since the limit of detection is a lot lower with cancer specimens, we'd likely want to push the sensitivity. There's no one-size-fits-all approach.

At ARUP, before we enter evaluation, we do development work

where we look at a broad spectrum of samples. After we evaluate the initial design of a test, we'll often go back and redesign components of it to improve performance.

We may be working on something for a year or longer before validation starts. If samples don't perform the way we expect them to, we might have to go back to the drawing board. It's a very long process.

How do you approach clinical verification before launching an LDT?

In our validation, we include samples that have a known diagnosis, whether those samples have been tested using other methods in our own lab or in an external lab.

In some instances, we get samples from our patients, ranging from those who have lifelong inherited conditions to those with sudden-onset diseases like acute myeloid leukemia (AML). Other times, we buy samples from another laboratory that has validated that the patients they came from have a specific mutation we're interested in.

Testing "normals" is also important. You want to include a good spectrum of samples, from positive and negative known clinical cases as well as patients known to not have the clinical disorder.

How has bioinformatics changed your LDT validation and implementation process?

Bioinformatics has become a standard of care in multiple fields, including oncology and inherited disease. We get massive amounts of data from genomic sequencing, and we need a way to handle it all. Bioinformatics tools do that, and they make it easier to target more regions that were difficult to test in the past.

I'm not talking about artificial intelligence (AI) here. Bioinformatics tools on their own have revolutionized our classification of samples. As samples are tested, we have a catalog of variants that we're seeing in patient samples and an internal database — so we know that we have a sample that has X variant in Y gene.

When we do validation work, we're able to query that database and figure out if we have samples with variants in the genes of interest. We can pull samples for validation from our database. Additionally, bioinformatics allows us to reprocess our data when there are changes in the scientific literature. In those cases, we may be able to reanalyze and provide a diagnosis that we couldn't before.

To touch on AI, we have yet to use it in any sort of validation work. We have used it to help generate tables, but ARUP is a bit more cautious than some other labs regarding how we're using the technology. While there are some significant benefits, there are also concerns. We want to be careful, especially considering that we're handling patient data.

How do you design an LDT workflow that balances business needs with clinical requirements?

A lot of factors go into the determination. The business aspect involves determining how a test fits into the current lab workflow. Does using this different method still get us to the same clinical answer? What value does it add? Whenever possible, we try to design tests that fit into our workflow and utilize the platforms we already have.

Also, it's worth considering whether a test is being designed for a relatively common disorder, a condition that affects one in a million patients, or a disease for which we're going to see three cases in a year. Often, we will still onboard tests for rare diseases because there are people who need them. But it's important to think about how to fit them neatly into the workflow so the cost of maintaining them is minimal.

Other times, business efficiency has to take a back seat. Regardless of the implications to our workflow, the clinical question needs to be answered. In these cases, we will onboard the test. We operate under a different model than labs that have to report to shareholders. The clinical need for a test is the ultimate driver for us.

What advice would you give to a lab preparing to launch its first modern molecular LDT?

Don't rush. In the long run, taking the time to develop the test correctly will pay dividends. If you cut corners, you end up needing to do corrections anyway — and you don't want to have to do that after a test has gone live.

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Regulatory Roundup



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FDA authorizes robotic blood draw device

The Food and Drug Administration (FDA) recently announced authorization of Aletta, the first standalone robotic device that can draw blood from a patient's arm without hands-on intervention by an operator.

One supervising phlebotomist can oversee up to three Aletta devices at the same time, according to the authorization, which also specifies that Aletta should be used with adults in outpatient settings.

After the phlebotomist initiates each session, the Aletta autonomously handles the blood draw. It uses near-infrared light and Doppler ultrasound to locate a suitable vein and distinguish it from arteries. If it finds no appropriate vein, the device will not attempt the procedure.

After finding a suitable vein, Aletta applies a tourniquet, prepares the skin, inserts and disposes the needle, changes collection tubes, and applies a bandage. The supervising phlebotomist confirms that collection tubes are filled in the correct order and verifies that all tubes are adequately full following the procedure.

The device continuously applies disinfectant to the skin during the ultrasound scan. A trained professional cleans the device between patients.

The device may help address the current phlebotomist shortage in the U.S., FDA said.

AMYLOID PATHOLOGY TEST EARNS FDA CLEARANCE

The Food and Drug Administration has cleared Roche's Elecsys Phospho-Tau (217P) Plasma (pTau217) blood test, the company recently announced.

The single-biomarker, blood-based test aids in the identification of amyloid pathology associated with Alzheimer's disease in individuals 55 years and older with signs, symptoms, or complaints of cognitive decline. Elecsys pTau217 provides both rule-in and rule-out assessment of amyloid pathology using the same validated clinical cutoffs across primary and specialty care settings.

Designed for use on the Roche cobas platform, the test may help clinicians assess the likelihood of amyloid pathology earlier and identify patients for additional evaluation or specialist referral, according to Roche.

The assay provides positive, intermediate, and negative result categories to support assessment of the likelihood of amyloid pathology. Results are interpreted in conjunction with clinical information and other relevant findings.

COMPANION DIAGNOSTIC GETS ADDITIONAL FDA APPROVAL FOR CERTAIN ADVANCED BREAST CANCERS

Guardant Health has announced Food and Drug Administration (FDA) approval for its Guardant360 CDx as a companion diagnostic (CDx) to identify patients with hormone receptor (HR)-positive, *HER2*-negative advanced or metastatic breast cancer harboring tumors with *ESR1* mutations before radiographic progression who may benefit from treatment with Etcamah (camizestrant).

The approval is based on data from the SERENA-6 clinical trial, which used circulating tumor DNA monitoring to detect emerging *ESR1* resistance mutations before radiographic disease progression.

Study participants underwent serial testing with Guardant360 CDx every 3 months while receiving an aromatase inhibitor with a CDK4/6 inhibitor. Upon detection of an *ESR1* mutation before radiographic progression, the researchers transitioned eligible patients to camizestrant-based treatment. Patients treated under this new paradigm experienced 74% longer median progression-free survival with a 47% reduction in risk of deterioration in global health status and quality of life, according to Guardant.

The trial demonstrated the clinical value of proactively identifying disease progression earlier than radiographic imaging and adapting therapy sooner in the course of disease. Historically, biomarker testing in advanced cancer most often occurred after clinical or radiographic progression, Guardant said.

This latest FDA approval for Guardant360 CDx marks its 29th CDx indication across multiple tumor types globally, the company added.

AT-HOME FLU AND COVID-19 PCR TEST GETS FDA CLEARANCE

Visby Medical recently received Food and Drug Administration (FDA) clearance for the Visby Medical Flu and COVID-19 Test. According to the company, this is the first multi-viral, over-the-counter PCR test to receive FDA authorization.

Designed for home use, the Visby Medical Flu and COVID-19 Test enables consumers to quickly test for COVID-19 and influenza A and B, providing a PCR result in 30 minutes. This, in turn, will help consumers to make faster decisions about care, including whether to seek antiviral treatment or connect with a telehealth provider.

Unlike antigen tests, PCR testing can detect infections earlier and at lower viral levels, making it the gold standard for diagnosing respiratory infections such as COVID-19 and influenza. Earlier detection of these viruses is especially important because antiviral medications such as Paxlovid and Tamiflu are most effective when started early in the course of infection.

WHO GRANTS EMERGENCY USE LISTING FOR HEMORRHAGIC FEVER PANEL TEST IN RESPONSE TO EBOLA

The World Health Organization (WHO) has granted an Emergency Use Listing (EUL) to Cepheid's Xpert Hemorrhagic Fever Panel test to support the diagnostic response to the Ebola Bundibugyo virus (BDBV) outbreak in the Democratic Republic of Congo.

The Xpert Hemorrhagic Fever Panel test detects and identifies nucleic acids from the Ebola virus, as well as Crimean-Congo hemorrhagic fever virus, Marburg virus, and Lassa virus. The time to result is about 1 hour. The assay runs on Cepheid's GeneXpert Dx systems, which are widely deployed across Africa.

The WHO declared the Congo outbreak a public health emergency of international concern on May 17. This EUL enables healthcare providers and public health authorities to leverage Cepheid's rapid molecular testing technology to help identify suspected cases of BDBV and support timely outbreak containment efforts.

CE MARKING GRANTED TO SYNDROMIC TESTS FOR MERS-COV AND OTHER RESPIRATORY VIRUSES

bioMérieux has announced that its Biofire Respiratory 2.1 plus (RP2.1plus) Panel and Biofire Filmarray Pneumonia plus (PNplus) Panel have received CE marking in the European Union (EU) as Class D in vitro diagnostic devices.

This class of devices is subject to the most rigorous regulatory requirements under the EU In Vitro Diagnostic Regulation and is reserved for tests intended to detect pathogens that pose a high risk to public health. bioMérieux's new tests were given this classification due to the inclusion of Middle East respiratory syndrome coronavirus (MERS-CoV) on both test menus, according to the company.

The Biofire RP2.1plus Panel provides broad syndromic testing for upper respiratory infections in about 45 minutes while the Biofire Filmarray PNplus Panel supports the diagnosis of lower respiratory tract infections by detecting a wide range of bacterial and viral pathogens as well as key antimicrobial resistance markers in about 1 hour. Both panels deliver actionable results that can help clinicians make informed decisions earlier in the patient's care pathway, according to bioMérieux.

Industry Playbook



Funding secured to develop single-cell diagnostic for triple-negative breast cancer

One Biosciences recently announced it has received 3.3 million euros in funding from Bpifrance to support the Cancer Single-Cell Analysis for Therapy (CAST) project focused on triple-negative breast cancer (TNBC), carried out in collaboration with Institut Curie.

Current diagnostic methods for TNBC average signals across millions of cells, masking the tumor heterogeneity that drives resistance and treatment failure. In contrast, single-cell tumor profiling technologies for cancer care analyze individual cells rather than averaging the genetic and molecular features of an entire tissue. This approach identifies distinct cell subpopulations within the same tumor.

The 4-year CAST project aims to bring One Biosciences' OneMap to market as the first single-cell diagnostic platform designed to guide treatment decisions for patients with TNBC. OneMap combines single-cell transcriptomics and artificial intelligence to analyze tumors at the resolution of individual cells, directly from standard hospital biopsies. It delivers clinically actionable reports, according to One Biosciences.

The CAST program will focus on industrializing the OneMap platform, validating predictive biomarkers in TNBC, preparing for regulatory approval, and scaling One Biosciences' centralized clinical laboratory infrastructure in the Paris region to enable future commercial deployment.

COLLABORATION FOCUSES ON BLOOD-BASED MOLECULAR TEST FOR EBOLA AT POINT OF CARE

Co-Diagnostics and ReadyGo Diagnostics recently announced a collaboration to evaluate potential use of ReadyGo's sample-preparation technology with the Co-Dx PCR platform for blood-based molecular testing at the point of care.

The collaboration's initial focus will be decentralized Ebola virus detection and outbreak response.

Establishing blood as a compatible sample type would extend the Co-Dx PCR platform beyond the swab-based testing it supports today and into a broad category of bloodborne pathogens that swab sampling cannot reach.

The companies are evaluating two potentially complementary technologies. They are the Co-Dx PCR platform, a point-of-care PCR technology, and GoCollect by ReadyGo, a field sample-preparation system that prepares blood samples for molecular testing at the point of care. The collaboration will assess whether the technologies can operate together as part of a streamlined workflow that prepares the sample, detects the virus, and supports the outbreak response as one connected approach. The collaboration builds on earlier Co-Dx proof-of-concept work testing an Ebola assay using plasma as a sample type, according to the companies.

Co-Diagnostics officials said that while the partnership will initially focus on Ebola, the company hopes to expand the platform to HIV and hepatitis B and C.

ReadyGo officials noted that GoCollect takes sample collection and preparation into the field and works seamlessly with platforms

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such as Co-Dx to create a complete sample-to-result molecular testing solution.

ACQUISITION EXPANDS UROLOGY DIAGNOSTICS PORTFOLIO

Veracyte recently announced its acquisition of Convergent Genomics.

The acquisition adds Convergent Genomics' UroAmp platform, including its proprietary urinary tumor DNA (utDNA) technology, to Veracyte's product portfolio. To date, UroAmp has been clinically validated in non-muscle invasive bladder cancer (NMIBC), including therapy-response monitoring and post-treatment surveillance, Veracyte said.

NMIBC is generally confined to the bladder and may shed only limited tumor DNA into the bloodstream, making blood-based detection challenging. Urine, by contrast, comes into direct contact with the bladder and can provide a highly relevant source of tumor-derived genomic information. By analyzing this information, UroAmp could help guide treatment decisions and monitor patients throughout their care.

Veracyte expects to commercialize this test in late 2028, subject to reimbursement timelines. The company also plans to expand its use of the UroAmp platform to additional indications, including intravesical maintenance therapy monitoring and surveillance following treatment with curative intent.

COMPANY RAISES FUNDS TO SCALE RAPID POINT-OF-CARE MOLECULAR TESTING PLATFORM

Fuse has raised 1 million pounds to speed commercialization of its proprietary Flip platform and expand manufacturing capability at its United Kingdom headquarters.

The funds will support Fuse's development of rapid molecular diagnostics for pathogens and contaminants that are designed for use outside of specialized molecular labs.

The Flip platform combines amplification technology with low cost, disposable tests designed to enable rapid detection of pathogens and contaminants without specialist laboratory infrastructure. The instrument-free approach is intended to support a broad pipeline of molecular diagnostics; deliver lab-quality performance; and reduce complexity, equipment requirements, and delays associated with centralized testing in molecular labs, according to Fuse.

ACQUISITION CENTERS ON MOLECULAR DIAGNOSTICS FOR INFECTIOUS DISEASES

ABL Texcell Diagnostics and its parent company, Advanced Biological Laboratories, recently announced their intent to acquire 100% of the share capital of Vela Operations Singapore and Vela Diagnostics USA.

ABL is currently based in the European Union. The proposed acquisition would allow it to expand its operations and commercial footprint to the Asia-Pacific region and the United States, strengthening its position in the global market for molecular diagnostics for infectious diseases, the company said.

Advanced Biological Laboratories, ABL Texcell Diagnostics, and VDH Holding, the Vela Group's parent company, have all signed a nonbinding letter of intent.

AGREEMENT TO EXPAND POINT-OF-CARE CONCUSSION TESTING

BRAINBox Solutions recently announced it has entered into an agreement with Prolight Diagnostics to supply its Psyros instruments and cartridges for use in point-of-care (POC) delivery of BRAINBox's tests for diagnosis and prognosis of concussion, which is also known as mild traumatic brain injury (mTBI) or acute traumatic encephalopathy.

The supply agreement follows a successful collaboration that included a feasibility study, BRAINBox said.

Prolight's Psyros technology enables the rapid detection and measurement of single molecules from a drop of blood. The company's proprietary and multiplex-capable technology enables the measurement of biomarkers at extremely low concentrations, BRAINBox said.

BRAINBox continues to enhance and expand its patent coverage across highly specific and sensitive biomarkers and neurocognitive testing for TBI and neurodegenerative diseases, both alone and in conjunction with advanced imaging techniques.

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Ask The Expert

Multicancer (early) detection tests at a glance



By Stefani Thomas, PhD, DABCC, NRCC

What are MCEDs?

a: In the United States, >70% of cancer deaths arise from cancers without established screening strategies. Multicancer early detection (MCED) tests aim to address this gap by using a blood sample to detect signals associated with up to 50 cancer types.

MCEDs analyze tumor-derived biomarkers circulating in blood, such as cell-free DNA, circulating tumor DNA, cell-free RNA, and proteins. Technologies used include whole-genome sequencing, next-generation sequencing, reverse transcription PCR, immunoassays, and mass spectrometry. Several companies to date have advanced MCED technologies through late-stage biomarker development programs.

Despite the promise of MCEDs, evidence remains limited that these tests consistently detect early-stage cancers at sufficiently high rates or reduce cancer-specific mortality. Consequently, some experts argue that these assays are more accurately described as multicancer detection rather than multicancer early detection tests.

How well do MCEDs perform?

MCED performance varies substantially by cancer type. In general, these tests perform best for cancers that lack effective screening guidelines and less well for cancers already targeted by established screening programs. MCEDs are intended to complement, not replace, existing screening approaches.

To minimize unnecessary diagnostic evaluations performed because of false-positive results, most MCED tests are designed with very high specificity. For example, the recent PATHFINDER 2 prospective study of >35,000 participants reported that Grail's Galleri MCED test had a positive predictive value of 60.3%, negative predictive value of 99.2%, specificity of 99.6%, and episode sensitivity of 39.3%.

What are the risks of MCEDs?

A major concern is false reassurance. A negative result does not exclude cancer and could lead some patients to delay evaluation of their symptoms or forgo recommended standard-of-care screening tests. Conversely, positive results may trigger follow up procedures that expose patients to radiation and other risks, anxiety, and healthcare costs. Even true-positive findings can cause harm through overtreatment of a cancer that might never have become clinically significant. Additional unresolved issues include determining optimal screening intervals and ensuring appropriate follow-up pathways.

Are any MCEDs FDA-approved?

At present, no MCED test has full Food and Drug Administration (FDA) authorization specifically for population-based screening of multiple cancers. However, on September 23, an FDA advisory committee voted in favor of the premarket approval application for Grail's Galleri MCED test in adults aged 50 and older. Although the panel unanimously supported the test's safety and concluded that its benefits outweigh its risks, the narrow vote on effectiveness reflected continued caution and debate regarding the test's clinical utility.

How could MCEDs impact healthcare delivery in the future?

As the regulatory and health insurance coverage landscape surrounding MCEDs evolves, clinical adoption of MCEDs will likely expand. Broader adoption depends on generating evidence that the benefits of MCEDs outweigh potential harms. The Cancer Screening Research Network recently launched the Vanguard study, the first U.S. randomized trial of MCEDs, to inform the design of larger studies evaluating whether MCED screening reduces cancer mortality.

If proven effective, MCEDs could substantially expand access to cancer screening. Unlike current approaches that often require time-consuming procedures to screen for individual cancers, MCEDs can evaluate multiple cancers simultaneously from a blood draw obtained during routine healthcare visits. This convenience may help to improve participation among underserved populations.

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