September/October 2023

CLN Clinical Laboratory News

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IDENTIFYING WOMEN WITH BRCA MUTATIONS

93.88%

Sensitivity of a microRNA test panel

PAGE 6

Boosting Access to Digital Healthcare

Automated Lyme Disease Testing

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FEATURES

DEPARTMENTS

Precisely assessing GFR in living kidney-donor candidates helps identify individuals with preexisting kidney dysfunction, ensuring they are excluded from the donor pool.
p36

On the cover: Fernanda Reyes / iStock

Federal Insider

Federal Panel Debates Less Regulation for Some Infectious Disease Tests

The Food and Drug Administration's (FDA's) Microbiology Devices Panel will meet September 7-8 to explore whether to reclassify several types of infectious disease tests from Class III to Class II, potentially making them easier to bring to market.

The reclassification would reduce the regulatory burden for manufacturers by no longer requiring clinical trials or FDA premarket approval. Most manufacturers of diagnostic tests in Class II only need to show FDA that their new tests perform similarly to other tests already on the market.

Tests under consideration include nucleic acid and serology-based assays for diagnosing hepatitis B virus (HBV) infection or for managing HBV-infected patients. The panel also will consider serology-based assays for detecting past, recent, or current infection with human parvovirus B19. Finally, it will review assays used to help identify in vitro responses to peptide antigens associated with *M. tuberculosis* infection.
While the agency is not bound to take the advice of its advisory panels, it usually does.

NIH LAUNCHES TRIALS FOR LONG COVID TREATMENTS AFTER CRITICISM

The National Institutes of Health (NIH) has announced phase 2 clinical trials that will assess at least four potential treatments for long COVID, with plans to evaluate seven more treatments soon. These trials, a part of the NIH's Researching COVID to Enhance Recovery (RECOVER) initiative, aim to identify treatments for people suffering from long-term symptoms following SARS-CoV-2 infection.

RECOVER's Phase 2 clinical trials will study the impact of drugs, biologics, medical devices, and other therapies on this complex condition. The trials are designed to concurrently assess multiple treatments.

The RECOVER Initiative, a nationwide research program, seeks to understand, treat, and prevent long COVID. In its initial stages, the program conducted large-scale observational studies involving over 24,000 participants. Researchers also analyzed 60 million electronic health records and conducted over 40 pathobiology studies.

That observational approach hasn't been well received by many patients and scientists, who criticized NIH for spending most of its funding from Congress on programs that don't directly help patients. NIH has spent some $1 billion over nearly 3 years.

CMS TO PAY HOSPITALS 3% MORE IN 2024

The Centers for Medicare & Medicaid Services (CMS) issued a final payment rule for inpatient and long-term care hospitals that will increase operating payment rates for most hospitals by 3.1%. The rule also updates Medicare hospital quality measures that the agency says will foster safety and equity, while reducing preventable harm in the hospital setting. For example, it recognizes homelessness as an indicator of increased resource utilization.

"As part of CMS' health equity goals, we are rewarding hospitals that deliver high-quality care to underserved populations and, for the first time, also recognizing the higher costs that hospitals incur when treating people experiencing homelessness," said CMS Administrator Chiquita Brooks-LaSure. "With these changes, CMS is laying the foundation for a health system that delivers higher quality, more equitable, and safer care for everyone."

However, the American Hospital Association (AHA) called the payments "woefully inadequate." CMS "continues to finalize rate increases that are not commensurate with the near decades-high inflation and increased costs for labor, equipment, drugs and supplies that hospitals across the country are experiencing," AHA said in a statement.

For example, CMS cut payments for hospitals that treat many of the most vulnerable patients by almost $1 billion, according to AHA. "This staggering amount is based on CMS'…estimate that the rate of uninsured will decline from 9.2% in FY 2023 to 8.3% in FY 2024. This is an inexplicable assumption."

jxfzsy / iStock

Four Studies Show Nova POC Creatinine/eGFR as Accurate or More Accurate Than Laboratory Methods

These peer reviewed studies evaluated the accuracy of both Nova StatSensor and laboratory creatinine/eGFR methods versus the **gold standard measured GFR**, not estimated eGFR.

Nearly 1,000 patients in under resourced primary care settings in rural South Africa, agricultural settings in Nicaragua, and university hospitals in Belgium and France were studied.

Study One:

Accuracy Better Than the Laboratory Jaffe Creatinine/eGFR

"The performance of POC devices to detect eGFR in the range 60–89 mL/min/1.73 m2 is of particular interest…to detect individuals with early disease who may benefit from renal protective measures. There was improved accuracy in this area compared to laboratory Jaffe measurements."

Currin S et al. Evaluating chronic kidney disease in rural South Africa: comparing estimated glomerular filtration rate using point-of-care creatinine to iohexol measured GFR. Clin Chem Lab Med (2021).

Study Two:

Accuracy Comparable to the Gold Standard Measured GFR

"The use of a handheld blood creatinine monitoring system provides a good estimation of GFR as compared with a gold standard method for GFR determination. Creatinine measurement and GFR estimation provide good results either with capillary blood or with venous blood and can be thus easily used in clinical practice to screen patients"

Lemoine S et al. Point of care creatinine derived eGFR measurement in capillary blood for identifying patients at risk. Practical Laboratory Medicine 31 (2022).

Study Three:

Accuracy Equal to the Laboratory IDMS Traceable Creatinine/eGFR

"Consequently, the specificity of the venous and capillary blood testing post-calibration alignment was 100% and 98.3% respectively, indicating the device is suitable to screen for CKD in POC settings and is a reliable method to assess a patient's renal status in the field."

DuBois J et al. Creatinine standardization: a key consideration in evaluating whole blood creatinine monitoring systems for CKD screening. Analytical and Bioanalytical Chemistry 414 (2022)).

Study Four:

Accuracy Equal to the Laboratory Enzymatic Creatinine/eGFR

"When compared to the iohexol determinate GFR, POC performance seems valid for screening of high-risk patients because its performance for GFR CKD classification is comparable to the routine method."

Stojkovic V et al. Estimated glomerular filtration rate using a point of care measure of creatinine in patients with iohexol determinate GFR. Clinica Chimica Acta 499 (2019).

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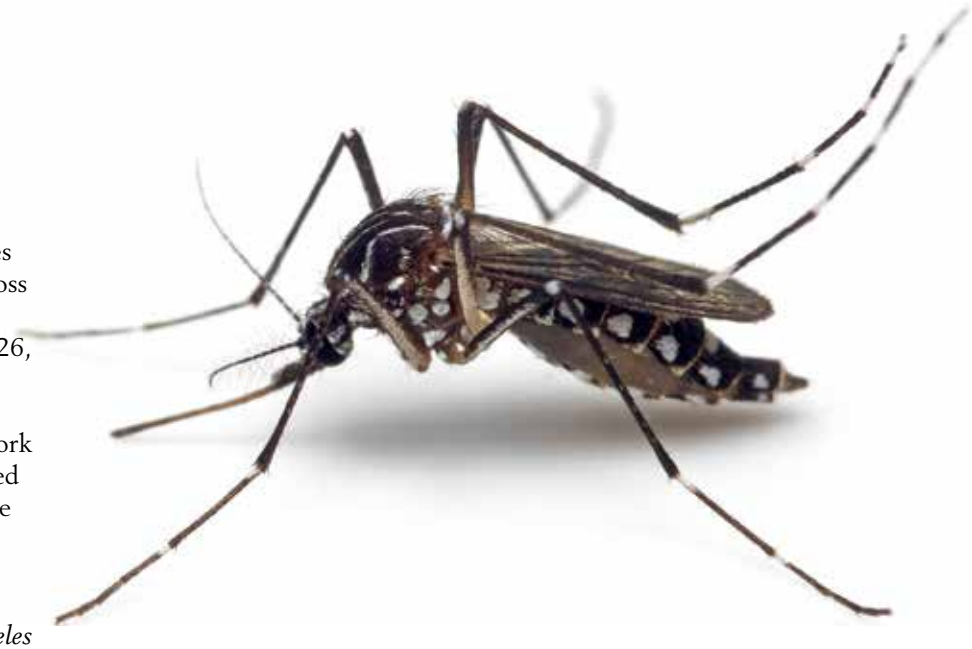
Bench Matters

Malaria Resurfaces

Rodney E. Rohde, PhD, MS, SM(ASCP)CM, SVCM, MBCM, FACSc

Priya Dhagat, MS, MLS(ASCP)CM, CIC, CHEP



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The spillover of zoonotic diseases continues to make headlines across the globe, from SARS-CoV-2 to Mpox to Yellow Fever. On June 26, 2023, the Centers for Disease Control and Prevention (CDC) distributed a Health Alert Network notification about locally acquired malaria in Florida and Texas—the first cases in the U.S. in two decades. Although the risk of locally acquired malaria remains low, CDC warns that the *Anopheles* mosquito vectors are found throughout many regions of the country and are capable of transmitting malaria if they feed on a malaria-infected person. Likewise, CDC must plan and establish access for IV artesunate, a first-line treatment for severe malaria cases.

CASES WITHIN THE U.S.

On June 23, 2023, the Texas Department of State Health Services (DSHS) reported a case of locally acquired malaria in a Texas resident with a history of working outdoors but no history of travel outside the state or country. DSHS has been working with local health departments to follow up on the case and determine whether other people have been exposed. To date, no other locally acquired malaria cases have been identified in Texas.

As of July 19, 2023, there have been seven locally acquired cases of *Plasmodium vivax* (*P. vivax*) malaria in Florida. These seven cases in Florida and the one in Texas show no evidence to suggest that the cases in the two states are related. All patients were promptly treated at area hospitals and are recovering. The Florida Department of Health has issued a statewide mosquito-borne illness advisory. Both states are advising everyone to take precautions to avoid mosquito bites.

LABORATORY DETECTION OF MALARIA

Diagnosed cases of malaria in the U.S. usually are from travelers returning from malaria-endemic countries. Due to its rare occurrence in the U.S., clinicians may be unfamiliar with the disease, thereby leading to a delay in diagnostic testing and patient care. Likewise, clinical laboratorians and public-health laboratorians may lack experience with malaria and fail to detect parasites upon blood smear microscopic examination.

Diagnosis can be challenging, given that signs and symptoms mimic other diseases and include fever, chills, sweat, headaches, muscle pains, nausea, and vomiting. Thus, confirmatory laboratory testing is critical and necessary for rapid treatment of the patient and to prevent further spread of infection in the community.

The gold standard for detecting malaria continues to be spreading a drop of the patient's blood as a "blood smear" on a microscope slide and staining it to give the parasites a distinctive appearance. The microscopic examination of a patient's blood is the most rapid, multiplex screening—and potentially confirmatory test—of the different protozoan stages of malaria, such as ring forms, schizonts, trophozoites, and gametocytes.

Rapid diagnostic tests (RDTs) offer a useful alternative to microscopy in situations where reliable microscopic diagnosis is not available. These immunologic RDTs detect antigens derived

from malaria parasites. Like a common pregnancy test, these kits use a dipstick or cassette format to provide results in 2–15 minutes. Importantly, RDTs should always be validated.

Labs also can detect malaria using PCR-based molecular tests with species-specific techniques using common commercially available kits. While these tests are very sensitive and specific, the need for rapid diagnostics is critical for prompt treatment.

Serology testing can detect antibodies against malaria parasites, using either indirect immunofluorescence or enzyme-linked immunosorbent assay. However, these techniques are most often utilized in epidemiological studies of past infections, since they do not detect current infections.

Moreover, there are ongoing developments in malaria diagnostics. Flow cytometry and the overall category of nucleic acid amplification tests in PCR, loop-mediated isothermal amplification, and molecular-based point-of-care testing (POCT) is rapidly advancing in the world of all infectious-disease detection. Importantly, glucose-6-phosphate dehydrogenase (G6PD) testing is critical in G6PD-deficient phenotypes common in malaria-endemic areas. This is because the use of primaquine, an 8-aminoquinoline for the radical cure of *P. vivax*, is a major risk factor for hemolysis in these groups. POCT G6PD testing solutions have been commercialized in recent years and offer the potential to maximize the benefits of *P. vivax* radical cure while minimizing the risk.

Higher temperatures, heat waves, rainfall, and floods are all factors that create favorable conditions for mosquito populations.

In addition to ordering the most common diagnostic tests listed above, physicians should conduct an initial workup and request a complete blood count and a routine chemistry panel. These additional tests will be useful in determining whether the patient has uncomplicated or severe manifestations of the malaria infection, including severe anemia, hypoglycemia, renal failure, hyperbilirubinemia, and acid-base disturbances.

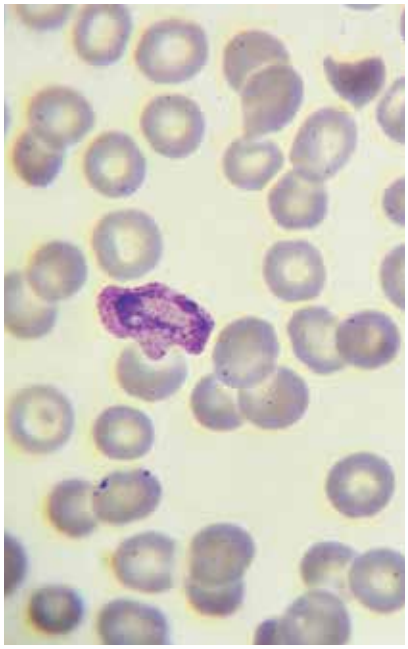

Figure 1. ***P. vivax*** **in a thin blood smear.**

The risk of locally acquired, as well as, imported cases of malaria and other infectious diseases continues to increase due to climate change: Higher temperatures, heat waves, rainfall, and floods are all factors that create favorable conditions for mosquito populations. Enhanced surveillance for mosquito-borne infections and sustainable methods for controlling mosquito populations are critical public- health strategies that should be prioritized given the ongoing risk of locally acquired cases.

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The Sample

Pediatric Reference Intervals for Trace Elements and Toxins Recommended

A recent study suggests the first pediatric reference intervals (RIs) for a comprehensive trace element panel using both triple quadrupole inductively coupled plasma tandem mass spectrometry (ICP-MS/MS) and high-resolution sector field ICPMS (HR-SF-ICPMS) technology. (J Appl Lab Med 2023; doi: 10.1093/jalm/jfad019).

Elemental deficiency and toxicity can have serious implications, especially in pediatrics. Trace element monitoring in children is an important part of renal, metabolic, and gastrointestinal disease management, but few studies have completed reference value profiling of trace elements in healthy children and adolescents with up-to-date analytical technology.

The researchers reported comprehensive reference values for 13 plasma and 22 whole trace elements from the Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER). Study findings suggested that some trace elements require age-specific interpretation for appropriate clinical decision making. ICP-MS/MS and HR-SF-ICPMS were concordant for most assays. This supports the feasibility of common trace element RIs in pediatrics.

The researchers measured trace elements in whole blood and plasma samples using ICP-MS/MS in 172 subjects and HR-SF-ICPMS in 161 subjects. They established RIs and normal exposure limits according to Clinical and Laboratory Standards Institute guidelines.

None of the elements required sex partitioning, although 8 required age partitioning. Reference value distributions determined via ICP-MS/MS and HR-SF-ICPMS demonstrated excellent concordance with few exceptions. They included molybdenum, cobalt, and nickel.

In a discussion of three of the most ordered nutritional elements (copper, zinc, and selenium), the researchers noted that results from both methods had overlapping RIs and 90% confidence intervals. Additionally, the total difference between the upper and lower limits are within 15% for all three elements.

These results suggest that both instruments displayed similar analytical performance in terms of interference removal and results generation.

These findings support the feasibility of common trace element reference intervals in pediatrics, the researchers concluded.

SIMPLE TEST MAY DETERMINE OVARIAN OR BREAST CANCER RISK

Recent proof-of-concept research details a potential inexpensive first-line screening method for *BRCA1* and *BRCA2* mutations in healthy women at high genetic risk for ovarian or breast cancer (Nat Comm 2023; doi: 10.1038/s41467-023-38925-4).

With an eye toward early detection of cancer, improving prevention efforts, and focusing genetic counseling and testing among high-risk women, the researchers sought to determine whether circulating microRNAs (miRNAs) might vary by *BRCA1/2* mutational status and whether circulating miRNAs profiles could be used to identify germline *BRCA1/2* mutations among otherwise healthy women.

To derive a serum miRNA-based diagnostic test, the researchers used samples from 653 healthy women from six international cohorts. Of these, 53.6% of samples were from women with *BRCA1/2* mutations and 46.4% were from women with wild type *BRCA1/2*. All individuals were cancer-free before and at least 12 months after sampling.

RNA sequencing followed by differential expression analysis

JGalione / iStock

identified 19 miRNAs significantly associated with *BRCA* mutations, 10 of which were ultimately used for classification: hsa-miR-20b-5p, hsa-miR-19b-3p, hsalet-7b-5p, hsa-miR-320b, hsa-miR-139-3p, hsa-miR-30d-5p, hsa-miR-17-5p, hsamiR-182-5p, hsa-miR-421, and hsa-miR-375-3p. The final logistic regression model achieved area under the receiver of operating characteristic curve 0.89 (95% CI: 0.87–0.93), 93.88% sensitivity and 80.72% specificity, in an independent validation cohort.

Mutated genes, menopausal status, or having preemptive oophorectomy did not affect classification performance.

The researchers concluded that laboratories may use circulating microRNAs to identify *BRCA1/2* mutations in patients at high risk of cancer. This method may offer an opportunity to reduce screening costs, they added.

Study findings suggest that some trace elements require age-specific interpretation for appropriate clinical decision making.

PREDIABETES MAY INCREASE FRACTURE RISK FOR MIDDLE AGED WOMEN

Recent research suggests that prediabetes in midlife women may be a risk factor for future fractures (JAMA Netw Open 2023; doi: 10.1001/jamanetworkopen.2023.14835).

Diabetic bone disease and fractures are increasingly recognized as end-organ complications of diabetes. However, whether prediabetes is also a risk factor for fractures is uncertain.

In response to this question, researchers conducted a multicenter, longitudinal study of 1,690 women of median age 49.7 and various races and ethnicities from the Study of Women's Health Across the Nation cohort. The women were premenopausal or early in perimenopause at the study's start and transitioned to menopause during the study. They did not have type 2 diabetes or take bone-beneficial medication before menopause.

Mean follow-up time was 12 years. During that period, women had a baseline visit and 16 follow-up visits involving fasting blood glucose tests. Type 2 diabetes was defined as a fasting blood glucose level of 126 mg/dL or more, or taking certain drugs: metformin, sulfonylurea, meglitinide, thiazolidinedione, dipeptidyl peptidase 4 inhibitors, glucagonlike peptide-1 receptor agonists, or insulin. Prediabetes was defined as a fasting glucose of 100–125 mg/dL.

Outcome measures were time to first fracture after start of the menopause transition (MT), with censoring at first diagnosis of type 2 diabetes, initiation of bone-beneficial medication, or last follow-up. The researchers used Cox proportional hazards regression to examine the association (before and after adjustment for bone mineral density) of prediabetes before the MT with fracture during the MT and after menopause.

Compared to not having prediabetes at any visit before the menopause transition, having prediabetes at every visit prior to the transition was associated with a 120% greater hazard for fracture during the transition to menopause and after. This association was independent of bone mineral density at the start of the menopause transition.

Targeting Lab Staffing Shortages

A new ADLM white paper recommends labs—and regulators—rethink how work is performed and recognized.

Following decades-long lab staffing shortages that reached crisis levels during the COVID-19 pandemic and a wave of retirements, a new white paper from the Association for Diagnostics & Laboratory Medicine (ADLM, formerly AACC) suggests updating CLIA regulations to better reflect current technology.

The white paper also recommends reserving high-complexity testing for staff with medical laboratory scientist (MLS) credentials, assigning technicians to run other assays, developing alternate career entry points for nonlaboratorians, and better highlighting the value of laboratory medicine.

BY DEBORAH LEVENSON

Despite ADLM and other organizations working with accredited college programs to train new laboratorians, troublesome vacancy rates persist. Results include greater workloads and more overtime for existing staff, reduced numbers of tests available in-house, and greater use of reference labs, said Erika Deaton-Mohney MT(ASCP), CPP, a coauthor of the white paper. She is a point-of-care and compliance coordinator at Bronson Healthcare in Kalamazoo, Michigan. This situation "has a negative impact on patient care. Laboratory results are taking longer and sometimes are unavailable to providers when they need them," Deaton-Mohney added.

"It's clear the complexity model for testing methods is antiquated," —Erika Deaton-Mohney

DETAILING THE PROBLEM

The white paper points to staff shortages prior to and during the COVID-19 pandemic. A 2018 American Society for Clinical Pathology (ASCP) study found average vacancy rates of 7–11% in clinical labs, with vacancy rates as high as 25% in some areas. Meanwhile, a 2020 ASCP vacancy survey showed an average 5-year retirement rate of 12.3%. Also in 2020, the Bureau of Labor Statistics projected that lab technologist and technician positions would increase by 11% by 2030. A 2022 Health Resources and Service Administration report projected an increase in demand for technologists of 22% between 2012 and 2025.

A key problem is that some CLIA provisions are outdated, the paper maintains. CLIA aims to enhance patient safety, but requirements for personnel performing moderate- and high- complexity testing have changed little since 1988, when Congress passed the law. At that time, clinical laboratories had no computers, total lab automation in chemistry and microbiology was generally unavailable, the human genome had not been sequenced, and PCR was new.

In contrast, today labs have automation of the preanalytic, analytic, and postanalytic steps of testing and smart instruments that manage and perform quality control, maintenance, and calibration verification to reduce the likelihood of analytical errors. Middleware ensures results' accuracy by creating rules for acceptance before reporting them. Laboratory information system rules also reduce the likelihood of error and patient risk. However, CLIA has not addressed these improvements, the paper notes.

CLIA currently stipulates who can perform tests based on tests' risk and complexity, training and experience of the staff performing tests, circumstances surrounding use of reagents, necessary operational steps, availability of QC material, and complexity of interpreting results. This framework "may overestimate the potential risk to the patients and unnecessarily place testing in the high-complexity category," the white paper states

It recommends revamping complexity designations based in part on the ease or difficulty of performing testing. Assays currently considered high complexity that may warrant reclassification include those for which middleware automatically performs calculations, manual but relatively simple ELISA tests, and modified FDA-cleared tests, according to the white paper.

Modified FDA-cleared tests have been subject to minor changes by labs to enhance their utility, explained Christopher Farnsworth, PhD, white paper coauthor and associate professor in the pathology and immunology section, head of clinical chemistry at Washington University School of Medicine in St. Louis. "They are the same tests, but they work just a little bit differently." The paper notes that modifications do not affect manufacturers' claims.

"It's clear the complexity model for testing methods is antiquated," Deaton-Mohney said.

Previous page: Yale New Haven Hospital / Greg Gibson

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RECOMMENDATIONS

The white paper suggests laboratory test reclassification based on performance complexity. Reclassification should entail moving those tests currently designated as high-complexity, but with relatively simple analytical requirements into the moderate-complexity testing category, while applying the existing personnel requirements.

"We've had all these new technologies introduced into the laboratory; things we use daily. A lot of the steps performed [when CLIA took effect] are no longer done," Farnsworth said. "Nobody's mixing their own reagents anymore for standard laboratory tests, for example. The system for designating who can perform testing and the assays' complexity should be based at least in part on the difficulty of required to operate instruments."

As many tests become simpler to perform, labs also have seen an explosion in the use of molecular assays, especially PCR testing, during the COVID-19 pandemic. Such tests require highly trained laboratorians. For this reason, the white paper also recommends changes to the CLIA complexity model that recognize the value of the MLS certification and require it for performing high-complexity tests.

Another key recommendation is developing educational programs that provide alternate career entry points for nonlaboratorians. At the same time, labs should provide a separate track for those with MLS credentials to advance within the lab and broader healthcare community.

The paper also calls for better recognition of lab staff as crucial members of the healthcare team.

"Labs need to get better at quantifying the impact of clinical lab testing." —Jon Harol

Deaton-Mohney said that the profession should better promote itself as a "solid career, with solid pay, professional growth, and career advancement opportunities."

DOCUMENTING THE VALUE OF LAB MEDICINE

Jon Harol, president and founder of Lighthouse Lab Services, said he agrees with the white paper's call for more stratification of skill sets. With a dearth of lab staff, "we need to create workflows and adjust regulations to allow the more automated and simpler tests to be performed by lower-level lab staff while still falling underneath the guidance of a qualified medical lab director," he added.

Harol also agrees that labs should better advocate for the value of laboratory medicine by highlighting the importance of lab results in healthcare. The Medicare MolDx program, which involves labs in roughly half of states, already asks labs to do so, he noted.

The MolDx program determines coverage, coding, and pricing of molecular pathology services. It assigns a "Z code" to laboratory-developed tests before labs can get reimbursement for them. To get reimbursed, labs must demonstrate tests' analytical validity, clinical validity, and clinical utility.

Harol predicts that commercial payers will implement similar requirements. "Labs need to get better at quantifying the impact of clinical lab testing," he said.

Demonstrating clinical utility is a huge challenge, Harol noted. It requires showing that a test drives long-term health benefits. Unlike clinicians, laboratorians do not have long-term relationships with patients. Harol suggested that labs team up with providers and other stakeholders to extract clinical utility data.

To alleviate the shortage of lower-level technicians, Harol suggests labs look to phlebotomists. Labs could offer phlebotomists on-the-job training, or the profession could develop a certification program for them. But first labs must solve the larger problem of job dissatisfaction, especially for less experienced staff, Harol emphasized.

He cited Lighthouse's 2022 Wage and Morale Survey, which found that, among its 1,112 respondents, lab staff with 5 or fewer years of experience were less satisfied than their more experienced peers, with 41% of the less experienced staff reporting they are moderately or extremely unsatisfied. Notably, the ADLM white paper emphasizes that recruitment efforts should be done in a diverse, equitable, and inclusive manner.

Farnsworth noted that the white paper's recommendations are not set in stone. Rather, they are intended as a starting point for finding solutions. "If there are folks that are really interested in engaging in this problem, join the discussion. This is a problem that's plaguing us all," he said.

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Tick season keeps expanding. Are you up to date on the latest developments in disease detection?

A REVIEW OF DIAGNOSTIC TESTING AND AUTOMATION FOR

LYME DISEASE

Many people become more active as they emerge into the warmth of spring and summer after enduring a long winter—and so do the ticks that often find them. Tick-borne diseases (TBDs) cause significant morbidity globally, including in the United States, where more than 50,000 cases are reported annually to the Centers for Disease Control and Prevention (CDC).

And that is just the tip of the iceberg when it comes to estimating the true burden of disease, since many cases go undiagnosed or unreported. With Lyme disease, for example, approximately 35,000 cases are reported to the CDC each year—but the true incidence of infection may be nearly tenfold higher, studies suggest (*1*). This underscores why it's important for clinicians to hold appropriate suspicion for tick-borne infections, as informed by a patient's geographic exposure history, time of year, and clinical presentation, and to apply relevant diagnostic testing and treatment. Taking these measures is essential not only for optimal patient care, but for the epidemiologic surveillance of these menacing vectors and the pathogens they spread.

This article summarizes the current state of diagnostic testing for Lyme disease and highlights recent progress toward fully automated testing, which will allow clinicians to make timelier, more accurate decisions.

TICKS AS DISEASE VECTORS

Numerous tick genera are capable of spreading bacterial, parasitic and/or viral pathogens to humans. Among these, *Ixodes* species are the most concerning, given their ability to transmit seven human pathogens, including *Borrelia burgdorferi* (the most common causative agent of Lyme disease in North America), *Anaplasma phagocytophilum*, *Babesia species*, *Ehrlichia muris euaclairensis*, and *Powassan virus*, among others.

Because *Ixodes* ticks can harbor all these pathogens, they carry a risk of cotransmission and coinfections. Among patients with Lyme disease, for instance, anywhere from 2% to 20% (depending on geographic location) are coinfected with *Babesia microti*, and up to 10% will also be positive for *A. phagocytophilum* (*2*, *3*). Thus, testing for coinfections is warranted for many patients, particularly those at risk for babesiosis, since the treatment for this protozoan infection differs from that used for tick-borne bacterial pathogens.

DIAGNOSTIC TESTING FOR LYME DISEASE

While molecular methods remain the testing modality of choice for diagnosing most TBDs, this is not the case for Lyme disease. Molecular testing for detecting *B. burgdorferi* remains insensitive, largely due to the limited and transient bacteremia associated with infection. According to a recent metaanalysis, molecular testing of blood and cerebrospinal fluid for Lyme disease was associated with a median sensitivity of 18% and 22% across studies, with the highest sensitivity observed in synovial fluid (median, 77%) and erythema migrans (EM) tissue biopsies (median, 68%) (*4*).

BY SARAH WHEELER, PHD, FAACC AND ELITZA S. THEEL, PHD

Molecular testing for *B.burgdorferi* remains insensitive.

Notably, EM rashes are considered pathognomonic for Lyme disease, and patients who present with such lesions (alongside appropriate geographic tick exposure) can be diagnosed clinically. Serologic testing is not indicated for these individuals, because the humoral immune response is still developing and would likely be undetectable by current assays. Molecular testing of EM biopsies is primarily beneficial in situations where the lesion does not have a classic "bull's-eye" appearance or if there is a need to rule out rare conditions that mimic EM such as Southern Tick Associated Rash Illness (STARI).

Due to the limitations associated with molecular assays, diagnostic testing for Lyme disease remains based on detecting an anti-*B. burgdorferi* humoral immune response using an algorithmic, two-tiered testing approach. To appropriately utilize the assay and interpret the results, it's important to have a clear understanding of immune response kinetics, alongside individual assay-specific caveats (e.g., *B. burgdorferi* antigens used, analytical specificity, etc.). Antibodies to *B. burgdorferi* can be detected 1–2 weeks after infection and typically peak over the first 1–3 months. Some individuals, particularly those with disseminated infections, will remain IgG seropositive for 6 months or longer.

Importantly, antibacterial treatment can affect the clinical sensitivity of serologic assays. This is particularly apparent in patients with EM, for whom prompt initiation of treatment can dramatically blunt immune response, resulting in up to half of these individuals remaining seronegative on convalescent testing (5).

Currently, there are two two-tiered testing algorithms endorsed by the CDC for diagnosing Lyme disease: the Standard Two-Tiered Testing Algorithm (STTTA) and the Modified Two-Tiered Testing Algorithm (MTTTA). Many assays have been cleared by the Food and Drug Administration (FDA) for use in either algorithm or both of them.

The Standard Two-Tiered Testing Algorithm

The STTTA was developed and widely implemented following guidance from the Second National Conference on Serologic Diagnosis of Lyme disease in 1994, which recommended initial testing of at-risk patients using an enzyme immunoassay (EIA) or immunofluorescence assay (IFA). For seronegative patients, clinicians were encouraged to either consider an alternative diagnosis or, in the instance of recent exposure (≤ 30 days), to repeat testing on a convalescent sample and assess for seroconversion. For initially seropositive patients, the guidance recommended reflexive testing by separate, anti-*B. burgdorferi* IgM and IgG immunoblots, with IgM testing indicated only for patients with less than 30 days of symptoms.

The IgM and IgG blots have unique antigen combinations and interpretive criteria that have often led to confusion among both clinicians and patients. IgM immunoblots are considered positive if they detect antibodies against at least 2 out of 3 possible *B. burgdorferi* antigens (23 kDa, 39 kDa, 41 kDa), whereas IgG blots are considered positive if they detect at least 5 out of a possible 10 antigens (18 kDa, 21 kDa, 28 kDa, 30 kDa, 39 kDa, 41 kDA, 45 kDa, 58 kDa, 66 kDa, 93 kDa).

Importantly, these criteria are only applicable for North American immunoblots, which are based on antigens specifically from *B. burgdorferi* strain B31; these blots and criteria are not appropriate for, and would not detect immune responses against, other Lyme-disease-causing Borrelia species.

The Modified Two-Tiered Testing Algorithm

In 2019, the CDC endorsed the MTTTA, which essentially replaces the standard algorithm second-tier IgM/IgG immunoblots with either a single, total antibody EIA or separate IgM and IgG EIAs. These second-tier EIAs should be based on *B. burgdorferi* antigens that differ from those used in the first-tier EIA. The MTTTA offers numerous advantages over the STTTA. Perhaps most importantly, it has improved sensitivity, particularly for patients with early Lyme disease.

Irrespective of the MTTTA assay combination, its sensitivity is 10%–30% higher in patients with EM as compared to the STTTA (56%–74% vs. 41%–58%, respectively) (5). At later stages of infection, sensitivity is equivalent between the algorithms, approaching 100% in patients with late Lyme disease. Specificity is likewise similar.

Additionally, because the many first- and second-tier assays for the MTTTA are not specific to *B. burgdorferi* B31, they likely detect antibodies to a wider variety of Lyme-disease-causing Borrelia species, potentially eliminating the need for multiple serologic assays (6, 7). More studies are needed to better define the accuracy of

Previous page and top right: Erik Karits / Unsplash

MTTTA assays as a sensitive approach for *pan-Borrelia* antibody detection for Lyme disease.

The MTTTA also eliminates any confusion associated with immunoblot interpretation, since this approach provides only qualitative "positive," "negative," or "equivocal" results. Another key advantage is that the MTTTA can fully automate the entire algorithm—which would allow a larger number of laboratories to perform testing for all tiers onsite, rather than sending samples out to reference laboratories for second-tier immunoblot testing.

LYME SPECIALTY LABORATORIES

Any discussion of testing for Lyme disease must deal with assays offered through "Lyme specialty laboratories." These facilities offer a variety of assays, including both novel, lab-developed tests and FDA-cleared assays to which the labs apply alternative interpretive criteria. Importantly, while the CDC's recommended criteria for interpreting FDA-cleared tests is supported by extensive studies, the same is not true for many assays offered through Lyme specialty laboratories, which often are not evaluated independently or assessed in the peer-reviewed literature.

One review that compiled performance data on some of these assays found that such testing is not well validated, and, concerningly, has limited sensitivity and specificity (*8*). Consequently, results from Lyme specialty laboratories are not recommended by the CDC and should be interpreted with caution. Whenever possible, they should be confirmed using well validated methods.

AUTOMATION OF LYME DISEASE TESTING

The expanding prevalence of Lyme disease has led to an increase in annual testing volumes, which has in turn driven demand for automated screening options. While modern clinical laboratories have many levels of automation available for Lyme disease screening, there are a limited number of assays offering fully automated, random-access instrumentation, which is the goal for many facilities handling high screening volumes, particularly amid ongoing staffing shortages (Table 1).

The available automated, random-access assays include those that differentiate IgG from IgM, as well as total immunoglobulin assays, which are often specialty instruments with testing menus focused on infectious disease serology and autoimmune diseases. This poses a challenge for smaller hospital laboratories in rural areas with a high prevalence of Lyme disease. These institutions may lack the financial resources to implement such platforms for the sole purpose of performing one or two assays.

The majority of available serology tests for Lyme disease are ELISA-based assays (examples in Table 1), which are amenable to batch testing automation through manufacturer or third-party ELISA automation processors. ELISA automation platforms offer labs some flexibility, since the menu of additional assays that can be placed on them is extensive and instrument costs are often more modest than random-access platforms.

The introduction of the MTTTA has enabled improvements to second-tier testing workflows that go beyond the processing enhancements made to immunoblot testing over the years. Initially, second-tier testing for the STTTA relied on classic Western blots that used whole-cell lysate. These not only required manual processing, but necessitated visual interpretation of the results for the presence or absence of bands by a technologist.

By contrast, contemporary immunoblots can use recombinant antigens that are mechanically applied, or "stamped," onto nitrocellulose membranes, which are subsequently processed on semi- or fully automated instruments (examples in Table 1). Nevertheless, the process remains somewhat cumbersome, requiring specialized equipment to process the blots and limited assay menus to leverage introduction of this testing in-house.

Additionally, while many blotting methods can now be more objectively interpreted using optical densitometry scanning, some assays may still require a human to make the final visual adjudication for the presence or absence of bands, in accordance with CDC's recommendations, especially when densitometry interpretations are inconclusive.

The MTTTA has not completely eliminated the need for batch testing of second tier assays, but it has significantly expanded the potential for automation and eliminated the need for visual interpretation. The same ELISA automation processor used in first-tier testing also can be used for second-tier testing, improving instrument utilization and turnaround time compared to send-out confirmation by immunoblotting. ELISA-based assays approved for MTTTA are still limited, and to

Table 1. Examples of Automated Lyme Disease Serologic Assays (not exhaustive)

Manufacturer	Assay Name	Assay Type	B. burgdorferi Antigens	Approved/Cleared for 1st or 2nd Tier Testing
bioMérieux*	VIDAS Lyme IgG II	ELFA	DbpA, OspC, VlsE	1st tier
bioMérieux*	VIDAS Lyme IgM II	ELFA	DpbA, OspC	1st tier
Bio-Rad*	BioPlex 2200 Lyme Total Assay	MFI	OspC, p58, VlsE	1st tier
DiaSorin*	Liaison Lyme Total Antibody Plus	CLIA	Bb VlsE, Bg VlsE, Ba OspC	1st tier
DiaSorin*	Liaison Lyme IgG	CLIA	VlsE1/pepC10	1st or 2nd tier
DiaSorin*	Liaison Lyme IgM	CLIA	Ba OspC, Bb VlsE	1st or 2nd tier
Bio-Rad	Platelia Lyme IgM	ELISA	Whole-cell antigen strain B31	1st tier
Bio-Rad	Platelia Lyme IgG	ELISA	Whole-cell antigen strain B31	1st tier
EUROIMMUN	Lyme ELISA (IgG/IgM)	ELISA	Bb B31 VlsE, OspC	1st tier
Gold Standard Diagnostics	B. burgdorferi VlsE-OspC IgG/IgM	ELISA	rVlsE, rOspC	1st or 2nd tier
Gold Standard Diagnostics	B. burgdorferi IgG/IgM	ELISA	Whole-cell antigen Bb B31 and 2591	1st or 2nd tier
Gold Standard Diagnostics	B. burgdorferi IgG	ELISA	Whole-cell antigen Bb B31 and 2591	1st or 2nd tier
Gold Standard Diagnostics	B. burgdorferi IgM	ELISA	Whole-cell antigen Bb B31 and 2591	1st or 2nd tier
Zeus Scientific	Borrelia burgdorferi IgM	ELISA	Whole-cell antigen strain B31	1st or 2nd tier
Zeus Scientific	Borrelia burgdorferi IgM	ELISA	Whole-cell antigen strain B31	1st or 2nd tier
Zeus Scientific	Borrelia VlsE/pepC10 IgG/IgM	ELISA	VlsE1/pepC10	1st or 2nd tier
Zeus Scientific	Borrelia burgdorferi IgG/IgM	ELISA	Whole-cell antigen strain B31	1st or 2nd tier
EUROIMMUN	Anti-Borrelia US EUROLINE-WB (IgM)	Immunoblot	B31 lysate, p41	2nd tier
EUROIMMUN	Anti-Borrelia US Western blot (IgG)	Immunoblot	B31 lysate	2nd tier
Gold Standard Diagnostics	GSD B. burgdorferi B31 IgG	Immunoblot	p18, p21, p28, p30, p39, p41, p45, p58, p66, and p93	2nd tier
Gold Standard Diagnostics	GSD B. burgdorferi B31 IgM	Immunoblot	p24, p39, p41	2nd tier
ViraMed Biotech Ag	Borrelia All-In-One ViraChip	Microblot, 96 well plate format	p17, p18, p19, p21,p23,p30, p39, p45, p58, p93, VlsE	1st and 2nd tier
ViraMed Biotech Ag	Borrelia B31 ViraChip IgM	Microblot, 96 well plate format	p23, p39, p41	2nd tier
ViraMed Biotech Ag	Borrelia B31 ViraChip IgG	Microblot, 96 well plate format	p18, p23, p28, p30, p39, p41, p45, p58, p66, p93	2nd tier

date many are based on whole-cell sonicates. For now, only one random-access fully automated analyzer is currently approved for use for both tiers of the MTTTA.

It's worth noting that, in the last year a Phase 3 clinical trial was initiated for the Pfizer and Valneva vaccine against B. burgdorferi. Known as VLA15, this vaccine is a multivalent, recombinant protein vaccine that targets the outer surface protein A (OspA) of six different B. burgdorferi serotypes. Although OspA is not present in many of the recombinant screening assays, potential cross-reactivity with assays using whole-cell sonicates is of concern.

IMPORTANCE OF TIMELY LYME DISEASE TESTING

Being able to accurately and promptly diagnose Lyme disease is increasingly important as prevalence rises. While Lyme disease is not itself life-threatening, it is common in differential diagnoses that may include more critical conditions—raising the stakes for making the correct diagnosis, particularly in summer months, when patients' possible exposure to *B. burgdorferi* is high.

For example, in children presenting with a swollen, painful knee without a history of trauma to the site, the differential diagnosis includes septic arthritis—which often includes a trip to the operating room—in addition to Lyme arthritis and other conditions. Without rapid, readily available screening for Lyme disease, these pediatric patients may receive surgical intervention for an issue that could have been treated medically. In less critical cases, where the probability of Lyme disease is high, clinicians will often empirically treat for Lyme before testing results are available, leading to the potential overutilization of antibiotics.

Offering first-tier LD testing in-house is increasingly common in high prevalence areas, with second-tier testing sent out to reference laboratories. During the summer months, this process can take days to weeks, thereby forcing clinicians to make diagnostic decisions based on first-tier testing alone. This can contribute to over-treatment and missed alternative diagnoses.

MTTTA's improved sensitivity in early disease and ability to perform batch automation on both tiers represents important progress towards providing clinicians the information they need as quickly as possible. However, we still lack choice in random-access, fully automated MTTTA assays, the primary benefits of which are rapid, same-day testing for both tiers.

Continued development of recombinant, random access, fully automated MTTTA assays will give clinicians access to more timely and accurate diagnostic information, resulting in better care for patients with Lyme disease and other conditions included in the differential diagnosis.

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A Strategy for Boosting Equitable Access to Digital Healthcare

Several studies have reported that healthcare providers who actively engage patients in patient portals to review laboratory test results, schedule appointments, and review visit summaries increase the discovery of medical errors (*1*). Active patient engagement also improves medication adherence, helps patient-provider communication, allows patients to participate in their healthcare decision-making process, and improves healthcare outcomes and satisfaction (*1*).

However, patients with limited English proficiency (LEP) find it challenging to reap these benefits if they cannot access or understand the information from their providers. Since the COVID-19 Public Health Emergency declaration has ended, we have had an opportunity to evaluate the experiences we gained during the pandemic. Now we are working to improve the quality of healthcare, in particular digital access for LEP patients and others in disproportionately affected urban and rural areas.

EXPANSION OF TELEHEALTH SERVICES BEFORE AND BEYOND THE CORONAVIRUS PANDEMIC

The landscape of patient portals has changed from stand-alone services used for registration to integration with electronic health records (EHRs). Integrated portals also promote laboratory data sharing. This was one reason the Centers for Medicare & Medicaid Services (CMS) released its final rule (CMS-2319-F) to ensure that every person in the United States could see, obtain, and use all electronically available information that is relevant to their healthcare (*2*).

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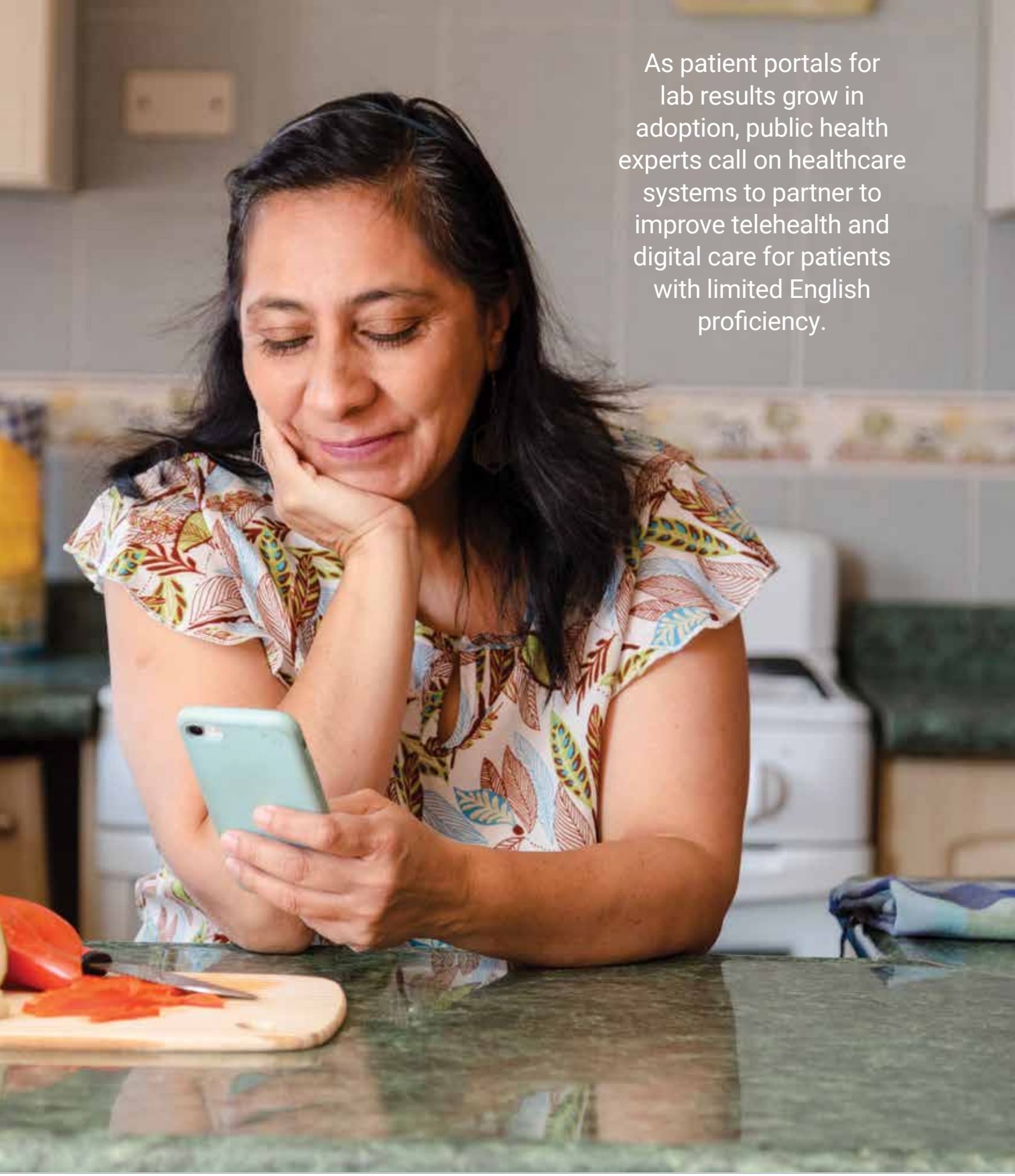

As patient portals for lab results grow in adoption, public health experts call on healthcare systems to partner to improve telehealth and digital care for patients with limited English proficiency.

During the pandemic, CMS expanded coverage for telehealth, and the availability of portals integrated with EHRs that report laboratory test results increased remote patient care opportunities. This propelled public awareness of test ordering, the availability of different test methods for infectious diseases, and test result reports and interpretations (*3*).

While some interventions supported digital healthcare access for all patients, protective isolation also highlighted healthcare inequities and unique challenges that LEP patients face in accessing, reading, and understanding their test results. Several healthcare organizations demonstrated how to overcome this barrier. For example, Massachusetts General Hospital (MGH) deployed a portal that improved access for LEP patients and reduced the burden for providers (5).

MGH offered educational materials on the registration process in multiple languages and included low-literacy scripts that dealt with privacy concerns. Privacy was important because of patients' concern about being identified by U.S. Immigration and Customs Enforcement because of their healthcare-related information in the portals. In addition, MGH portals did not require patients to download an application to their phone or computer to join a telemedicine session, and medical interpreters were able to access patient platforms. MGH integrated the interpreters as a third party with access to EHRs at each facility (*3*).

Research also shows that tests are the top reason patients access portals—87% in urban areas and 81% in rural areas.

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INSIGHTS FROM EMERGENCY DEPARTMENT VISITS

Patients with LEP are more likely than English-speaking, non-Hispanic patients to access care in emergency departments (ED) due to a lack of insurance coverage and primary care providers (*1*). This makes the ED a key location for engaging patients with portals and other digital services.

One study documented the number of individuals enrolled in a portal based on their language characteristics (*5*). The patients in the study accessed their test results in the EHR while visiting the ED. The researchers observed increased portal-based test result viewing among ED patients over the 1-year study, even among those not enrolled at arrival. This study suggests that patients are inherently interested in viewing their laboratory test results and clinical data during clinical encounters with healthcare providers (*5*). Similar experiences in EDs in different geographical regions among underrepresented patients may support the generalizable application of this study's observations.

THE CMS FRAMEWORK FOR HEALTH EQUITY: A LANGUAGE ACCESS PLAN

CMS is committed to taking an integrated approach to health equity. The recently updated CMS Framework for Health Equity encourages healthcare providers to remedy systemic equity barriers so that all patients have a fair and just opportunity to attain optimal health regardless of race, language, or other factors.

A key priority of the CMS Framework for Health Equity includes language access, health literacy, and providing culturally tailored services. The CMS Framework describes opportunities

for providers to assess their practice environments and develop plans so that patients can have the highest level of meaningful access to medical services. The guidelines include recommendations for assessing the number of individuals with LEP who interact with the organization to understand the language needs of patients and their caretakers.

Promoting the availability of language and medical services on an organization's website also is beneficial to LEP patients and their caretakers. CMS recommends that a language access plan include a description of how the organization will train staff on policies and procedures for providing language assistance services. In addition, language access plans should include quality monitoring and a framework for continuous quality improvement (*6*).

CONTINUING CHALLENGES IN RURAL AND DISPROPORTIONATELY AFFECTED URBAN AREAS

One key requirement for a successful telehealth visit is access to broadband internet. Some people who live in rural areas still do not have equitable access to healthcare given a lack of broadband access. There are also urban pockets, known as Wi-Fi deserts, that lack broadband internet access. Wi-Fi deserts often are in large cities where disproportionately affected populations reside and limited digital literacy is prevalent.

Importantly, while such disparities were evident prior to the pandemic, the increasing reliance on telehealth services postpandemic may worsen the problem (*7*). A study showed that Hispanic (15%), African American (10%), Asian (6%), and other non-Hispanic (3%) populations continue to fall behind in patient portal access and use compared to non-Hispanic whites (66%) in urban and rural areas (*8*).

Research also shows that tests are the top reason patients access portals—87% in urban areas and 81% in rural areas (*8*). Despite similar rates of providers maintaining a patient portal system, adjusted analyses found that people who live in rural areas had lower odds of being offered access by their healthcare provider compared wtih their urban counterparts (*8*).

Another challenge is that third-party language interpretation services can be difficult to integrate into telehealth video visits. In research, bilingual, language-concordant personnel often were essential for efficient, high-quality patient experiences. Audio-only visits were optimal in reaching patients of older age, and those with LEP and limited digital literacy. Continued use of telemedicine by these populations is likely to be contingent on reimbursement policy decisions.

Community-level support also can increase patient digital literacy and the availability of technological resources for high-quality language services in telehealth (*9*).

WORKING TOWARDS HEALTH EQUITY

Although digital healthcare access has many proven benefits and offers promising solutions to many public health barriers, our experience during the pandemic has proven that their success depends on solving the problem of widening disparities for different populations/geographical regions (*4*).

The government may need to expand subsidized wireless internet access in communities with limited resources. But education and training by healthcare systems and community health workers also can increase telehealth uptake and patient portal usage (*10*). Such efforts also may improve digital literacy and understanding of test results in disproportionately affected communities (*6*).

Multilevel barriers to digital healthcare access remain at the patient, health system community, and policy levels (*10*). Patients need our concerted efforts to evaluate successes and barriers in various patient populations in diverse urban and rural geographical regions (*10*).

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FOCUS ON MOLECULAR DIAGNOSTICS

Sexually Transmitted Infections and Women's Health

By Jen A. Miller

One size does not fit all when it comes to sexually transmitted infection (STI) testing. This is especially true because each STI affects populations in different ways, and laboratories need to utilize the right testing methodology to offer the most effective results.

In a recent interview, Salika Shakir, PhD, D(ABMM), medical director, Microbial Amplified Detection at ARUP Laboratories and assistant professor (clinical) at the University of Utah School of Medicine, discussed approaches to STI testing, and how to make sure that the right tests—with proper sample collection—are deployed to all patients.

What technologies does your laboratory use for STI testing?
We use molecular testing for some of the common STIs, including chlamydia, gonorrhea, and *Trichomonas vaginalis*. We also do PCR testing for *Mycoplasma genitalium* and other STIs such as HIV, HBV, and HCV, which are screened by serology. We perform HPV testing with a combination of cytologic and molecular testing. For syphilis, we follow the algorithms outlined by the Centers for Disease Control and Prevention (CDC). We also developed a molecular laboratory test to target those pathogens that cause genital ulcer disease: *Treponema pallidum*, which is the etiologic agent of syphilis, herpes simplex virus Type 1 and 2, chlamydia L serovars, plus *Haemophilus ducreyi*, which have low incident rates in the U.S.

How do PCR methods and culture techniques complement each other for diagnosing vaginitis and sexually transmitted infections? What are the strengths and limitations of these approaches?
We have molecular tests that are useful for microorganisms that are difficult to culture, such as *Chlamydia trachomatis* and *Mycoplasma genitalium*. There are culture-based tests that labs still use for *Neisseria gonorrhea*.

There are many advantages to molecular testing. They overcome some of the limitations of microscopy and culture-based approaches, can be high-throughput, and they demonstrate increased sensitivity and specificity. They can also detect pathogens even in samples with low bacterial and viral loads from asymptomatic patients. You can use a single sample to test all these different pathogens by targeting their DNA or RNA.

Molecular testing is rapid, and it gives more information from a single patient sample. Most of these tests also give results much faster than traditional methods such as culture. That's a big advantage because providers are not waiting for those results for several days. Instead, it's just a few hours.

I know that in some places, culture-based testing is still used for vaginitis, but here we moved ours onto a molecular platform that targets bacterial vaginosis, trichomoniasis, and candidiasis.

How do you approach validating and optimizing the selected targets in a panel for clinical use?
We use clinical samples for validations and verifications, testing first for sensitivity to detect all the different targets in the panel.

We also make sure the results are specific to that target, and that there's no cross reactivity. For example, with the genital ulcer disease panel we created, we wanted to ensure our targets didn't cross react with other bacterial species, such as skin flora, to avoid false-positive results.

We also make sure our results are reproducible, and test multiple times at an appropriate limit of detection to make sure we get the same result. These are conducted using CLIA regulatory standards.

Can you discuss how the target patient populations might influence the use of panels and how this may impact panel content selection?
There are pathogens that are considered optimal for screening, such as chlamydia and gonorrhea. They can both be asymptomatic, and we have good screening guidelines and recommendations for both men and women. Oftentimes with *Chlamydia trachomatis* and *Neisseria gonorrhea*, you can find *Trichomonas vaginalis*.

Trichomoniasis is one of the most common nonviral STIs. There are no guidelines for routine screening, but there are screening guidelines for those who are considered high risk, such as patients who have multiple

sex partners, who have had intercourse with infected individuals, or are on HIV PrEP. Laboratories are not privy to some of that information, but we offer this knowing the prevalence of these pathogens in the community.

Screening recommendations are also patient population-dependent. The guidelines for women who have sex with men, men who have sex with women, and men who have sex with men are all different.

Here again, you can have panels where, if it's an individual vaginal swab test, you can identify *Chlamydia trachomatis*, *Neisseria gonorrhea*, *Trichomonas vaginalis* or *Mycoplasma genitalium*—all four targets with a single sample.

What should clinicians consider when interpreting results from a molecular panel that includes multiple targets? How do you educate them on this?

As laboratorians, we must work with clinicians to decide what is best for patients, based on what we offer. A lot of it depends on the STI epidemiology, sexual behaviors of the patient population, and who would benefit from screening. We also talk about what samples are appropriate for screening or testing, and how they should be collected. We're helping them understand one size doesn't fit all.

Explain the importance of sample type and how the lab can work with clinicians to optimize this.

This is an important opportunity for education. For example, we provide information through test directory and consultative services. We have information on our landing pages and lectures to explain the CDC's most up-to-date recommendations for screening and testing.

That includes which swabs are optimal. A study just came out this year showing that using urine instead of vaginal-swab testing could result in 400,000 missed STI cases each year (Ann Fam Med 2023; doi: 10.1370/afm.2942). That's a big deal.

We tell our clinicians that if an individual with a vagina walks into a clinic, the best type of sample would be a vaginal swab. We help them understand that not all samples are equal, and that sometimes an individual needs multiple swabs taken, depending on their exposures, sexual activity, and anatomy.

Can you share your experience with reimbursement for panel testing, multiple target testing?

It's always a big question for payers to reimburse panel testing, especially when there are multiple targets. Data is still being generated for panels with more than five targets and whether those are clinically useful.

Sometime ago, we ran into this issue when we first offered a vaginitis panel molecular test. There was concern about reimbursement, but soon after, the Centers for Medicare and Medicaid Services and most of the other large payers said it was reasonable to perform targeted or expanded panels for vaginitis.

Looking ahead, what do you see as important areas of ongoing research and development in molecular testing for STDs?

Having easy access to, and more cost effective, rapid point-of-care (POC) testing will be useful. There are some FDA-cleared or CLIA-waived test sets available, but they're not widespread, and the cost of the assays can be prohibitive.

There is also a social stigma associated with STI testing, and it can be hard to get a patient back into the office—an important reason POC tests are helpful. If the patients could wait for results, clinicians could send them home with the right antibiotic therapy. It would improve patient screening overall.

I'm also really interested in self-collection for STI testing. There are FDA-cleared assays that have self-collected vaginal swabs approved for testing in the clinician's office setting where, of course, urine is sort of self-collected. There are also studies to show rectal and throat self-collection can be done, and is even preferred, because it has been shown to result in great patient satisfaction, if you provide good collection instructions.

If anything, the pandemic has shown us that we can do this. When we were going through the COVID-19 pandemic, and STI clinics had to shut down and direct those resources to COVID testing, many healthcare clinics didn't have providers who were able to collect specimens, so self-collection became an acceptable method.

There also have been new studies about self-testing and home-based testing. That's something for us to look out for. Providers and laboratories must be involved to ensure high quality testing, but I see great potential there for improving population health.

Jen A. Miller is a freelance journalist who lives in Audubon, New Jersey.
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INTERVIEW WITH TABATHA E. EAST, MBA, MLS(ASCP)

Trends in Sexually Transmitted Infections and Public Health

By Jen A. Miller

Public health officials are often the first point of contact for people who think they might have a sexually transmitted infection (STI). But they do so much more than that. These lab medicine professionals, clinicians, and others are part of a world-wide effort to detect and track which STIs are circulating within a population, identify which strains are becoming drug resistant, and influence how physicians can best test, treat, and help their patients.

CLN spoke to Tabatha E. East, MBA, MLS(ASCP), assistant director of clinical and environmental microbiology in the division of laboratory services at the Tennessee Department of Health, about STI testing and surveillance in the state. The discussion also tackles how public health laboratory professionals help the local communities they serve while also playing a role in the global fight against antimicrobial resistance.

Have you observed an increase in STIs? What's been surprising or unusual?

We've been seeing an increase in Hepatitis B, but we believe that likely is attributed to the updated Centers for Disease Control and Prevention (CDC) screening and testing recommendations.

In March of 2023, CDC updated their hepatitis B screening and testing recommendations to expand risk-based testing to include persons currently or formerly incarcerated in a jail, prison, or other detention setting; persons with a history of STIs or multiple sex partners; and persons with a history of hepatitis C virus infection.

We haven't seen this yet in the numbers, but anecdotally we're also observing an increase in syphilis—and it's more than the ordinary, transient cases.

In some ways, I don't know what is unusual anymore because during the pandemic, we saw a drastic decrease in STI testing. We're working hard to learn what our new normal is as we start to see a rebound in testing volumes: Are these new cases or cases that have been there for a given period?

Have you implemented new strategies for increasing access to testing and connecting patients to care?

STI testing is available at local health departments and a subset of community-based organizations. Both insured and uninsured residents of Tennessee have access through local health departments.

We also have a strong outreach program to our rural and underserved populations within the state. We have 95 counties in Tennessee, and every county has a minimum of one health department. We have an extensive reach.

How is molecular testing helping to tackle the rise in STIs?

The main advantage of molecular testing is the speed at which labs can deliver results.

On top of the sensitivity and the specificity, there are also differences in collection devices. Some organisms, like *Neisseria gonorrhoeae*, are not viable long outside the body, and with culture-based technologies, those organisms can die before the sample arrives at the laboratory.

But with the media solution used for molecular collection devices, it's okay if organisms die. Since molecular platforms detect genetic material, the organism doesn't have to be viable for diagnosis.

This is hugely advantageous for rural areas. For certain specimen types and assays, samples can remain at room temperature for approximately a month. For culture-based collections, by the time specimens are collected and returned to the laboratory, specimen integrity has been compromised—often rendering the test unusable.

What factors do you consider in whether molecular or other types of testing are most appropriate?

It depends on where the patient needs to be serviced. If we need to have that easier specimen transport, that would tend to make molecular testing the preferred option.

It's true that molecular testing is also more expensive than culture-based testing. But even though that's an expense we incur on the laboratory side, the fact that it offers a faster turnaround time— sometimes several days before they would have a culture result — makes patient impact huge.

In addition to what is being done on the laboratory side for identification and the clinician's side for treatment, epidemiologists are playing a pivotal role in the containment of disease through data monitoring, contact tracing, and so much more.

How do you view multiplex testing of STIs versus single pathogen testing?

From a laboratory efficiency standpoint, it's beneficial to have multiplex testing, especially for screening at-risk populations. On the other hand, because we do see patients with a previous positive status for one organism, it's still useful to have the singleplex option.

For example, most assays have chlamydia and gonorrhea testing together as a multiplex test. But if a patient already had a positive chlamydia test, received antibiotics, and the clinician ordered testing again to make sure that the infection has cleared, there may not be a need a multiplex assay.

What is your approach on testing for unexpected STI pathogens based on symptoms and epidemiology of the local population?

We have performed prevalence studies here at the Tennessee Public Health Laboratory. There are some organisms—like *Mycoplasma genitalium* and *Trichomonias vaginalis*—which are not common STIs that the public knows of, and not commonly screened for, so they can go undiagnosed. Due to how slow growing these pathogens are, we cannot allow patients to go undiagnosed and untreated for that long. For these pathogens, the introduction of nucleic acid amplification testing has been a game changer for turnaround times.

Since these organisms do not present like textbook infections or are asymptomatic, it is important to include them in routine screening of at-risk populations. While men typically present with symptomatic or asymptomatic urethritis, complications in women can be much more severe. *Mycoplasma genitalium* infections in women often are asymptomatic but can lead to pelvic inflammatory disease, spontaneous abortions, and infertility. Furthermore, studies have shown co-infection of HIV and *M. genitalium* increase shedding of the HIV virus in patients not taking antiretroviral therapy (ART).

The caveat to adding unexpected or unanticipated STI pathogen testing is that we must ensure we are good stewards of laboratory resources.

Where do you see opportunities for more collaboration?

Here in Tennessee, we all work closely together and communicate often, including the STI program directors, epidemiologists, clinicians, nurses, and other providers. For example, if there is an emerging issue, we might call the team together and say, "what do you think about doing a pilot study to see if we do need to onboard this testing?" Right now, we have a couple of *Trichomonas* pilots so we can make solid, data-driven decisions.

Recently, Tennessee participated in a *M. genitalium* prevalence study with our state public health laboratory partners in the Southeast region. We were able to use the data from that study in cost expansion requests to legislators. All of us working together—and seeking out the best data—helps make those decisions.

How important is molecular testing in antimicrobial resistance surveillance and managing STIs?

We're not yet performing molecular antimicrobial resistance testing (AMR) in our lab. There's still a lot that's being done through agar dilution or automated AST. I know it would be helpful for clinicians to have those AST results when they receive a a positive, and it's also beneficial when patients have drug allergies.

Tennessee is one of seven CDC Antimicrobial Resistance Laboratory Networks (ARLN), testing current and emerging organism resistance. Part of ARLN is Gonococcal (GC) ARLN, where the state is one of four regional laboratories in the country. This program does extensive AMR work, specifically with *Neisseria gonorrhoeae*. So, if you're hearing about super gonorrhea—yes, it is real.

We work with a lot of clinics across the country that send gonorrhea isolates to us to do drug susceptibility testing where we use the agar dilution method. While agar dilution is the gold standard for AMR, disk diffusion and Etest are also available. Commercial assays have yet to be deployed for molecular or automated AMR testing for gonorrhea.

How are you using these tests to detect drug-resistant strains and guide treatment?

We're using them for both. They help us know the right treatment route and alert us to when we're starting to see resistance and need to take other actions. As surveillance data has shown drug resistance in gonorrhea, the pathogen has received global recognition and overdue attention.

Jen A. Miller is a freelance journalist who lives in Audubon, New Jersey.
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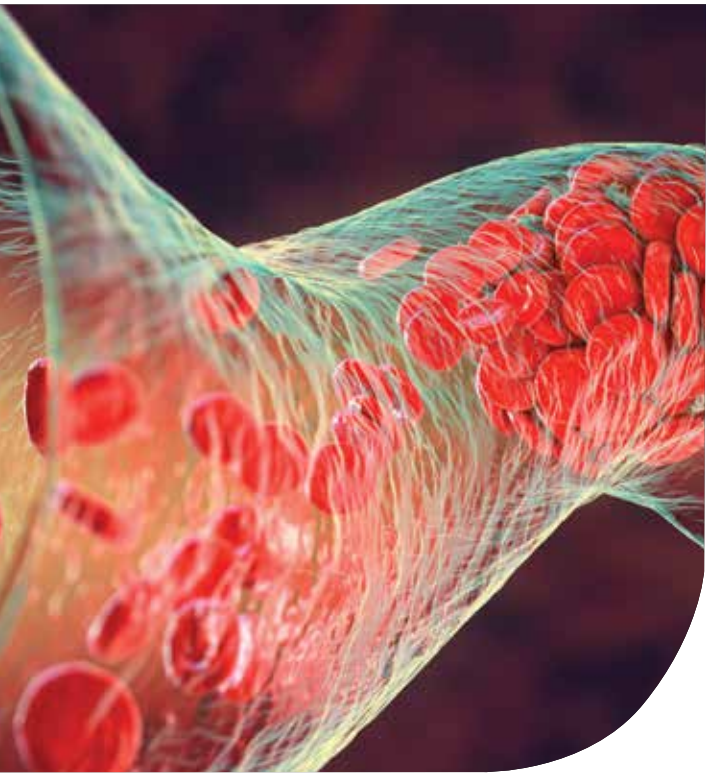
Regulatory Roundup



Surmodics Thrombectomy System Gets 510(k) Clearance

Surmodics recently announced it received 510(k) clearance from the Food and Drug Administration for its Pounce LP (Low Profile) Thrombectomy system.

The new product will help clinicians treat acute limb ischemia, which is associated with 30-day amputation and mortality rates as high as 30% and 11.5%, respectively.

Introduced in 2021, the Pounce Thrombectomy system is intended for the nonsurgical removal of thrombi and emboli from the peripheral arterial vasculature in vessels 3.5–6 mm in diameter. The addition of the low-profile (LP) model will allow for more efficient clot removal in below-the-knee peripheral arteries 2–4 mm in diameter, Surmodics said.

Surmodics officials said that catheter-directed thrombolysis in vessels below the knee is limited against organized clot and requires ICU admission, while small-diameter aspiration thrombectomy devices may struggle to remove organized material in the distal lower extremity. Expansion of the Pounce platform's treatment range allows the company to address tibial clots, an important component of treatment in a vulnerable patient population.

FDA CLEARS CYTOVALE'S INTELLISEP SEPSIS TEST

Cytovale's IntelliSep test has received 510(k) clearance from the Food and Drug Administration (FDA).

According to Cytovale, IntelliSep is the first FDA-cleared test to assess cellular host response to aid in the diagnosis of sepsis in emergency department patients and contribute to rapid life-saving decisions. The test provides results in under 10 minutes from a standard blood draw.

IntelliSep categorizes patients into three bands according to their probability of sepsis. The test, which runs on the Cytovale system, assesses immune response using immune cell morphology. By applying pressure to thousands of cells and observing their reaction, IntelliSep can show distinct changes in white blood cells from septic patients. These changes are captured in images and then characterized using a proprietary algorithm.

Test results may help providers optimize clinical outcomes and empower hospitals to improve resource utilization. IntelliSep also may support hospital efforts to meet guidelines set by the Centers for Medicare & Medicaid Services for timely sepsis treatment, known as SEP-1, according to the company.

HOLOGIC SARS-COV-2/ FLU A/B/RSV ASSAY RECEIVES CLEARANCE

Hologic recently announced 510(k) clearance from the Food and Drug Administration for its Panther Fusion SARS-CoV-2/ Flu A/B/RSV assay.

The test detects and differentiates four of the most prevalent respiratory viruses: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), influenza A (flu A), influenza B (flu B), and respiratory syncytial virus (RSV). The assay runs on the fully automated, high-throughput Panther Fusion system, which provides initial results in approximately 3 hours and can process more than 1,000 tests in 24 hours.

The system, along with Hologic's respiratory virus menu, offers various testing options from a single sample and allows healthcare professionals and laboratories to personalize patient testing based on medical history and local prevalence, according to Hologic.

Dr_Microbe/iStock

The Panther Fusion SARS-CoV-2/Flu A/B/RSV assay launches with the new RespDirect collection kit, which enables laboratories to directly load samples for processing on the Panther Fusion system without any uncapping or specimen transfer steps, potentially saving time and reducing errors, repetitive stress injuries, and exposure to viruses.

BD GETS CLEARANCE FOR AI SOFTWARE FOR MRSA DIAGNOSTICS

BD recently announced 510(k) clearance from the Food and Drug Administration for its new BD Kiestra Methicillin-resistant Staphylococcus aureus (MRSA) imaging application.

The BD Kiestra MRSA application uses artificial intelligence (AI) to interpret bacterial growth, release negative specimens with minimal human interaction, and automate the traditionally labor- and time-intensive task of inspecting petri dishes to determine bacterial growth. As a result, laboratory personnel can spend more time on higher-value analysis.

The application can evaluate single specimens or group together the large volume of plates with non-significant growth for batch review and release of negative results, possibly reducing the burden on technicians.

The MRSA imaging application uses AI algorithms to look for specific culture characteristics on the BBL CHROMagar MRSA II plate. Based on that information and analysis by BD Synapsys informatics, plate images are automatically organized and sorted into worklists for laboratory scientists and technicians.

Company officials said their products help labs deal with ongoing labor challenges by allowing labs to use their limited staff more efficiently.

ROCHE CSF ALZHEIMER'S DISEASE ASSAYS GET FDA CLEARANCE

Roche has announced that its Elecsys beta-Amyloid (1-42) cerebral spinal fluid (CSF) II (Abeta42) and Elecsys Total-Tau CSF assays (tTau) have received 510(k) clearance from the Food and Drug Administration (FDA).

The Elecsys CSF Abeta42 and tTau assays—used as a tTau/Abeta42 ratio—measure two biomarkers of Alzheimer's disease (AD) pathology, beta-amyloid and tau proteins, in adults aged 55 and older being evaluated for the disease.

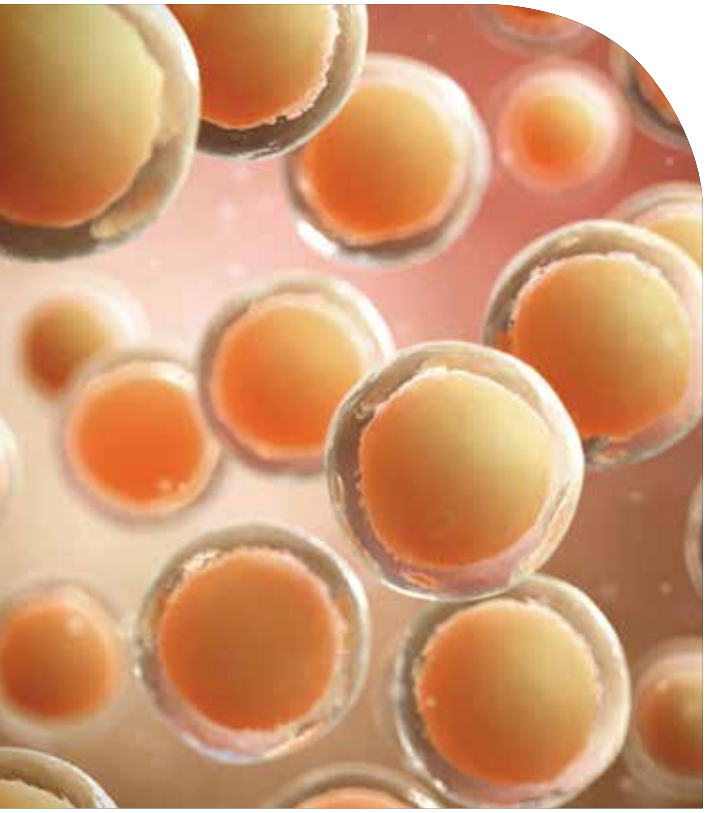
The FDA-cleared Elecsys tTau/Abeta42 ratio supports timely AD diagnosis and treatment decision-making and expands Roche's AD CSF portfolio to include biomarkers for all three main pathological processes of Alzheimer's—amyloid plaques, tau tangles, and neurodegeneration.

Scalable Elecsys AD CSF assays can be added to any of Roche's cobas fully automated immunoassay analyzers, giving patients broad access to testing in a timely manner.

Currently, AD diagnoses are largely made by ruling out non-Alzheimer's causes based on a number of evaluations, including various cognitive exams, routine laboratory tests, and neuroimaging with MRI or CT scans of the head. Additional evaluations with biomarkers specific to AD can identify underlying pathological changes early in the disease, Roche said.

The appropriate use recommendations for new and emerging Alzheimer's medicines call for confirmation of amyloid pathology via CSF tests and PET scan imaging, the company noted.

Industry Playbook



Deal Focuses on Full-Field Digital Cell Morphology Technology

Siemens Healthineers has announced an agreement to distribute Scopio Labs technology for examination of blood cell samples from digitized slides.

Scopio's full-field digital cell morphology platforms are intended for use in the central laboratory adjacent to hematology analyzers to examine patient blood cell samples digitally and remotely, instead of on a slide under a microscope. The process is quicker than traditional manual microscopy, according to Scopio representatives.

Scopio has granted Siemens Healthineers global rights to distribute the Scopio X100 and Scopio X100HT digital solutions. The technology involves integrated artificial intelligence decision support and gives laboratory professionals a highly efficient way to standardize white blood cell differentials, red blood cell morphology, and platelet estimations, the company said. Remote review capabilities mean laboratory professional expertise will no longer be limited by physical location.

This technology complements Siemens Healthineers' existing hematology portfolio to provide more expansive end-to-end workflow solutions, according to Siemens Healthineers.

BIOMÉRIEUX AND JMI LABS PARTNER AGAINST ANTIMICROBIAL RESISTANCE

bioMérieux and JMI Laboratories have announced a 6-year partnership to evaluate the performance of rapid and innovative microbiology diagnostics as important tools in the battle against antimicrobial resistance (AMR).

JMI Laboratories, now a part of Element Materials Technology, specializes in advancement of antimicrobial therapies, state-of-the-art surveillance, and post-market observations and insights in the antimicrobial susceptibility testing (AST) field. JMI's Sentry Antimicrobial Surveillance, which monitors worldwide pathogens and the changes in resistance patterns, collects about 40,000 clinical isolates of bacteria and fungi annually through 150 medical centers worldwide.

Antimicrobial stewardship programs must continually evaluate AST results against new and emerging strains of pathogens that may have developed new resistance mechanisms or additional levels of resistance to current treatments.

The new partnership allows bioMérieux to continually assess AST results and validate against evolving global antimicrobial susceptibility data collected through the Sentry program.

PARTNERSHIP PILOTS PANCREATIC CANCER SCREENING TEST

Microba Life Sciences and Biomed have announced a collaboration involving pilot research that could potentially discover novel microbiome biomarkers for pancreatic cancer.

The pilot will use Microba's proprietary metagenomic sequencing technology and bioinformatic tools.

Pancreatic cancer has one of the highest mortality rates of all major cancers, typically late detection. However, survival rates improve with diagnosis in early stages of the disease.

The project is expected to run through late 2023. It will deploy Microba's Community Profiler (MCP), a metagenomic platform technology. MCP can produce comprehensive and accurate species profiles of human gastrointestinal samples.

Mainz Biomed is currently commercializing its flagship product

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ColoAlert, a detection test for colorectal cancer. In December 2022, the company started a U.S. study of a colorectal screening test that may integrate the company's portfolio of novel gene expression biomarkers. These biomarkers are the focus of current and forthcoming research.

FREENOME ACQUIRES ONCIMMUNE

Freenome has announced acquisition of Oncimmune, an immunodiagnostics developer with a commercialized lung cancer blood test that has received a CE mark, an autoantibody platform, and a research development platform pipeline of more than seven cancer detection signatures.

Oncimmune's EarlyCDT Lung technology detects elevated levels of autoantibodies in the earliest stages of lung cancer.

The acquisition gives Freenome access to Oncimmune's pipeline of autoantibody targets for other cancer indications and augments Freenome's multi-omics platform with additional non-tumor-derived signals to capture a more comprehensive view of the tumor microenvironment.

PARTNERSHIP TO STREAMLINE DRUG DISCOVERY

OmicsEdge and Almaden Genomics have launched a service that will analyze genomic data from clinical trials.

The service leverages Almaden's g.nome platform to streamline the iteration process and can both accelerate the drug discovery process and eliminate trial-and-error with abilities such as identifying causal variants that make ideal drug targets. The companies said the service will enable labs to conduct quick analyses of patients or trial participants' medical conditions and genomics. The information gives valuable insight regarding genomic criteria and how it elevates risk.

g.nome has changed bioinformatic pipeline development with its visual drag-and-drop workflow builder and curated library of tools, in contrast to the usual laborious work of building pipelines with solutions hand-coded by a limited number of highly skilled bioinformaticians. The platform integrates with Jupyter Notebook and eliminates the need for coding in most applications and allows the broader research team to actively participate in the pipeline iteration and executing processes, g.nome said.

PARTNERSHIP FOCUSES ON ADVANCE IMMUNOTHERAPY RESPONSE TEST

Culmination Bio and Cofactor Genomics have partnered to leverage samples and data from one of the largest U.S. biobanks to fuel the development of Cofactor Genomic's OncoPrism test in 11 cancers.

The partnership aims to build cancer biomarkers targeted by the Predicting Immunotherapy Efficacy From Analysis of Pre-treatment Tumor Biopsies (PREDAPT) clinical trial.

Cofactor's OncoPrism assay is a laboratory-developed test powered by a sophisticated, multidimensional immune biomarker built to predict which cancer patients are likely responders to monotherapy of immune checkpoint inhibitors, such as Keytruda (pembrolizumab).

The partnership's first focus is studying cancers of the head, neck, and lung, and will soon expand into nine other indications for which the study is approved. These include triple-negative breast, cervical, colorectal, esophageal, gastric, kidney, liver, and urothelial cancers.

Early readouts for the head and neck cancer biomarker show that Cofactor's approach is twice as accurate as the PD-L1 biomarker in finding the subset of patients who respond to immune checkpoint inhibitors.

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Ask The Expert

What's the Best Approach for Evaluating GFR in Living Kidney Donors?

Sarrah Lahorewala, BDS, PhD

Why is it important to precisely evaluate glomerular filtration rate (GFR) in kidney donor candidates?

A: Kidney transplants from living donors are widely recognized as the optimal approach for treating end-stage renal disease (ESRD). They lead to improved graft and patient survival rates. However, the procedure increases the donor's risk of kidney and cardiovascular diseases. Precisely assessing GFR in living kidney-donor candidates helps identify individuals with preexisting kidney dysfunction, ensuring they are excluded from the donor pool. It also guarantees the selection of candidates with minimal risk of developing ESRD, thereby optimizing the overall success of kidney transplantation for both donors and recipients.

What clinical methodologies are available for assessing GFR? What are their pros and cons?

GFR can be either measured—for example, by assessing creatinine, iothalamate, or iohexol clearance—or estimated based on the serum or plasma concentration of creatinine and/or cystatin C.

Estimated GFR (eGFR) is a widely used screening approach that calculates GFR based on serum creatinine and/or cystatin C concentrations, as well as the patient's age and sex. The recommended eGFR equations are the 2021 CKD-EPI creatinine, 2012 CKD-EPI cystatin C, and the 2021 CKD-EPI combined creatinine-cystatin equations.

A key advantage of using creatinine-based eGFR is the widespread availability of creatinine measurements, making this method simple, cost-effective, and standardizable. However, creatinine levels can be affected by factors other than GFR, such as muscle mass and diet—which may lead to inaccuracies, particularly in individuals with normal or mildly reduced GFR. Significant deviations from true GFR may be observed in individual patients.

Cystatin C, an endogenous filtration marker like creatinine, is not influenced by muscle mass or diet, potentially making it more reliable. Combining measurements of creatinine and cystatin C in eGFR equations has been shown to improve accuracy compared to eGFR based on either marker alone. However, the superiority of cystatin C-based eGFR over creatinine-based eGFR has not been unequivocally established.

With measured GFR (mGFR), endogenous or exogenous filtration markers such as creatinine, iothalamate, or iohexol are used to directly measure GFR. Iothalamate and iohexol are administered to patients intravenously, and plasma and/or urine clearance of the markers is measured to determine GFR. Creatinine clearance (CrCl) is calculated by measuring creatinine in a 24-hour urine sample and comparing that to the patient's serum creatinine concentration.

While CrCl is more reliable than eGFR using serum creatinine alone, it can overestimate GFR by 10–20% due to distal tubular secretion of creatinine. Inaccurate urine collections can also lead to errors, further compromising the reliability of CrCl.

Measured GFR using exogenous markers is considered the gold standard for assessing GFR due to its high accuracy and sensitivity to changes in renal function. However, mGFR methods require specialized facilities, expertise, and analytical methods. The administration of exogenous markers and the collection of samples for plasma or urine clearance measurements can be time-consuming, invasive, and costly. Additionally, variations in the timing and number of samples collected can affect the accuracy of the measurement.

Which method is most appropriate for evaluating living kidney-donor candidates?

The most accurate method is mGFR using exogenous markers. Although convenient, eGFR equations lack the necessary accuracy for donor evaluations and should be used cautiously. Creatinine clearance often overestimates GFR and is susceptible to errors in collection.

Using mGFR ensures a reliable assessment of GFR, while eGFR equations and creatinine clearance can provide supplementary information. It is essential for clinicians to carefully consider the advantages and limitations of each method when making decisions regarding donor eligibility.

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