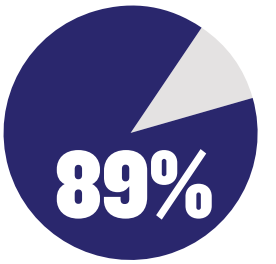
June 2023

CLN Clinical Laboratory News

PREDICTING NEED FOR LIVER TRANSPLANT



Sensitivity of model for end-stage liver disease including lactate dehydrogenase

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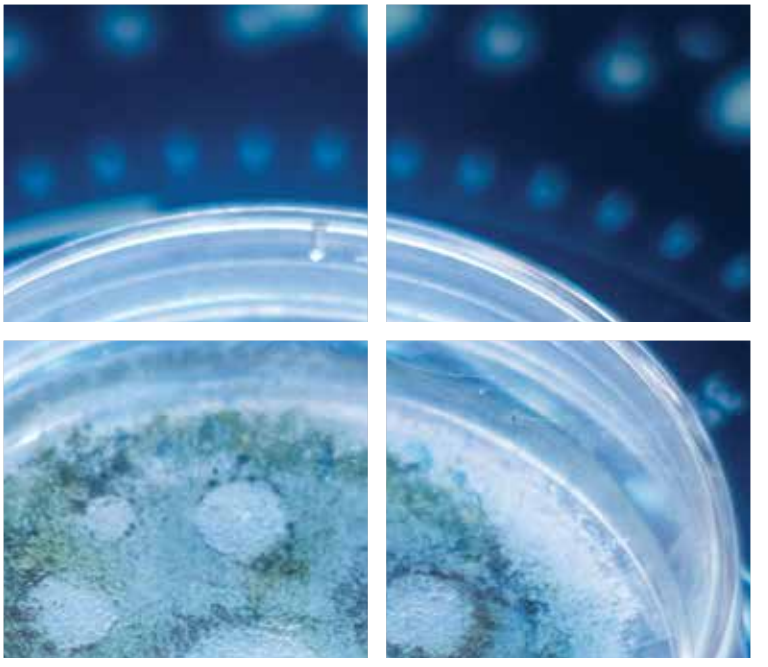
The Promise of Automation in Clinical Microbiology



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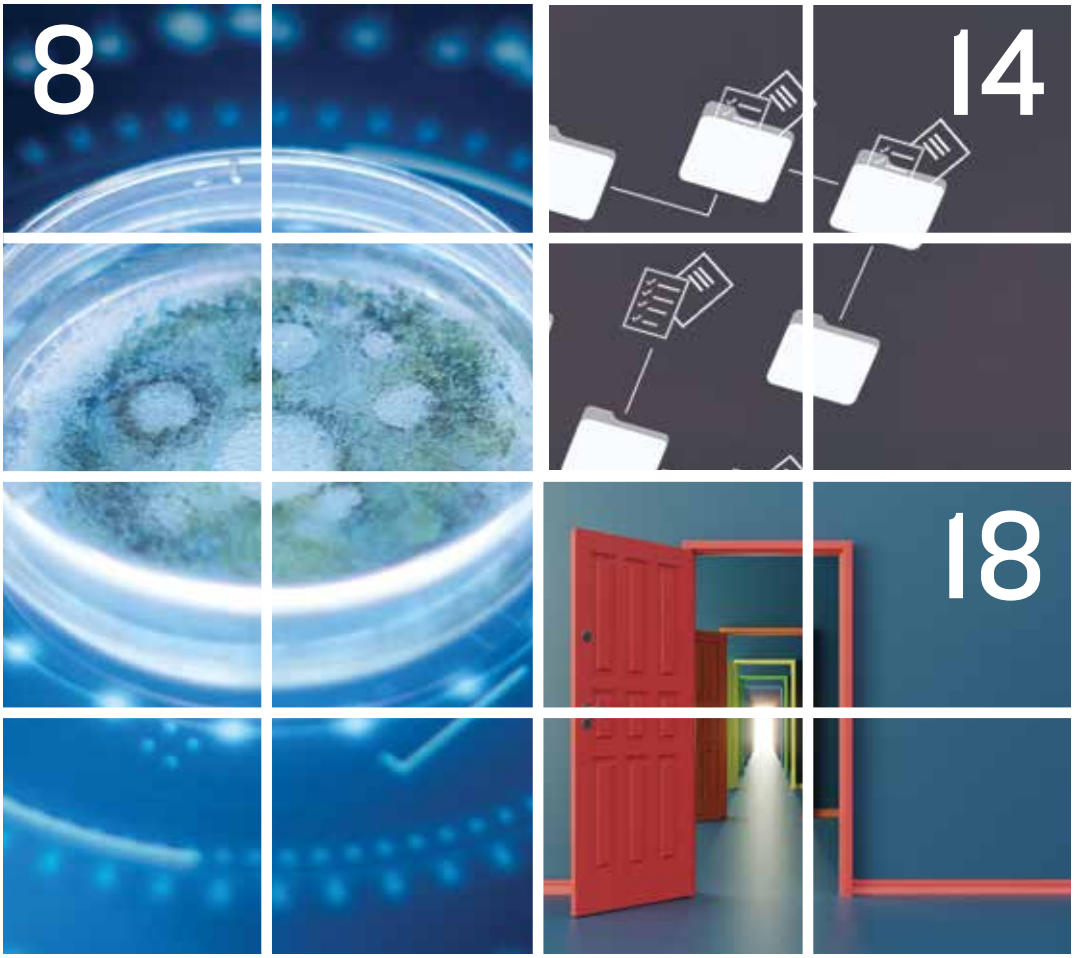

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Federal Insider

Laboratory Organizations Urge Congress to Address Workforce Shortages

AACC, in concert with a broad coalition of laboratory advocacy organizations, is urging Congress to take action on the growing shortage of laboratory professionals in the United States. A letter, signed by the 24 organizations in the coalition, was sent to the Senate Committee on Health, Education, Labor, and Pensions. Together, the organizations represent approximately 350,000 laboratory professionals.

The letter underscored the fact that the COVID-19 pandemic has exacerbated the existing shortage of laboratory professionals.

"Currently, most medical and public health laboratories suffer from significant personnel shortages, and many are operating at or near crisis-mode," the letter says. "Staffing shortages now have the potential to undermine the ability of these laboratories to provide timely test results, which is imperative to both the public health and patient access to quality care."

The coalition is urging Congress to include laboratory professionals in all federal workforce programs, including grants to training programs, scholarship and fellowship programs, and loan repayment programs. Currently, laboratory professionals, and in particular entry-level laboratory professionals, are unable to benefit from these programs.

This letter also asks Congress to consider how tackling visa issues could help improve the shortage. The letter is the latest in a series of efforts by AACC and other laboratory advocacy organizations to raise awareness of workforce issues.

According to the letter, the workforce shortage persists due to several factors, including high educational costs; lack of familiarity with laboratory medicine as a career option; declines in the number of training programs and students trained; and high workload, stress, and burnout.

FTC PROPOSES NEW RULES ON HEALTH BREACH NOTIFICATION AND WARNS OF BIOMETRIC PRIVACY RISKS

The Federal Trade Commission (FTC) is seeking comment on proposed changes to the Health Breach Notification Rule (HBNR) that include clarifying the rule's applicability to health apps and similar technologies.

The FTC also warns of the increasing risks associated with the collection and use of biometric information. Increasingly, healthcare apps collect such "digital biomarkers" to track consumers' health.

The HBNR requires vendors of personal health records (PHR) and related entities that are not covered by the Health Insurance Portability and Accountability Act (HIPAA) to notify individuals, the FTC—and, in some cases, the media—of a breach of unsecured personally identifiable health data. It also requires third party service providers to vendors of PHRs and PHR-related entities to provide notification to these vendors and PHR-related entities following the discovery of a breach.

The FTC proposes changes to the HBNR that would include revising several definitions to clarify the rule's application to health apps and authorizing the expanded use of email and other electronic means of providing notice of a breach to consumers.

In a separate announcement, the FTC also warns of the increasing risks associated with the collection and use of biometric information—data that depicts or describes physical, biological, or behavioral traits, characteristics, or other measurements. Some biometric technologies claim to determine characteristics ranging from a person's age, sex, or race to the individual's aptitudes or demeanor.

The FTC's policy statement cautions that businesses that collect or use biometric information must comply with the law. Businesses must carefully consider the risks associated with collecting and using biometric information and take steps to mitigate those risks, the agency says.

Consumers should take steps to control their own biometric information, according to the FTC. They should be careful about what biometric information they share with businesses and should only share their biometric data with those they trust. Consumers should also use the privacy settings on their devices, such as smartphones.

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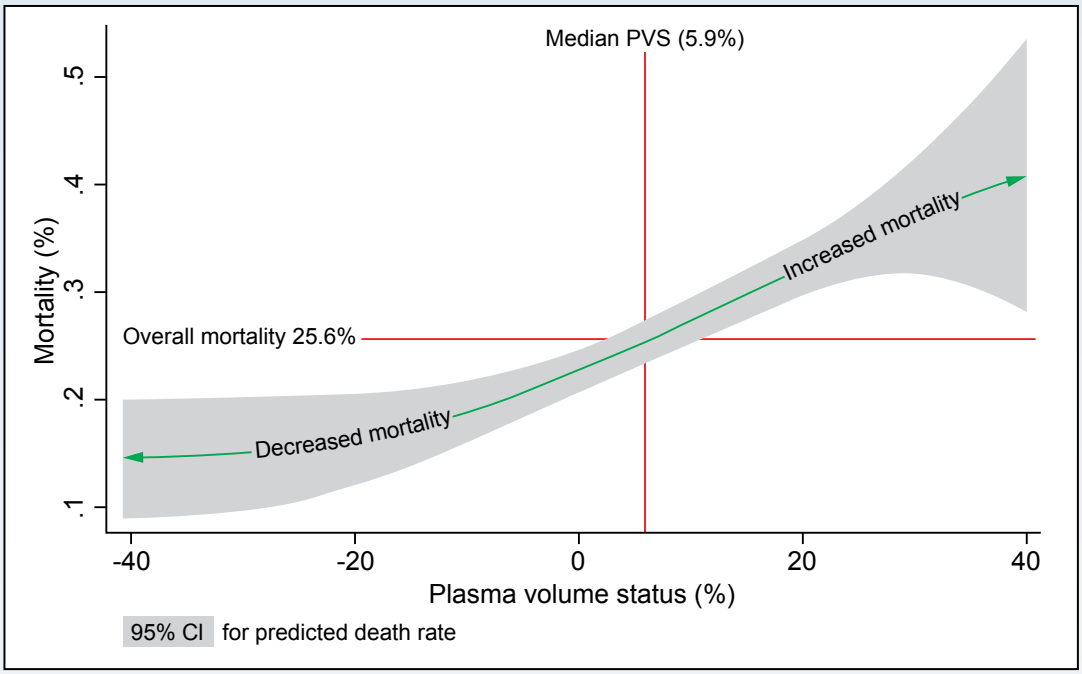
Plasma Volume Is Associated with Patient Mortality, ICU Days, and Ventilator Days

Patients with acute respiratory distress syndrome (ARDS) are particularly vulnerable to adverse effects of fluid overload. Plasma volume status (PVS), defined as the percentage deviation from ideal plasma volume, has emerged as a rapid, noninvasive method to assess volume status and prognosis:[1]



According to this recent study from Johns Hopkins University Medical Center:

"We demonstrate that elevated PVS is associated with greater risk of mortality and fewer ICU- and ventilator-free days even after adjustment for age, sex, and degree of critical illness. Plasma volume status could be considered for risk-stratification and to direct therapy, particularly fluid management." [1]

Plasma Volume Now Available On A Blood Gas Analyzer

Nova's Prime Plus blood gas analyzer automatically calculates patient plasma volume with the Strauss formula, which uses measured hemoglobin and measured hematocrit to calculate ePV (estimated plasma volume). Prime Plus reports ePV as part of a comprehensive panel including tests for kidney function, electrolytes, metabolites, gases, and acid/base.

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1. Metkus TS et al. Calculated Plasma Volume Status Is Associated with Mortality in Acute Respiratory Distress Syndrome. Crit Care Explorations 2021; 3(9).

Bench Matters

Big Efficiencies in Small Labs

By David Shiembob, MBA, C(ASCP)

You could be forgiven for thinking that bigger is always better when it comes to clinical laboratories. "Economies of scale," "total lab automation," and "centralized core laboratory" are all common phrases heard in the industry, and they imply that the main way to gain efficiency is through size. The reality is that smaller laboratories play an essential role in the delivery of patient care by offering laboratory services close to the patient, whether that is by providing rapid results for inpatients or outreach services to geographically isolated communities. It is also true that smaller laboratories often have less support compared to large facilities, making it difficult to utilize staff and instruments efficiently. The good news is that, whether you are a team member, manager, or medical director in a smaller laboratory, there are various approaches you can take to overcome these challenges.

Leverage System Resources

Many small hospitals are part of larger health systems, but the level of system integration laboratories have with each other varies widely. Evaluating the system resources at your disposal is a logical place to start when considering how to improve operations at a smaller laboratory. The resources available will differ depending on the system, but key resources could include:

- Shared purchasing agreements for instruments and reagents,
- Software solutions—most obviously laboratory information systems and electronic medical records, but also programs such as customer relationship management solutions, document management systems, or learning management systems that may be in use elsewhere in the health system,
- Policies and procedures, and
- Guidance from specialists and experts at other locations.

There may be alternative forms of support available to labs that are part of an independent hospital. Many independent hospitals choose to enter partnerships or affiliations with related hospitals. These may be either peer institutions or larger

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health systems that provide certain services to the smaller hospital. It may be possible to access some of the resources listed above through these types of arrangements.

Organize Effectively

As a laboratory consultant, I sometimes encounter the stereotype that small laboratories are inherently disorganized or out-of-date compared with larger facilities. Having visited many laboratories in my work, I can confidently state that lab quality is independent of size. I have seen large laboratories that were cluttered and chaotic, with the main means of communication consisting of Post-it notes. I have also seen small laboratories that were extremely well organized and efficient, even though they were not considered to "centers of excellence" or flagship labs for the health system.

Laboratory managers can make progress in organizing laboratory space and streamlining processes. Managers can implement these initiatives without outside resources or institutional support, making them particularly relevant for small laboratories.

A simple but important place to start is with a "5S" initiative, which stands for "sort, set in order, shine, standardize, and sustain." There are various online resources available that detail how to approach this project and engage your laboratory staff. The goal of a 5S initiative is twofold: First, to make it easier to navigate the lab, locate necessary items, and perform work with minimal distractions. The second goal, which is just as important, is improving staff morale, encouraging helpful recommendations, and increasing pride in the workplace.

Focusing on inventory management is another organizational initiative that provides benefits. Establishing formal order points for each supply item as well as tracking current lots and expiration dates in a uniform manner goes a long way to improve efficiency. It also can decrease costs and increase productivity by ensuring supplies remain in stock and are not wasted due to expirations.

Utilize MLS Staff Appropriately

Staff shortages are affecting many labs. While it is difficult to find qualified staff at all levels, the dearth of medical laboratory scientists (MLS) is the most acute. With staff shortages, laboratory staff have had to perform tasks outside of their everyday responsibilities. In addition to performing highly complex testing and verifying results, MLS staff were taking on tasks such as drawing blood and processing patient specimens. This challenge offers an area of improvement for smaller laboratories that once found it simple to hire MLS team members who could "do everything." Defining the various roles in the lab can mitigate the MLS shortage and decrease labor expenses, improving efficiency.

Grow Expertise Internally

Training staff and retraining personnel are important for any laboratory but especially for smaller laboratories that might have access to a limited applicant pool compared with larger institutions. Even smaller laboratories can benefit from creating career ladder job titles and specialty roles. Developing a clear pathway for advancement is a great way to increase retention and encourage experienced staff to take on more responsibilities.

Additionally, developing a relationship with local colleges pays dividends in many ways. If there is a laboratory program in the area, hosting students for clinical rotations provides a pipeline of these scarce candidates and is worth the effort. Furthermore, graduates with associate degrees in the sciences can be eligible to sit for the Medical Laboratory Technicians exam after 6 months of training, making relationships with these institutions beneficial.

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The Sample

Lactate Dehydrogenase Can Predict the Need for Liver Transplant

Lactate dehydrogenase (LDH) is prognostic for acute live failure (ALF) when used in a new version of the model for end-stage liver disease (MELD) score known as the MELD-LDH, new research confirms (JALM 2023; doi: 10.1093/jalm/jfac137).

To confirm previous proteomics findings in a small study, the researchers reviewed laboratory data from 238 patients with biochemical evidence of ALF admitted to a single medical center over 12 months. The researchers also reviewed laboratory data from a subset of 170 patients with encephalopathy.

LDH was strikingly elevated in nonsurvivors at the time of peak injury. Receiver operative curve characteristic (ROC) curve analyses revealed that LDH by itself could discriminate between survivors and nonsurvivors on the first day of hospitalization, although not as well as the MELD and MELD-LDH scores.

LDH by itself performed similarly to the MELD at the time of peak injury, while the MELD-LDH score moderately outperformed both. The MELD-LDH score had greater sensitivity and negative predictive value than the MELD and King's College Criteria (KCC). Plasma ALT values were similar between survivors and nonsurvivors and failed to discriminate between the two groups. LDH was significantly higher in nonsurvivors and performed as well as the MELD score at peak injury. Furthermore, the MELD-LDH score outperformed both LDH and the MELD, with area under the curve of 0.77, compared with 0.82 for the MELD and MELD-LDH, respectively, on the day of peak ALT.

When the researchers compared sensitivity, specificity, and predictive values for death for the KCC using an LDH cutoff of 2,000 U/L, a MELD cutoff of 30 derived from previous literature, and a MELD-LDH at a proposed cutoff of 0.3, the KCC displayed the greatest specificity but poor sensitivity. KCC specificity was 11% and 45% on the first day and the day of peak injury, respectively. MELD-LDH had greater sensitivity at day of peak, 89%, and negative predictive value (NPV) of 93, than either the LDH or MELD alone. At peak injury day, LDH had sensitivity of 72% and negative predictive value of 46 and MELD alone had sensitivity of 76 and NPV of 85. The researchers say these figures show that MELD-LDH is better at identifying patients who need a liver transplant.

When researchers limited their analyses to only patients who meet standard criteria for ALF by virtue of their encephalopathy and no chronic illness, results were similar.

These results confirm that LDH is prognostic in ALF patients, with similar performance to the MELD, the researchers wrote. They added that the new MELD-LDH score moderately increases sensitivity for death, and therefore transplant need, over the MELD. Although additional confirmatory studies are needed, the researchers state that careful use of these risk stratification tools might improve decision-making and donor organ allocation.

Md Saiful Islam Khan

PLASMA BIOMARKER MAY HELP DISTINGUISH TYPES OF DEMENTIA

Measuring plasma placental grown factor (PlGF)—a molecule that prompts development of new blood vessels—may help determine whether cognitive problems in older adults result primarily from vascular problems or another cause, such as Alzheimer disease, according to a recent study (Alzheimers Dement 2023; doi: 10.1002/alz.12974).

Researchers found that patients with higher plasma PlGF levels are more likely to have cognitive impairment or evidence of brain injury.

Clinicians typically rely on imaging to determine whether older adults' cognitive impairments are mostly caused by Alzheimer's disease or vascular issues. In response, the MarkVCID Consortium has worked to identify biomarkers of vascular drivers of cognitive impairment. It determined that PGIF may be useful for identifying patients whose cognitive impairment stems from vascular brain injury.

In the current study, researchers at five sites studied 355 patients who had blood collection, imaging, and cognitive testing. Patients with blood PlGF measurements in the top quartile were three times as likely to have cognitive impairment or dementia than patients in the bottom quartile.

Every unit increase in total PlGF in the blood was associated with a 22% increase in the likelihood of having cognitive impairment and a 16% increase in the likelihood of having imaging evidence of cerebral small vessel disease.

Plasma PlGF may function as a stable, reliable, and accurate diagnostic tool to identify patients whose cognitive impairment has suspected vascular causes, the authors wrote. The biomarker's accuracy increases across progressive stages of brain injury.

They added that plasma PlGF may be a useful adjunct in evaluating subjects with suspected vascular cognitive impairment and/or dementia. The researchers called for more research to determine how well the biomarker can prospectively predict future cognitive decline.

The researchers noted that their study was limited by low enrollment at some sites and random resampling into equal cohorts. Another limitation was lack of measures for comorbid Alzheimer's disease that may have limited plasma PlGF's ability to distinguish vascular contributions to dementia subtypes.

DIABETES AND OBESITY ROSE AMONG YOUNG ADULTS

The burden of most cardiovascular risk factors—some shown by lab values—is rising among young adults in the United States.

The most affected racial and ethnic groups are Blacks, Hispanics, and Mexican Americans (JAMA 2023; doi: 10.1001/jama.2023.2307).

Declines in overall U.S. cardiovascular mortality have stagnated in the past decade, in part due to worsening risk-factor control in older adults. However, little is known about prevalence, treatment, and control of these risk factors in young adults ages 20–44.

Researchers performed a serial cross-sectional analysis of National Health and Nutrition Examination Survey data from 2009–2010 to 2017–March 2020 for this age group. They sought to identify national trends in prevalence of hypertension, diabetes, hyperlipidemia, and obesity, as well as smoking rates.

The researchers also sought to determine rates of hypertension and diabetes treatment and among those who received treatment, degree of blood pressure, and glycemic control.

The researchers found diabetes prevalence rose from 3.1% to 4.1% and hypertension from 9.3% to 11.5%. Prevalence of hyperlipidemia decreased from 40.5% to 36.1%. Black young adults had the highest rates of hypertension, while increases in hypertension occurred among Mexican Americans and other Hispanics. Mexican Americans had a significant rise in diabetes rates, from 4.3% to 7.5%. Blood pressure control did not change much among those young adults treated for hypertension, but glycemic control was suboptimal for the entire study period, with about 1 in 2 adults with diabetes on therapy.

Understanding Laboratory Automation in Clinical Microbiology

Although often considered difficult to implement, automated systems for clinical microbiology labs hold promise—particularly in the wake of increased testing demands and staff shortages.

BY **DO YOUNG KIM, MD**

In many clinical laboratory disciplines, including clinical chemistry, molecular biology, immunology, and hematology, automation is now being used to complete every step of the workflow (*1*). Such "total" automation has been considered difficult to achieve in clinical microbiology due to the different microbiological specimen collection sites, from which microbiological specimens are collected, the complexity of their containers, the need to test for a large number of pathogens, and the high cost of automation relative to low specimen volumes (*2*,*3*).

However, that may be changing. Thanks to advances in technology and more centralized laboratory models, microbiology laboratory automation (MLA) systems have been developed and many labs worldwide are implementing MLA systems, which offer the potential to streamline workflows, optimize incubation conditions, improve the ability to track samples, and reduce errors and injuries.

Today, there are two major commercially available MLA systems: Kiestra by BD (Becton, Dickinson and Company) and WASPLab by Copan Diagnostics, Inc. This article explores the current state of MLA and highlights some exciting new developments that could shape the future.

SPECIMEN PROCESSING

An automated specimen processor can inoculate liquid-based specimens onto solid media or broth media. Once these specimens are scanned and loaded onto a processor, they are inoculated onto culture media that are pre-selected for their specific specimen type. A processor can store numerous types of culture media and label specimens with a barcode prior to inoculation for tracking and tracing. It also has a verification system to ensure that specimens are actually inoculated.

Non-liquid-based specimens can be processed semiautomatically. In other words, lab staff must manually inoculate them onto media and then add them to a processor for further steps. The inoculated solid media plates are streaked with a loop (Copan's WASP-DT) or a magnetic bead (BD's InoqulA). Lab staff have the option of selecting a streaking pattern from a library or customizing their own pattern.

In addition, these systems can prepare slides automatically for Gram staining. As one might expect, automating specimen processing can reduce variability from manual plate streaking, minimize cross

contamination, alleviate the risk of repetitive strain injury or exposure to hazardous material, and reduce the costs and time associated with specimen processing (*3*).

INCUBATION AND MONITORING OF CULTURE PLATES

Once specimen processing is complete, these automated systems transport plates on a conveyor belt to an incubator with the appropriate atmospheric conditions. MLA incubators have high storage capacities (795 to 1590 plates for WASP, 1,152 plates for Kiestra) and provide stable aerobic and CO2 atmospheres at constant temperatures. Users will receive a high-resolution digital image of a plate after it enters the incubator, and again at specific incubation times that they predefine based on specimen type. Additional images can be obtained at any time a user requests them.

The systems capture images of the plates at several light exposures and various angles. These images are then used to monitor the cultures. Using MLA software, lab staff can view the images at high magnification and assess images of different specimen types taken at various incubation times from the same patient. This can aid them in interpreting the culture.

Automated plate processes offer several advantages over standard workflows. They reduce the time that plates spend outside an incubator, thus optimizing incubation conditions and enhancing bacterial growth, including the emergence of rarely recovered and fastidious organisms (*4*,*5*), and they decrease the likelihood of contamination. They also allow for a more

continuous workflow, which is better suited to a 24/7 operation, as opposed to batch processing (*2*).

PLATE READING

Laboratory staff can use MLA software to read and interpret digital images of plates and mark on the screen which colonies require further work up, including subculture, organism identification, and antimicrobial susceptibility. They then can collect the plates with marked colonies from their incubator for further analysis.

There is an MLA product on the market that integrates artificial intelligence (AI) to automate the evaluation of plates. PhenoMatrix by Copan uses algorithms to detect organisms of interest, including methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococci (VRE), and group B streptococcus (GBS) on a chromogenic agar. Its performance has been evaluated and published (*6–9*).

PhenoMatrix also can segregate urine cultures according to whether they have no growth, growth, insignificant growth, or mixed growth. Moreover, users can specify colony counts for the software to do additional triaging. For example, the system can categorize urine cultures with less than 10 colony forming units (cfu). The software offers automatic colony recognition on standard media, and it can apply rules defined by users for more specified segregation algorithms.

BD Kiestra offers an imaging application for urine cultures and MRSA through its informatics system, which is called BD Synapsys (*10,11*). By using an AI algorithm coupled with user-created rules, the system can interpret digital images of plates with verified media, including certain chromogenic agars. It can segregate no growth or clinically nonsignificant growth based on user-defined rules.

ORGANISM IDENTIFICATION AND ANTIMICROBIAL SUSCEPTIBILITY

A technology called matrix-assisted laser-desorption ionization – time-of-flight mass spectrometry (MALDI-TOF MS) has revolutionized the identification of bacteria and fungi. It identifies organisms by analyzing their protein profiles and comparing them against known values in a database (*3*). MALDI-TOF MS has largely replaced traditional biochemical methods for identifying organisms because of its rapid turnaround time, low requirements for specimen volume, and per-test affordability (*2*).

There are two main systems on the market for MALDI-TOF MS, both of which are semiautomated: Bruker's MALDI Biotyper CA and bioMérieux's VITEK MS. In both cases, lab staff must manually prepare samples, which includes picking colonies from culture plates, spotting on sample plates, and applying matrices. The exception to this is if the lab has an MLA system in place to automate sample preparation.

For example, BD's IdentifA received approval from the Food and Drug Administration (FDA) to be used with Bruker's MALDI Biotyper CA. In addition, Colibri is FDA-cleared for use with Bruker's MALDI Biotyper CA and bioMérieux's VITEK MS. Colibri can be coupled with an AI system called PhenoMATRIX TAG, which automatically tags colonies on a culture plate to be picked by Colibri based on growth interpretation, as defined by custom rules.

There are also automated instruments available to help lab staff conduct antimicrobial-susceptibility testing (AST), one of their major responsibilities in clinical microbiology laboratories. Some automated AST instruments use broth microdilution methods that require manual preparation of a McFarland suspension. Copan's Colibri can prepare McFarland suspensions automatically with a nephelometer, and it is FDA cleared for use with bioMérieux's VITEK 2. It also prepares a plate for conducting a purity check from the suspension.

For disk-diffusion methods, the Radian system by Copan fully automates disk-diffusion testing by seeding Mueller Hinton plates with an automatically prepared McFarland suspension. It applies antimicrobial disks onto the seeded plate, providing digital images of the plate for automated zone diameter measurement and interpretation (*12*).

FUTURE DIRECTIONS

Advances in machine learning and AI are expected to bring further developments to clinical microbiology laboratories. For example, in a 2018 study, researchers evaluated automated Gram stain interpretation of blood cultures, supporting a proof of concept for a fully automated classification methodology (*13*). With MLA's automated Gram stain slide preparation and high-resolution digital imaging, one can envision a future where MLA offers a fully automated Gram stain process that includes Gram stain interpretation by AI.

In addition, as the use of AI for reading culture plates evolves, its applications may expand to cover more diverse specimen types (e.g., samples from stool, wounds, respiratory tract, etc.) for a wider range of organisms. Furthermore, if guidelines for disk-diffusion testing from positive blood culture broths can be applied to automated disk-diffusion AST processes, laboratorians may have a reliable and timely new option for retrieving one of the most critical test results in the clinical microbiology lab.

CONCLUSION

Although automating clinical microbiology laboratories brings challenges, technological advancements are rapidly expanding the realm of

Advances in machine learning and AI are expected to bring further developments to clinical microbiology laboratories.

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possibility. Since the first automated system for clinical microbiology was installed in 2006, multiple laboratories worldwide have implemented MLA.

Such systems can provide multiple advantages to clinical microbiology laboratories. First, they improve workflow by automating processes that are often time consuming and tedious when done manually, such as plate sorting, plate moving, plate streaking, and locating plates. By allowing more continuous workflows, the working hours of the laboratories can be extended, which benefits patient care.

In addition, standardized streaking yields a higher amount of isolated colonies and uninterrupted incubation processes, thereby improving the recovery of pathogens from culture (*3–5*). MLA also reduces human error (during plate streaking, labeling, etc.), which increases the quality of microbiological test results. Furthermore, eliminating the need for lab staff to perform repetitive tasks can alleviate ergonomic issues (*3*).

MLA's ability to provide reproducible results with image documentation is another strength. When combined with its barcoding capability, digital imaging offers traceability that can be helpful to laboratories (*3,14*). Digital images and traceability also create great learning opportunities for students and trainees, allowing them to view saved images at different timepoints. Moreover, some research indicates that MLA has a faster turnaround time than traditional setups (*15,16*), which could positively impact patient care and treatment cost.

Finally, the economic benefit that comes with improving laboratory efficiency cannot be overlooked, especially since microbiology laboratories are facing increasing testing demands while experiencing staffing shortages (*16*). Of course, this must be weighed against the high initial costs for procuring and installing MLA.

Certainly, system installation brings with it the risk of downtime and the need for a backup plan. However, it's helpful to bear in mind that MLA systems are modular in nature and that levels of automation can be individualized (*3*), allowing for a gradual transition.

Understanding the current state of automation in clinical microbiology, along with possible new developments on the horizon, is a good way to ensure your laboratory is on the best path.

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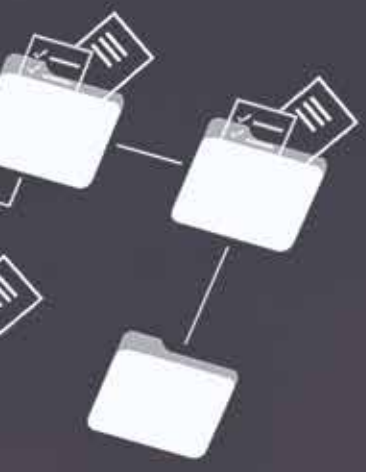
Diagnostic Data Without a Home

From continuous glucose monitors to consumer wearables, data abounds without a path to electronic medical records.



BY KIMBERLY SCOTT

As consumers increasingly interact with diagnostic data that originates outside of the clinical laboratory, healthcare systems are faced with the challenge of how to integrate this data in the electronic health record (EHR) and make it useful to clinicians.

Currently, integration of mobile health (mHealth) technology data into the EHR is immature, with few health systems throughout the country having the ability to bring patient-generated health data from remote patient monitoring tools into the medical record, according to Juan Espinoza, MD, chief research informatics officer with Lurie Children's Hospital of Chicago. Examples of patient-generated data include that taken from blood glucose monitors, blood pressure readings using home health equipment, or exercise and diet tracking using a mobile app or wearable device.

Typically, patient-generated data or test results that come from remote monitoring tools are printed and scanned into the medical record, noted James Nichols, PhD, DABCC, FAACC, medical director of chemistry and point-of-care testing at Vanderbilt University School of Medicine in Nashville, Tennessee. Patients are primarily responsible for capturing or recording this data, and patients also decide how to share it with healthcare providers.

In some cases, such as continuous glucose monitors (CGMs), a physician will simply look at a patient's app on their phone. Sometimes a middleware platform, such as Apple HealthKit, is used to aggregate and integrate patient-generated data with an EHR.

"Continuous glucose monitors collect a wealth of data, which can show trends and estimate the rise and fall of glucose over time," Nichols said. "Each CGM manufacturer has a different application that interacts with the cloud. What they do with that information is proprietary."

Early integration efforts for remote monitoring devices largely have focused on CGMs, and their use has increased substantially in recent years. "A handful of academic medical centers have built interoperability interfaces for CGMs, but this type of integration is still in its infancy," said Espinoza, who has led efforts to integrate CGM data into health records. "CGM devices were never designed for EHR integration. So we had to figure it out after the fact."

BARRIERS TO INTEGRATION ABOUND

In studies, healthcare providers have reported that disruption to clinical workflow and time constraints are top barriers to integrating patient-generated data into EHRs. A December 2020 report published in JAMIA Open concluded that, while work on integrating patient-generated data into EHRs appears to be at an early stage, this data has the potential to close healthcare gaps and support personalized medicine (doi: 10.1093/jamiaopen/ooaa052). The authors called for more efforts to understand how to optimize data integration, standards for EHR delivery, and clinical workflows.

Some EHR manufacturers, such as EPIC, are working on CGM modules, Espinoza said. However, myriad technical issues must be dealt with. One example is ensuring the correct patient identity, such as in the case of a child whose device is registered to a parent or who might have a different last name than the parent. There are also operational, legal, compliance, and financial problems.

GOVERNMENT INITIATIVES OFFER A NUDGE

The federal government is attempting to tackle some of these problems. The 21st Century Cures Act, signed into law in 2016, includes provisions on data sharing and interoperability to encourage the access, exchange, and use of electronic health data. In addition, a proposed rule from the Centers for Medicare and Medicaid Services requires healthcare facilities to implement technologies that support open application programming interfaces (APIs) that allow real-time, bidirectional data exchange between patients and providers.

"Rather than use general reference intervals, doctors could rely on a patient's own data to make decisions."
—James Nichols

The Office of the National Coordinator for Health Information Technology published a white paper in 2018 highlighting some of the challenges of collecting and using patient-generated data. These include the technical challenges related to accuracy of measurement, data provenance, and privacy and security concerns. The report concluded that clinicians and researchers should prioritize health conditions where the use of patient-generated data could have the greatest impact, and payers should expand reimbursement models to cover use of this data to drive positive health outcomes.

SIZING UP THE BENEFITS OF CGM DATA INTEGRATION

The benefits of integrating CGM data into the medical record are many, according to Espinoza. "Any time a clinician has to leave the EHR to go look for data elsewhere, it's lost time and lost efficiency," he said. "Because it's such a burden to leave the EHR to find data, some providers won't take that extra step. Integration will make it easier to look at the data, which in turn will improve patient care and decrease the likelihood of mistakes occurring."

Nichols agreed that integration of CGM data into the medical record would help clinicians improve patient care. "It would certainly personalize a patient's experience," he said. "Rather than use general reference intervals, doctors could rely on a patient's own data to make decisions."

In 2021, Espinoza was instrumental in forming a group to focus on the challenges involved in integrating CGM data into EHRs. Led by the Diabetes Technology Society, the group—which included more than 140 participants from industry, government, and academia—published a report with a set of data standards in November 2022 (www.diabetestechnology.org/icode).

According to the report, there are no common data management systems among CGM manufacturers. The lack of standards and failure to integrate with other healthcare data inside the EHR renders CGM data less useful than it could be. The iCoDE project was tasked with developing technical specifications to integrate CGM data into the EHR and creating workflows and guidelines to facilitate data integration efforts.

PILOT PROJECT SHOWS PROMISE

There is some evidence that integrating CGM data into the EHR improves patient care. A 2020 pilot project between HealthPartners Institute's International Diabetes Center (IDC) in Minneapolis and Abbott Diabetes Care allowed for CGM data to transfer from Abbott's cloud-based system, LibreView, to an EHR, allowing physicians to view patients' CGM data along with their laboratory results.

"CGM data provides a wealth of information, but without easy access, clinicians can't fully leverage this information for their discussions with patients and clinical recommendations," said IDC Medical Director Amy Criego, MD, at the American Diabetes Association's 81st Scientific Sessions in 2021. "We demonstrated that there's an effective way for clinicians to both view and track this data over time in the EHR, which we

expect will improve how they're able to support their patients."

BEWARE DATA FATIGUE

Although glucose monitors clearly provide useful data, there are questions about the value of other types of data, such as heart rate or temperature, from mHealth devices.

"Data by itself is not always useful unless there's an evidence-based protocol about what to do with it," said Ji Yeon Kim, MD, physician director, esoteric chemistry & immunology, special coagulation, and lab informatics for Kaiser Permanente Southern California Regional Reference Laboratories. Excess data can lead to data fatigue, which can be counterproductive, she said.

Kim suggested that health leaders think carefully about the types of data they want brought into the medical record and establish a protocol for how the data will be seen and used by clinicians.

Nichols acknowledged that figuring out just what data should be integrated into an EHR is something that clinicians are struggling with. "We are all still learning about what to do with all the data generated by at-home monitoring equipment and wearable sensors," he said. "It's all very new."

LAB PROFESSIONALS CAN CONTRIBUTE TO THE CONVERSATION

Both Espinoza and Nichols believe that there will come a day when integration of patient-generated data into the medical record is commonplace, but they say that time is still a way off.

"We have a long way to go," Nichols said, who noted that clinical laboratories can play a role in determining what types of data are selected for integration. He advises that laboratorians stay abreast of developments in this area, as well as contribute to the conversation by sitting on relevant work teams and advising clinicians. "Laboratorians are in a great position to do this," he said.

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HIV TESTING RECLASSIFICATION: A STEP TOWARDS EQUITY

A lower regulatory hurdle opens the door to new possibilities for boosting access to testing.

BY ASHLEY R. RACKOW, PHD, AND MARK A. MARZINKE, PHD, DABCC, FAACC

Access to routine HIV testing and linkage to care still pose significant barriers to HIV treatment and prevention (*3*). Globally, there are approximately 38 million people living with HIV, with an estimated 1.2 million in the United States (*1*). In the most recent surveillance report, the Centers for Disease Control and Prevention (CDC) estimated that approximately 13% of cases (156,000) remain undiagnosed, and 40% of new infections occur because of unknown HIV status (*2*).

To tackle this public health priority, the CDC launched the Ending the HIV Epidemic initiative, aiming to eliminate the HIV epidemic by the end of 2030. A core tenet is to prevent forward viral transmission by leveraging current and emerging testing technologies (*4*).

In May 2022, the United States Food and Drug Administration (FDA) took a step forward along this path and announced that it would reclassify HIV diagnostic tests from Class III to Class II medical devices (*13*). This is the first instance of medical device reclassification in the HIV testing landscape. Renewed regulatory classification of HIV diagnostic assays may have implications for time, cost, and new analytical developments, and may lead to increased testing availability.

Current tests include antibody (Ab), antibody/antigen (Ab/Ag), and RNA based testing. The latest CDC testing algorithm begins with an FDA-approved Ag/Ab immunoassay. Laboratories confirm positive results through a secondary method, starting with a supplemental antibody immunoassay that differentiates HIV-1 from HIV-2 antibodies (*8*).

Providing increased access to simple and routine testing empowers all individuals to know their status while destigmatizing testing. Identifying infections early and connecting people to treatment are proven to reduce HIV transmission, as shown in clinical trials and large community-based interventions (*5–7*). Developing and deploying HIV testing is instrumental in reducing global HIV incidence.

THE EVOLUTION OF HIV TESTING

Since 1985, when the first HIV screening test was designed, there have been several major methodologic improvements. The generations of HIV immunoassays are summarized in Table 1. A significant recent advancement was adding p24 antigen testing to immunoassay screens, which detects HIV-1 infection earlier than HIV antibodies alone. The p24 antigen, an HIV-1 capsid protein, appears within approximately 2 weeks of HIV infection and is a marker of recent HIV infection. However, as antibodies to the viral capsid protein are produced, p24 antigen levels become undetectable. This makes fourth and fifth generation assays particularly useful in populations with a higher proportion of recent infections.

While CDC recommends a combined Ab/Ag assay, third generation assays that detect antibodies against HIV-1 and HIV-2 remain the main technology used in point-of-care testing (POCT). Several feasibility studies have demonstrated the suitability and clinical utility of POCT and self-testing in community-based HIV mitigation strategies (*10–12*). However, OraQuick, the only FDA-approved

home test—as well as the majority of POCT—is based on third-generation technology. This underscores the clinical need for simple, deployable technology capable of detecting recent infections (9). FDA's action to reclassify HIV tests has the potential to speed newer technology to the point of care.

A NEW PHASE OF HIV TEST DEVELOPMENT

Before the agency's 2022 decision, FDA classified all HIV diagnostic tests under its highest risk classification. The European Union still classifies medical devices for HIV testing as class D testing, which is the highest regulatory risk category (*14*).

Traditionally, diagnostic assays are classified as either Class III or Class II devices. Class III, as the highest risk classification, encompasses devices that are life-sustaining or critical to health. At least one clinical trial is required to demonstrate utility and efficacy. Test manufacturers package these in a premarket approval (PMA) submission to the FDA.

PMAs require prospective enrollment in clinical trials, which is not only time- and cost-intensive but also is influenced by the target population for study inclusion. Results from the trial, including device performance and utility, are supposed to be readily translatable to a general population. This is a major strength of class III regulatory policy.

This article is part of a special collection on health equity, diversity, and inclusion in laboratory medicine. Guest Editor Dina Greene, PhD, DABCC, FAACC, LetsGetChecked and University of Washington, Seattle.

With HIV testing specifically, it will be important for new assays to be designed that can identify specific HIV subtypes and/or recent versus long-term infections. With the global decline in HIV incidence, recruitment of serodiverse individuals has become increasingly difficult, requiring larger cohorts and more time to assess the range of clinically relevant test results.

Class II devices are categorized as intermediate risk and do not require prospective clinical trials to demonstrate efficacy. Class II devices undergo a 510(k) review in which the device must demonstrate equivalence to another device on the market.

Regulatory requirements for Class II devices are largely focused on analytical performance and do not assess clinical utility. Further, Class II devices may be regulated with the addition of special controls that are specific to device type. This is the approach FDA is taking with HIV testing.

The new regulatory guidance for HIV device special controls includes strict requirements for labeling, documentation, and data submission indicating a change in performance characteristics, cross-method validation, and result interpretation (*13*).

Class II devices must meet the same analytical criteria as class III devices. Manufacturers often evaluate the performance of class II devices using specimens from a biorepository rather than prospective clinical trials. Analysis of banked specimens allows the process to include both acute and more established HIV infections, as well as analysis in specific populations, such as those with other comorbidities or sexually transmitted infections. However, the FDA reclassification does not provide prescriptive details about specimen number or sample characteristics required during validation, other than what is necessary to meet performance criteria.

In a survey of more than 200 medical device companies, the average total cost of bringing a Class III device to market through the PMA pipeline, including research and development, was approximately $91 million. Cost estimates from the FDA submission process alone range from $54–$74 million (*15*, *16*). In contrast, the costs for a 510(k) submission average $25 million, a reduction of 50–75% (Figure 1A).

This same survey also reported that the PMA submission process lasted 18 months, as opposed to the 510(k) process, which averaged 11 months (*16*) (Figure 1B). Time and costs associated with regulatory submission are frequently cited as the two largest factors that hinder medical device innovation.

FDA approval serves as an important international benchmark of quality. Thus, laborious and administratively burdensome regulatory processes can lead to delayed approval and availability of medical technologies to patients in the U.S. and abroad. On average, a new medical device will become available in the U.S. approximately 2 years after the same device is available in Europe due to decreased regulatory burden (*17*). From a cost and time perspective, changes in the FDA classification of HIV testing likely will incentivize medical device development internationally.

BRINGING BETTER TESTS TO MARKET

As new devices move through the regulatory process, representative

Table 1. Generations of HIV Testing

Test Generaton	Detects	Confirmatory Methodologies	Negative Window (weeks)	Clinical Implications
1	Anti-HIV1 IgG	Western blot, immunofluorescence	8-10	Blood product screening
2	Anti-HIV1 IgG Anti-HIV2 IgG	Western blot, immunofluorescence, ELISA	4-6	First diagnostic test
3	Anti-HIV1 IgG, IgM Anti-HIV2 IgG, IgM	Western blot, immunofluorescence, ELISA	2-3	IgG/IgM combination significantly reduced negative window
4	Anti-HIV1 IgG, IgM Anti-HIV2 IgG, IgM Anti-p24 Ag	HIV-1/2 differentiation assay, Qualitative PCR	2	p24 detection for acute infection, but only gives a total reactive or non-reactive result
5	Anti-HIV1 IgG, IgM Anti-HIV2 IgG, IgM Anti-p24 Ag	Qualitative PCR	2	Discriminates against HIV-1, 2 and p24 reporting individual results for each

sample analysis is integral to robust and translatable technology. Devices should be developed in relation to the populations they serve and should capture both the diversity of the population—considering factors such as geographic location, age, and background—as well as serodiversity. Serodiversity encompasses samples from HIV seronegative and HIV seropositive individuals, as well as individuals infected with different HIV-1 groups and subtypes.

Assay development with banked specimens can affords manufacturers the opportunity to assess device performance in a more inclusive and equitable fashion; however, the choice to do so remains with the manufacturer. This underscores the importance of strengthening global initiatives and supporting public health surveillance to advance equity in medicine.

The HIV epidemic remains a global public health priority, with the largest impact in historically underrecognized. Revising policy and incentivizing innovation will assist in the fight against HIV, but these efforts will not succeed without recognizing, including, and prioritizing those individuals who are most at risk.

Ultimately, the regulatory reclassification of HIV diagnostic devices opens the door for larger conversations surrounding increased deployment and implementation of medical devices to areas with the highest need, supporting the global mission to reduce, and ultimately eliminate, HIV transmission.

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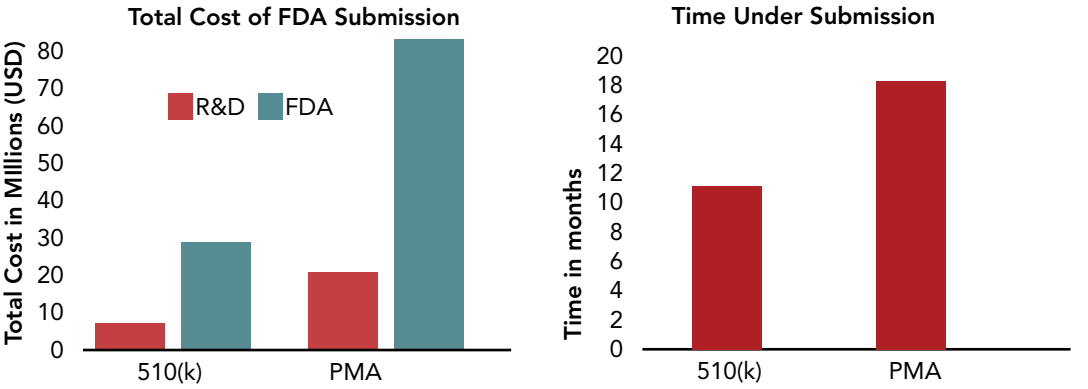
Figure 1. Average Cost and Time of FDA PMA and 510(k) Submissions



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The Ultimate Laboratory Medicine Event

2023 AACC Annual Scientific Meeting & Clinical Lab Expo

July 23–27, Anaheim, California

Laboratory medicine professionals from around the world will gather this summer in Anaheim, California, to celebrate 75 years of innovation and prepare for the future of laboratory medicine. For 5 days, AACC members and the whole lab community will come together as one body of thinkers, trailblazers, dreamers, and disruptors. Registration is open: meeting.aacc.org

Excitement and Anticipation

Surround AACC's 2023 Annual Scientific Meeting

BY JEN A. MILLER

What's it like to spend more than a year planning a scientific meeting for 20,000 people, and then be on the precipice of all that work being realized? "Exciting," said Amy Saenger, PhD, DABCC, FAACC, chair of AACC's 12-member volunteer Annual Meeting Organizing Committee (AMOC). She expressed her anticipation as the meeting is set to return to pre-COVID-19 attendance numbers for the first time in years.

CLN spoke to her about the process of planning this year's meeting and what attendees should expect.

What are you looking forward to the most about this year's meeting?

I'm mostly looking forward to having it be more like a normal meeting again, with almost everything in person. We expect attendance numbers to be back to or exceeding where they were prepandemic. I think we're all looking forward to just getting back to 'normal.'"

At the same time, we're also offering virtual options for some of our sessions. We've improved the delivery of virtual content to ensure attendees can access the information they need. While our aim is to have people attend in person, we acknowledge that it may not work for everyone, so we want to ensure they have the opportunity to participate.

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

We've taken a targeted approach and conducted extensive outreach for our sessions, which has been incredibly successful. The content now showcases more innovative approaches to lab medicine, expanding beyond the traditional laboratory setting. For example, during the pandemic, clinical laboratories adapted their testing methods to serve homeless shelters, correctional facilities, and long-term care facilities. We'll have sessions exploring these novel approaches and a broader focus on population health.

Clinical laboratorians have a lot of exciting things to share. We're going to see a lot of cutting-edge science that's coming out of lab medicine and clinical chemistry.

What else can attendees expect this year?

For this meeting, we've made a lot of changes to the format of the program that the AMOC is enthusiastic about. For example, we opened the poster sessions to all attendees, whether they're expo only attendees or full conference attendees. We did that because we're trying to increase the visibility of the posters and abstract presentations for everybody. It's a good and significant change.

We also changed the topics of the posters and the abstracts to better align with our AACC divisions, and we are hoping to increase attendance there. If divisions decide to do poster walks again, they can more easily do so. This is a return to how we did things a few years ago, and we realized this worked well, so we made the change.

We also were able to work with the AACC's journal *Clinical Chemistry* so that all our abstracts are indexed in the journal. I believe this also will boost visibility for all our authors, who put a lot of time and effort into doing these studies and presenting them.

Overall, attendees can expect to see a lot of excellent cutting-edge science and research in the field of laboratory medicine, and they should expect to have a lot of fruitful discussions and collaborations with their colleagues and other professionals in the field.

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Explore Pathways
in Cutting-Edge Science, Medicine, and Leadership

The AACC-curated pathways are one tool you can use to chart a course that meets your unique needs and interests. The following pathways highlight selected educational sessions in core and emerging areas of laboratory medicine. Industry Workshops, Lecture Series Presentations, and more than 800 booths from the AACC Clinical Lab Expo are mapped out online at meeting.aacc.org.

CARDIAC MARKERS, LIPIDS, AND LIPOPROTEINS

Calculated LDL-Cholesterol: Quo Vadis

Interactive Patient Case Presentation: A Discussion Between Laboratory Medicine, Cardiology, and Emergency Medicine Providers Addressing Utilization of High Sensitivity Cardiac Troponin Assays in Clinical Practice

High-Sensitivity Cardiac Troponin: Updates on Educational Recommendations from the IFCC Committee on Clinical Applications of Cardiac Biomarkers

High-Sensitivity Troponin: Strategies and Future Opportunities to Improve Patient Care

New ADA/ACC/HSFA Recommendations to Utilize Cardiac Biomarkers to Identify Risk of Heart Failure in People with Diabetes

Pediatric Lipid Screening: The Heart of the Matter

DIGITAL DIAGNOSTICS AND LAB INFORMATICS

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

The Pathology Informatics Service: A Model for Laboratory Improvement and Education

Artificial Intelligence and Machine Learning in the Clinical Laboratories: Fundamental Concepts, Clinical Use Cases, and Future Considerations

A Roadmap to Successful Data Analytics Projects at your Institution Today and in the Future

2023 Data Analytics Competition: Forecasting Future Preanalytical Errors

Generalizability of Machine Learning Models in Clinical Laboratory Medicine

LABORATORY MANAGEMENT AND LEADERSHIP

Communication as a Mechanism for Building and Keeping Teams Effective

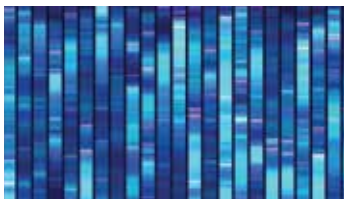
Risky Business: Mitigation Strategies for FDA-Modified and LDT Assays Using Alternate Specimen Types

Project Management in Laboratory Medicine: Principles and Applications in Large and Small Laboratories

AACC Healthcare Forum: Meeting the 21st Century Needs of the Laboratory Workforce

Optimal Testing: AACC's Guide to Lab Test Utilization

Laboratory Medicine Career Toolkit: What We Were Never Taught



MOLECULAR DIAGNOSTICS

Next Generation Sequencing for Laboratorians: Understanding the Essentials

Hype, Hope, or Already Here: The Status of Non-Invasive Prenatal Screening and Liquid Biopsies

Genomic Testing and the Complexity of Introducing Emerging Technologies in Laboratory Medicine

External Quality Assessment and Alternative Assessment in Molecular Diagnostics: Findings from an IFCC Survey

Molecular Respiratory Testing Considerations in a Post-Pandemic Era

Biochemical and Molecular Insights into Newborn Screening Disorders Both Old and New

POINT-OF-CARE AND DIRECT-TO-CONSUMER TESTING

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

Hyperglycemia in the Hospital: Are Our Tools for Measurement Accurate Enough?

Making Meaningful Medical Decisions by Incorporating Point-of-Care Testing: Case Based Discussions for Thoughtfully Implementing Point-of-Care Testing in Various Settings

Direct-to-Consumer and Direct Access Testing: A Discussion from Clinical, Laboratory, and Informatics Viewpoints

Continuous Glucose Monitoring Devices: A Friend or Foe to Clinical Laboratories

Emerging Technologies for the Next-Generation of Point-of-Care Testing

POPULATION HEALTH AND EQUITY

Interpretation of Pediatric Toxicology Results in the Assessment of Child Maltreatment

Representation Matters: The Importance of Gender Diversity from the Bench to the Bedside

Leprosy: Diagnostic Challenges in the Endemic Country of Brazil

Stronger Together: Eliminating Racial Healthcare Inequities by Mitigating Systemic Racism

Compliance vs Care: Providing the Highest Quality Care on Unsteady Legal Ground

AACC Academy Conversations between Clinical Laboratorian and Clinicians: In Vitro Fertilization and Ectopic Pregnancy

FOCUS ON MOLECULAR DIAGNOSTICS

An interview with Sherin Shaaban, MD, PhD, FACMG

How Technology Is Driving Adoption of Pharmacogenomics

BY JEN A. MILLER

Technology in laboratory medicine has been growing in leaps and bounds, and not just because of the demand for better and faster COVID-19 testing. Advances in pharmacogenomics (PGx), which looks at a patient's genetic background to determine whether a specific drug or a specific drug dose will be effective, is bringing a new level of precision medicine to patient care.

We asked Sherin Shaaban, MD, PhD, FACMG, to explain how the progress in instruments, methods, and other areas has influenced uptake of PGx testing. Shaaban is the medical director of pharmacogenetics and molecular genetics and genomics at ARUP Laboratories in Salt Lake City, Utah. She is also an assistant professor of pathology at the University of Utah School of Medicine.

How do you see advancements in lab technology like real-time PCR, microarrays, and mass spec contributing to the adoption of PGx?

These technologies contribute in multiple ways, including that they enable high throughput testing of clinically actionable variants. In other words, a laboratory can test many variants for many genes and offer that testing to many patients.

The field is moving rapidly too. Technologies can reveal genome-wide information. That helps laboratory test for more variants, but it also enables discovery. We end up identifying variants that we didn't even realize play a role in PGx.

We can make a case that these technologies are still relatively inexpensive when we consider the benefits that come from them. Many of these platforms have come down significantly in cost, so investing in them doesn't impose a heavy financial load on an institute that is thinking of adopting PGx.

Think about prescribing the same dose of medicine for each person. It's not going to work for everybody. Giving people the wrong dose, or drugs that won't work, costs the U.S. economy billions of dollars in terms of doctor visits, hospitalizations, and side effects. Considering those costs, the investment in the platforms and providing PGx tests are cost-effective.

How can the infrastructure built up for molecular testing from COVID-19 testing contribute to the expansion or adoption of PGx?

So many labs invested in instrumentation and creating labs specifically for COVID-19 testing. They can really capitalize on that trained workforce, especially as some of those same technologies could be used for PGx testing.

In addition, some companies and vendors allow for exchange of instrumentation. So that COVID-19 testing infrastructure wasn't totally wasted effort or investment, and it potentially can be translated into an investment into PGx.

Where do you see opportunities for better collaboration in lab medicine in PGx?

I think there is huge room for collaboration because few labs perform PGx right now, and PGx is one of those specialties that really requires experience. A lab with PGx expertise can help another lab build up their program and share their experiences and challenges they faced in adopting the technology so that a laboratory new to PGx can avoid the same problems.

As the field increasingly moves toward precision medicine, PGx will be a major player in the field. Collaborations between those who have experience in conducting those PGx tests, and those who don't but are interested and don't know where to start, are going to be critical moving forward.

Laboratorians also have opportunities to work with pharmacists who can bridge the gap between laboratory testing and physicians. They can help translate the results into actionable insights for physicians about the choice and dosage of specific medications.

What do you see as the most exciting areas where PGx is becoming standard of care?

PGx really allows us to tailor treatments for better patient care. We're moving to the era of precision medicine where each one of us should be treated individually. One size does not fit all, and PGx is enabling clinicians to know not just that a given drug will work, but also that the patient will need a specific dose to avoid developing side effects.

Alternatively, we can say that a drug won't work on a particular patient so we're not wasting the

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patient's time or our time — or more importantly, avoid a drug that could harm the patient.

There are several major areas where PGx has become critical: oncology, psychiatry, gastroenterology, and cardiology to name a few. Many physicians in these specialties are quite savvy about PGx testing and implementation, especially at major academic medical centers. The goal is to have more physicians in other specialties and in various health care settings more comfortable ordering and interpreting PGx testing. Clinical studies and scientific evidence are building up in many other specialties where PGx can play a role in patient care.

Are there areas where clinical evidence is limiting PGx?

Just like we need more studies, we need larger studies. In the U.S., we need a larger number of institutes to enroll more patients to give us the strong evidence we need. In February 2023, a European study published in the Lancet, with data collected across 18 hospitals, examined a 12-gene PGx panel. The study showed the clinical utility of pre-emptive PGx testing reducing adverse drug reactions by a third, which in turn is predicted to translate into a significant economic value for PGx implementation. The same authors are working on a cost-effectiveness analysis to be published separately.

We need to be conducting these kinds of larger studies at more institutions in the U.S., such as what the National Institutes of Health is doing with the All of Us research program, which includes PGx. That's especially needed because diversity still is a major limitation when it comes to PGx research. Most studies right now are conducted among Caucasians. So, we need not just larger studies, but also more inclusive studies.

What are the barriers to greater use of PGx?

With the expansion of next generation sequencing in molecular testing, laboratories will be dealing with a large number of variants. Translating these findings into data the providers can understand and use in patient management is not an easy task.

Variants of unknown significance in particular, where we do not know if the effect of such variant is benign or pathogenic, are problematic. Providers could find that data confusing or not helpful, which could deter them from ordering PGx testing. That is why we need to invest in more functional studies to help identify the role of these kinds of variants. There's still more work to do.

The debate about the clinical utility of PGx is still ongoing. Some believe the evidence about PGx's effectiveness is still not there — and of course advocates for PGx counter that. Others will say it's cost prohibitive, and that instead of being able to just prescribe a drug, PGx is adding an additional layer of testing (and cost) and hence it becomes a limitation.

Moreover, provider education is a must. Without proper efforts to educate physicians in various specialties about which PGx tests to order and how to interpret the results, providers' discomfort ordering such tests will continue to be a bottleneck in practice.

How can clinical laboratorians better educate clinicians?

Laboratories should be able to offer consultations. I receive calls all the time from providers who, for one reason or another, ordered a PGx test, but they really don't know what to do with the results. These consultations are very valuable both to the lab and to the clinician.

Consultations also can encourage those who are interested in PGx but are a little hesitant about it. And it can help others who doubt their ability to interpret results so that they gain more confidence. Additionally, we also should be part of those research studies we were talking about earlier. We're a critical player in that work.

Another effective way to broaden education and acceptance around PGx is through scientific meetings. There, we also can listen to providers and see why they think PGx has limited clinical utility. If you can rebut those ideas and communicate the value of PGx — that would be a valuable outcome. Lastly, advocacy efforts with decision makers, whether within one's institute or at the national level, could be another way to encourage PGx adoption.

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FOCUS ON MOLECULAR DIAGNOSTICS

An interview with Peter H. O'Donnell, MD

Progress on Pharmacogenomics Becoming the Standard of Cancer Care

BY JEN A. MILLER

Pharmacogenomics (PGx) has been widely used in many medical disciplines, including oncology, where it helps determine if specific treatments may be toxic to patients or if they will work at all.

While PGx has been found useful in certain clinical management, several factors need to be addressed before PGx can become the standard of care for every cancer patient in this country.

We spoke with Peter H. O'Donnell, MD, associate professor of medicine at the University of Chicago, about how PGx has already changed oncology, and how it will transform therapeutic practice in the future.

What are the most exciting areas where PGx is becoming standard of care for cancer medication management and improving patient outcomes?

There is a global debate right now around preemptive PGx testing for variants of the DPYD gene that can guide treatment with fluoropyrimidines, used in the treatment of solid tumors such as colorectal, pancreatic, gastric, breast, and head and neck cancers. There is widespread recognition that patients who carry variants in DPYD may be at higher toxicity risk, and that upfront dose-reduction in such individuals decreases toxicity, including potentially fatal toxicities. The attention around this has been a positive step in the march towards more personalized care.

However, I must admit that I am biased about this topic. I believe that PGx is important for safety, protecting patients, and using medications in a way that takes advantage of all the tools that we have available to us in 2023. That includes genomic information about the patient.

But I can see the other side of this debate, especially in this field where the bar is high for adoption. I'm an oncologist, and all oncologists want to ensure they're doing everything they can to keep their patient alive and ensure survival. The hesitance around DPYD testing is well-intentioned because we want to make sure that we're not rushing into this and sacrificing cure.

We also need to make sure we're doing DPYD testing in a way that acknowledges equity and diversity. It's clear that not all test panels for DPYD are the same, and that could create disparities and lead to patients receiving results that are falsely reassuring. Those shortcomings need to be considered.

How should this testing better acknowledge patient diversity?

I'm of the opinion that there are five clinically actionable variants in DPYD that we should be considering. If a test panel, for example, only includes two of those five variants, and a patient doesn't have either of those two, then a report will say that the patient is a normal metabolizer when, in fact, it may be that we're just missing another variant they could be carrying.

How is this an equity issue? Of those five variants, there's some debate around the fifth variant, often referred to as the African variant, which was discovered in people of African descent. Our institution believes that it's important to include this variant in DPYD testing. Otherwise, we could be creating disparities if we're only testing for variants identified in people of European descent.

What else in this field is exciting to you when it comes to PGx and cancer care?

Right now, DPYD is the hottest topic, but there are other important applications of PGx in this field, too. We also currently support testing for the UGT1A1 gene for irinotecan, another drug used for solid tumors. Variation in that gene has been known for a long time, but testing for it has had spotty adoption.

I also think there's a huge opportunity in cancer care to think about the role of PGx for pain medication use. Such a huge part of cancer care is making sure we're dealing with a patient's pain. The use of PGx for managing pain is something our institution is studying right now.

Finally, cytotoxic chemotherapy, while still a mainstay for many kinds of cancers, is considered one of the older types of therapies now. Immunotherapies have, of course, revolutionized the care of cancer and the practice of oncology. I would say that PGx is in the nascent stage around immunotherapies, with a lot of promise.

What are the primary barriers to adoption of PGx in cancer care?

There is a high bar in oncology for the adoption of PGx. It's usually used for some kind of upfront dose reduction or avoidance of therapy. For some

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cancers, there is no other alternative treatment. What would an oncologist do if their patient has high risk of toxicity, and yet this is the only therapy that exists to treat a patient's disease?

The second is one that's particularly relevant to clinical laboratorians: turnaround time. Patients often need to start their cancer therapy quickly. It's not uncommon for a patient to start within a week after the clinical consultation. How many labs can turn around a PGx test in that span of time?

Finally, we face a knowledge gap for providers. It's not a criticism of providers, but PGx is something that most practicing physicians—let alone practicing oncologists—were not taught in medical school. They are learning it on the fly. They're following their associations' guidelines around this, and professional associations have been slow to embrace it.

In addition, it is important for institutions that are using PGx to provide clinical decision support at the point of care. They can't just put a 'star allele' result in a patient's chart and expect a clinician to know what to do with that information.

And yet, while oncologists—just like all providers—may feel underprepared or under-educated in the germline PGx space, I would argue that, at the same time, oncologists are among the best prepared for considering such information compared to other clinicians. That's because oncologists are already used to interpreting genomic information—on the somatic side. They have a lot of experience thinking about it. Oncologists could potentially be "leading-edge" adopters, or champions, of similarly considering germline PGx information during prescribing.

What are the drivers for PGx adoption?

First, academic institutions are often the leaders in these efforts, which I think will filter down to community practices. Second, patients and patient advocates are demanding PGx as part of safe and effective prescribing. That's really important. We must listen to the patients.

Third, improvements in technology are making this something where it's hard to find a reason not to do it. It's become very affordable. The ability to genotype is old technology at this point, so we don't encounter the same kinds of technological barriers we did 15 years ago. Those have been solved.

Going back to barriers, though, one still left is, how do we make this accessible wherever the patient shows up? We're seeing a lot of siloing of this information within an institution that performs this testing. If, however, a patient shows up at an ER down the street, how do we design the system so that patients have ownership of their information, and it travels with them?

Do you see opportunities in the expansion of molecular testing to accelerate PGx?

Every oncologist runs next-generation somatic tests on their patients. If it's become the standard of care to test the somatic genome, why wouldn't we just complement that with the germline genome? We could bundle test orders and have the somatic and germline done with one test. In 2023, technology is certainly there to do that.

Where can oncologists and clinical laboratorians collaborate?

I see an opportunity in the development of clinical decision support. Most clinical laboratories are used to generating molecular reports that are too long, too dense, and unreadable for the average clinician.

So, we need to make them more interpretable, and we need to provide solid decision support—or interpretations—that accompany those raw lab results.

For example, we could design and write these reports in a way that helps with clinical decisions. Or even better, put the information within the clinical workflows, rather than in a 'report.' That allows the information to be pushed to the clinician—at the moment when the prescription is being considered—rather than sought within a difficult-to-find report among a larger array of results. That would promote adoption.

Where do you think PGx will be in 20 years?

My dream is that for every patient who walks into a doctor's office or hospital, we're scanning a QR code, or using some other technologic or electronic means of utilizing that information, which has already been obtained, maybe at birth, and making that accessible at the point of care. That way, no prescription is written without germline PGx information being considered. I believe we can one day get there.

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Regulatory Roundup

FDA Clears Abbott Test for Concussion

Abbott has received clearance from the Food and Drug Administration for a blood test that detects traumatic brain injury (TBI). According to the company, this is the first laboratory test that is commercially available in the U.S. for this indication.

The Alinity i TBI test, which delivers results in 18 minutes, measures ubiquitin C-terminal hydrolase L1 (UCH-L1) and glial fibrillary acidic protein (GFAP). In elevated serum concentrations, UCHL-1 and GFAP are tightly correlated with brain injury.

The test is approved for use in patients 18 years of age or older who present with suspected mild TBI (Glasgow Coma Scale score of 13–15) within 12 hours of injury to assist in determining whether a computed tomography (CT) scan of the head is needed.

Alinity i TBI has 96.7% sensitivity and 99.4% negative predictive value and runs on Abbott's high throughput Alinity i laboratory instrument. The test previously received European Union clearance and has been available in markets outside the U.S. since 2021.

The test could help reduce the number of unnecessary CT scans by up to 40%, potentially reducing costs to the healthcare system and patients, and minimizing time spent in the emergency department, Abbott said.

FDA OKS POINT-OF-CARE INSTRUMENT FOR FENTANYL

The Food and Drug Administration has granted Bioeasy USA, a subsidiary of Shenzhen Superbio Technology (Superbio), clearance for a point-of-care immunofluorescence analyzer to qualitatively detect fentanyl in human urine.

Bioeasy USA has partnered with Carolina Liquid Chemistries (CLC) to distribute the product in the U.S. under the brand name RYAN. CLC has a fentanyl urine detection kit that is intended for use with RYAN and that detects fentanyl in urine at a cutoff concentration of 1.0 ng/mL.

This test provides a preliminary result, which means that results must be confirmed with a more specific, alternative chemical method.

INFECTIOUS VAGINITIS TEST GETS FDA CLEARANCE

BD recently announced it has received Food and Drug Administration 510(k) clearance for the BD Vaginal panel to be used on the BD Cor System.

Originally granted marketing authorization for use on the BD Max system in 2016, the BD Vaginal panel is the first microbiome-based PCR assay that uses a single swab and test to simultaneously detect organisms associated with *bacterial vaginosis* (BV), *vulvovaginal candidiasis* (VVC), and *Trichomonas vaginalis* (TV) and report a clear positive or negative result for each condition separately.

This 510(k) clearance for the BD Vaginal panel on the BD Cor System is the first for the high-throughput version of the test.

Using a single test for BV, VVC, and TV could reduce the need for repeat testing and unnecessary treatments, the company said.

FDA GRANTS EUA TO QUEST COVID-19 KIT

The Food and Drug Administration recently granted emergency use authorization to Quest Diagnostics for the Quest Covid-19 Nucleic Acid test collection kit. This kit is designed for the self-collection of anterior nasal swab specimens for use with tests that detect SARS-CoV-2 nucleic acid. Included in the kit are specimen collection and storage materials, as well as instructions for returning the kit to a drop-off location.

CUE HEALTH RECEIVES FDA EUA FOR MONKEYPOX TEST

Cue Health has received emergency use authorization from the Food and Drug Administration for a molecular test to detect the monkeypox virus.

This nucleic acid amplification test runs on a Cue Reader and can be performed at any CLIA-waived facility. It delivers results in 25 minutes and is intended to expand patient access to fast, accurate testing.

The test requires a Cue Sample Wand for collecting lesion samples or dipping into viral transport medium containing a specimen. The Cue Sample Wand is then inserted into the Cue Cartridge, which is placed inside the Cue Reader, and results are delivered to a mobile device.

The test demonstrated high accuracy in trials, achieving 100% concordance with the monkeypox test from the Centers for Disease Control and Prevention on the clinical samples tested, according to Cue.

FDA GRANTS 510(K) CLEARANCE TO DIASORIN FLU AND COVID-19 TEST

DiaSorin recently announced that it has received 510(k) clearance from the Food and Drug Administration (FDA) for its Simplexa COVID-19 & Flu A/B Direct assay.

The test detects and differentiates among influenza A, influenza B, and SARS-CoV-2 viruses so physicians can recommend appropriate treatment for each patient.

The assay offers clinical laboratories a sample-to-answer diagnostic workflow that generates actionable results with minimal hands-on time.

The real-time reverse transcription-PCR assay is performed using nasopharyngeal swab samples. Designed for use on the Liaison MDx instrument, it detects viruses in a little over an hour. The assay requires no separate sample extraction or processing. It can test up to eight samples simultaneously.

This test adds to the company's FDA-cleared menu of molecular assays used to diagnose COVID-19 and common respiratory infections.

Company officials said they hope the test will help ease the burden on clinical labs by eliminating the need to run multiple tests for each patient to reach a diagnosis.

SEXUAL HEALTH TEST FOR WOMEN GETS FDA NOD

The Food and Drug Administration has granted Visby Medical 510(k) clearance and a CLIA waiver for its second point-of-care assay, Visby Medical Sexual Health test.

The PCR test detects sexually transmitted infections caused by *Chlamydia trachomatis, Neisseria gonorrhoeae, and Trichomonas vaginalis* in women. It gives results in under 30 minutes, enabling clinicians to test and treat in a single patient visit.

The test provides results with about 97% accuracy, according to Visby.

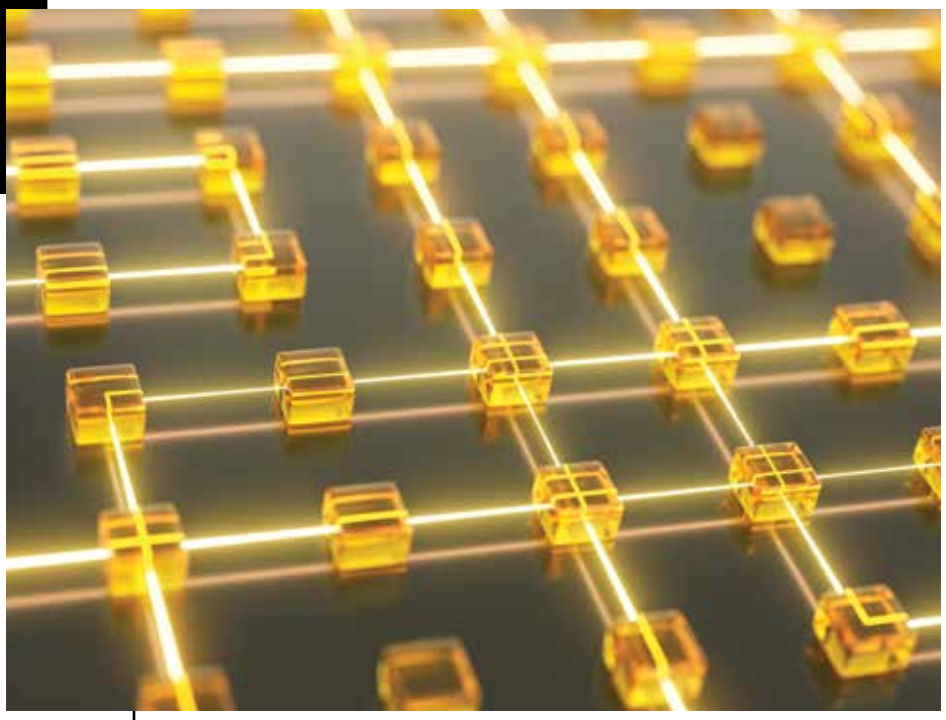
Company officials noted that testing for sexually transmitted infections often has a turnaround time of 2 to 5 days. They added that the Centers for Disease Control and Prevention recently reported a nearly 30% increase in gonorrhea and chlamydia between 2015 and 2019.

Industry Playbook

Biosero and Analytik Jena Partner on Automated Liquid Handling Workflow

Biosero and Analytik Jena have entered a comarketing agreement to promote applications of their combined laboratory automation technologies.

Analytik Jena offers innovative laboratory instrumentation for numerous scientific applications. These include the Biometra TRobot II, a thermal cycler for PCR; the qTOWER real-time PCR thermal cycler with a 12-color plate scanner; and the CyBio FeliX liquid handler. The CyBioFeliX platform allows liquid handling in automated laboratory setups and is suitable for several applications.



Biosero provides Green Button Go laboratory automation software to schedule, coordinate, and manage the physical flow of materials and the digital flow of information on a single workstation, throughout an entire laboratory, or across facilities on a research campus.

The comarketing agreement showcases the value of pairing Analytik Jena instrumentation with Green Button Go software for a seamless, fully automated experience that allows users to increase laboratory productivity while minimizing hands-on time, the companies said.

PERKINELMER COMPLETES DIVESTITURE OF ITS APPLIED, FOOD, AND ENTERPRISE SERVICES BUSINESSES

PerkinElmer has completed divestiture of its Applied, Food, and Enterprise Services businesses to the New Mountain Capital investment firm.

The resulting life sciences and diagnostics business is focused on developing and delivering novel scientific breakthroughs. It will share the PerkinElmer name pending approval of a new name, PerkinElmer officials said.

The company's two core business areas, life sciences and diagnostics, help drive scientific innovation impacting human health. Within life sciences, the company is focused on supporting pharmaceutical and academic scientific advancement from the earliest stage of discovery all the way to the clinic. In diagnostics, the company develops new assays, systems, and complete workflows to help better diagnose diseases throughout the continuum of care of human health across all lab settings.

New Mountain Capital officials said they look forward to partnering with the new PerkinElmer business to drive continued growth and innovation for the benefit of all stakeholders including the company's customers, employees, and other business partners.

VECTOR LABORATORIES ACQUIRES CLICK CHEMISTRY TOOLS AND FLUOROPROBES

Vector Laboratories has bought both Click Chemistry Tools and Fluoroprobes to better serve partners across biopharma and the life sciences.

Vector specializes in innovative proteomic and glycomic research

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solutions, while Click Chemistry manufactures chemistry linkers used in sets of chemical reactions that rapidly, specifically, and efficiently join molecular building blocks to form new compounds, as well as labeling reagents. Fluoroprobes specializes in developing fluorescent probes and dyes.

These acquisitions aim to expand Vector Laboratories' manufacturing and bioconjugation capabilities. The acquisitions contribute to their long-term strategy to accelerate the pace of protein detection innovation. Additionally, the acquisitions expand the company's capabilities and technology for labeling, detecting, and conjugating products. Overall, Vector officials hope that this will enable them to offer a new level of flexibility in what customers can accomplish with Vector tools.

Company officials also noted that they have acquired a manufacturing facility that will increase security of supplies for customers.

PARTNERSHIP TO DEVELOP COMPANION DIAGNOSTIC FOR AML DRUG

Qiagen has a new strategic partnership with Servier, a global pharmaceutical group, to develop a companion diagnostic test for Tibsovo, an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for the treatment of the blood cancer acute myeloid leukemia (AML).

AML is a hard-to-treat cancer of the blood and bone marrow. IDH1 mutations are present in 6–10% of AML cases. Under the agreement, Qiagen will develop and validate a real-time PCR test that can be used to detect IDH1 gene mutations in AML patients' whole blood and bone marrow aspirates.

The companion diagnostic will run on the Qiagen Rotor-Gene Q MDx device. Qiagen's regulatory teams will support clinical validation and its approval in the U.S., the European Union, and Japan.

Qiagen officials said the partnership benefits AML patients and strengthens the company's ability to develop companion onco-hematology diagnostics.

Servier officials expect the partnership will help expand patients' global access to Tibsovo.

SPECTRUM ACQUIRES ALIMETRIX AND MICROARRAYS TO IMPROVE TESTING

Spectrum Solutions recently announced acquisition of Alimetrix and Microarrays.

Spectrum Solutions said that the acquisition, combined with its contract manufacturing and unique biospecimen collection devices, results in a portfolio of products and services that enhance the overall patient testing experience.

Alimetrix's molecular laboratory capabilities and Microarrays' expertise in manufacturing array-based products, now coupled with Spectrum's capabilities, create a comprehensive suite of products and services that accelerates Spectrum's market strategies.

Spectrum's core services include assay development, contract manufacturing, and clinical testing business support services, as well as Spectrum SimplyTest, a family of validated, highly sensitive multiplex laboratory-developed tests for both direct-to-consumer and physician-directed testing. Another key service is Spectrum Compounding RX Pharmacy, an onsite, multistate licensed, patient-specific compounding pharmacy partner with direct-to-patient dispensing capabilities.

Spectrum officials said the acquisitions will enhance the company's portfolio and help the company develop a transformative, decentralized healthcare platform aimed at innovating biospecimen collection and laboratory testing.

Alimetrix and Microarrays officials said that joining forces with Spectrum will extend their capabilities to more people and help individuals and communities take control of their health.

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Ask The Expert

Challenges Labs Face When Implementing Minimum Retesting Intervals

EXPERT
By Asmita Hazra, MD

What is a minimum retesting interval?

A: A minimum retesting interval (MRI) is defined as the minimum time before a test should be repeated. A relatively recent addition to the test utilization toolbox, MRI is based on a test's properties such as analytical characteristics and biomarker half-life, as well as the clinical context in which the test is used.

Implementing MRI reduces hospital-acquired anemia, risk of injury, pain, anxiety, sleep disruption, the need for transfusions, length of hospital stay, and even mortality. By reducing oversampling artifacts, using MRI can decrease false alerts, thus cutting down on unnecessary subsequent workups.

It also can help institutions cut back on "low-value" tests, such as routine blood work performed on stable inpatients, which rarely yields intervention-worthy results when repeated. This is significant because such low-value testing diverts personnel, materials, time, and money away from high-value testing. Additionally, implementing MRI can reduce biomedical waste, as more than a third of the volume of diagnostic blood samples is usually discarded, along with contaminated disposables.

What interventions are most useful for getting practitioners to implement MRI?

The three major types of interventions are: educational efforts, changes in computerized physician order entry (CPOE), and audit and feedback (A&F) interventions. These approaches often are combined.

Educational efforts might include presentations, seminars, flyers, and emails. Relevant information could be relayed or distributed at team discussions or rounds, for example, or through guidelines, standard operating procedures, and algorithms. Materials might note the test's cost and projections of healthcare savings associated with using MRI.

Integrating MRI alerts and rules into CPOE is the most directly actionable approach. A computerized decision support system in the CPOE provides an optimal intervention opportunity because it is specific to a given clinical scenario.

CPOE interventions may include soft- or hard-stop interventions such as alerts, pop-ups, rejection rules, cost displays, order-form modifications, and more.

A&F approaches could come in the form of weekly and monthly reminder letters following educational efforts or feedback on an individual's ordering habits relative to peers.

No matter which intervention is used, obtaining buy-in from all stakeholders increases the likelihood of success. Laboratory stewardship committees should include representatives from the hospital administration, clinics, and laboratories. It's also important to involve residents and junior physicians.

What are some hurdles to implementing MRI?

Many clinicians either don't know about MRI or react defensively when asked to use it. Educational efforts could help address these obstacles, but such initiatives require a lot of effort.

Automating intervention through CPOE is the most effective approach, but it's also labor intensive, as it involves modifying order sets, s uggesting new order forms, or instating time limits.

As for A&F interventions, it can be difficult to determine the best frequency for reminders and to ensure consistent follow-through on feedback.

Another roadblock is a lack of strong scientific evidence to convince ordering practitioners to implement MRI. Because there is a large degree of variability in study designs, test utilization principles applied, test parameters, and clinical outcomes evaluated, even meta-analyses of the data are hard to find. Moreover, there is little research on the sustainability of implementation programs. There are differences among guidelines about MRI for the same target parameters, and very few studies have looked at the relationship between reduced testing and missed diagnoses.

Finally, since paper medical forms are still used in many parts of the world, a lack of medical-record integration also poses a challenge to implementation.

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