June 2022

CLN Clinical Laboratory News

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MACHINE LEARNING ENHANCES DRUG SCREENING

91.3%

Positive predictive value for data-driven mass spec method

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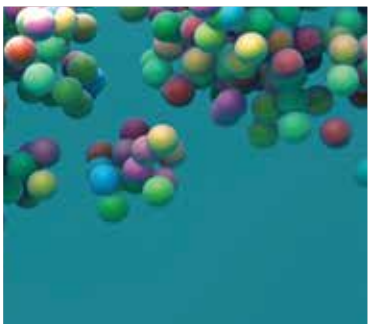
New Evidence for Monitoring Biologics

Improving POC Lipid Screening



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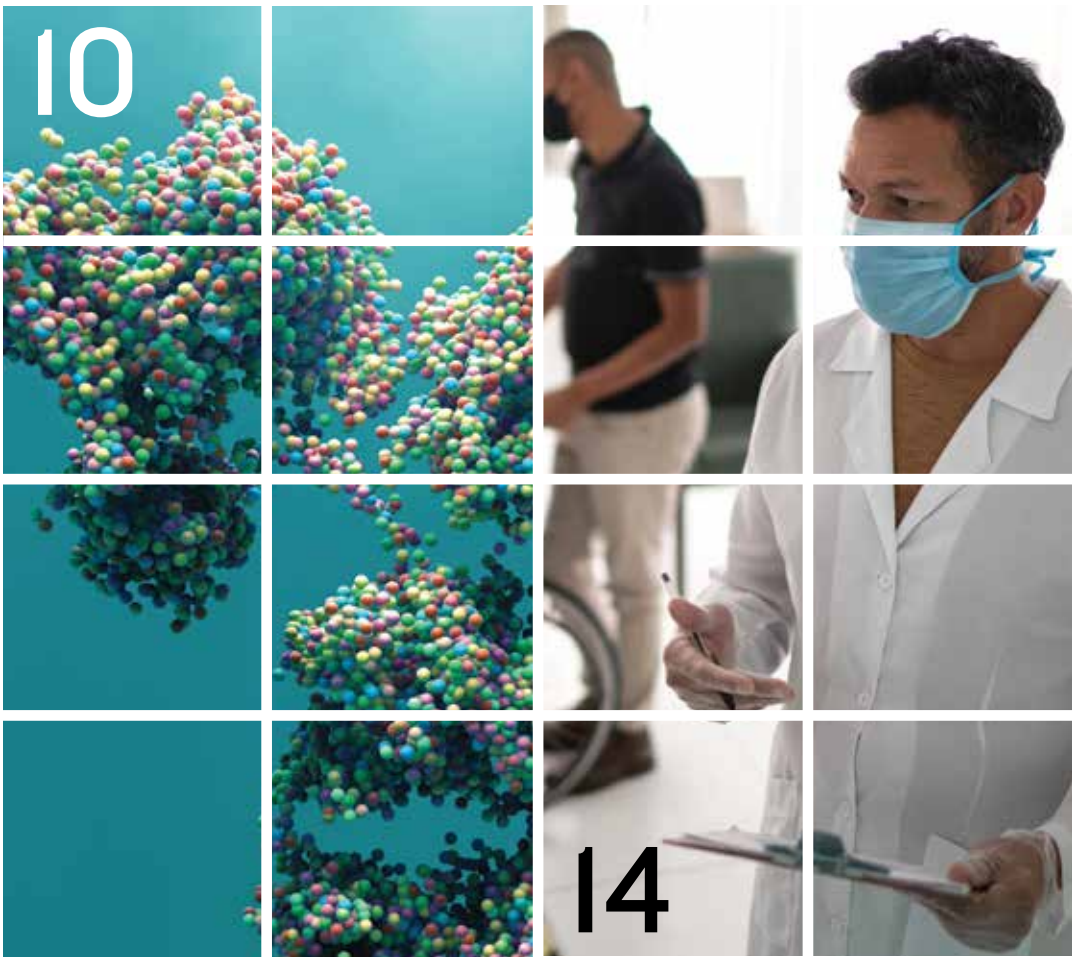
Features



Departments

There are several strategies that both clinical and laboratory teams can take to ensure accurate measurements for patients with abnormal levels of binding proteins.
p32

On the cover: Design Cells / iStock

Federal Insider

A Quarter of Medicare Patients Experience Harm in Hospitals

A report from the Department of Health and Human Services (HHS) Office of Inspector General (OIG) found that in data analyzed from October 2018, 25% of Medicare patients experienced patient harm during their hospital stays. This is a slight decrease from OIG's last report, based on 2008 data, that found 27% experienced harm. Nearly half of these events OIG considered preventable, and their cost to Medicare was estimated to be $325 million.

The OIG study divided harmful events into two categories. They considered adverse events those problems that led to longer hospital stays, permanent harm, life-saving intervention, or death. Twelve percent of patients during the time period were affected by such issues. The second category was temporary harm, which covered events that required intervention but did not cause lasting harm, prolong hospital says, or require life-sustaining measures. These affected 13% of patients, and OIG noted that some of these were serious and could have caused further harm.

The most common type of harmful event was medication-related, at 43%. The remaining categories included patient care-related (23%), such as pressure injuries; procedures and surgeries (22%); and infections (11%).

"Although HHS agencies have reported progress during the past decade toward improving patient safety, protecting the health and safety of HHS beneficiaries remains one of HHS's top management and performance challenges," OIG said. The agency recommended that Medicare update and broaden its lists of hospital-acquired conditions to capture common, preventable, and high-cost harm events; explore expanding the use of patient safety metrics in payment structures; and develop interpretive guidance for surveyors assessing hospital compliance.

$5 MILLION WILL ADVANCE EQUITY IN CANCER SCREENING AT HEALTH CENTERS

The Department of Health and Human Services (HHS) announced $5 million in funding for community health centers aimed at increasing equitable access to cancer screenings. HHS said the funding was part of the Biden administration's Cancer Moonshot initiative.

"Cancer screening saves lives—and it should be accessible to all Americans," said HHS Secretary Xavier Becerra. "In partnership with National Cancer Institute-designated cancer centers, we are giving community health centers in underserved communities funding to provide life-saving cancer detection and referrals to treatment."

The funding will focus on access to breast, cervical, and colorectal cancer screening, areas in which HHS reported disparities based on an individual's race or ethnicity, income, and insurance status. With support from National Cancer Institute-Designated Cancer Center partners, the funding also will help ensure that these patients have hands-on assistance accessing high quality cancer care and treatment, HHS said.

The Biden administration's Cancer Moonshot aims to reduce the death rate from cancer by at least 50% over the next 25 years. Its areas of focus include improving diagnostics, preventing cancer with cancer vaccines, dealing with inequities in care, and targeting treatments using genetics and immunology.

A RECORD 35 MILLION PEOPLE ENROLL IN AFFORDABLE CARE ACT COVERAGE

The uninsured rate has approached an all-time low, in part due to record numbers of people enrolling in Affordable Care Act (ACA) plans, according to the Department of Health and Human Services (HHS).

Combining the total enrollments for Medicaid expansion, ACA marketplace coverage, and related state programs, enrollment reached an all-time high in early 2022. About 21 million of the total comes from people in states and territories who gained healthcare coverage due to the ACA's expansion of Medicaid to low-income adults under 65. These high enrollments have been pushing down the uninsured rate, which in the fourth quarter of 2021 reached a nearly all-time low of 8.8% for the full population, compared to 10.3% in the fourth quarter of 2020.

The administration also sees additional state expansion of Medicaid as a path to advance healthcare equity. Of the nearly 4 million uninsured Americans who could gain coverage if additional states expanded their Medicaid programs, more than half are people of color, according to HHS data.

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Bench Matters

Rapid Web-App Development for the Clinical Laboratory

Daniel T. Holmes, MD, FRCPC

As laboratorians, we all encounter situations where we must undertake highly repetitive manual tasks—whether it be related to the accessioning process, specimen processing, data transfer between devices in a multidevice process, interpretation, quality monitoring, or report production. Often, we can define our processes, but we don't have a way to programmatically automate these tasks easily, so we resort to cutting and pasting data into a spreadsheet or manually extracting data and preparing the same report month after month. Another complication is that lab processes tend to be context and institution-specific; there is no off-the-shelf commercial software for our niche clinical environment.

In principle, we understand that software development for these tasks would be achievable if there were sufficient budget and time, but usually there isn't. There is also the hassle of the back and forth with programmers to help them understand laboratory processes. Sometimes, it's just easier to do it yourself, but most of us are only aware of Excel macros as a tool to achieving this end.

An Explosion in Open Source

Fortunately, in the last 10 years, there has been an explosion of open-source (i.e., free) data science and data analytics tools specifically designed to help users rapidly develop web-based applications to take care of their software needs, simple and complex alike. At the present time, it's fair to say that the most mature open-source tool for the development and deployment of a web-based custom software application is the Shiny package for the R programming environment. There are a number of excellent alternatives from the open-source community, such as Dash for the Python language or even leveraging a Jupyter notebook. Institutions can achieve similar goals if they already have a Tableau or Microsoft BI license, but these commercial, closed-source software tools are expensive.

Don't Fear the Jargon

To explain a bit more, Shiny is a tool in the R language that allows users to create an application that runs in the

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web browser without the installation of the R language on the computer of the end user. Shiny takes the pain out of creating interactive, reactive websites, allowing the programming to happen directly from the R language so that any calculations or manipulations can be made on the data using R code. The interactive graphical output can likewise come from the same R code.

connectivity of our liquid handlers, RNA/DNA extractors, thermocyclers, and the LIS to make interdevice data transfer and results review/release of our virology molecular tests free of human transcription. This software also handled and tracked SARS-CoV-2 samples that were pooled to increase our throughput in the fall of 2020 when there were reagent shortages for some of the high-volume automated systems.

We have also produced a color-coded dashboard that that displays which pending samples are nearing their target turnaround time and may need intervention on a core lab TV screen. Additionally, our outpatient requisition scanning and storage is run using R in combination with a number of other open-source tools that interpret requisition barcodes and store the PDFs in a retrievable manner.

The choice of how to deploy an app depends on the number of users, where users will access the app, the computational power available, the sensitivity of the data, the need for password authentication, and other considerations.

A user can then deploy the application on a single device, onto an on-premises server, onto a cloud-based server such as Amazon Web Services or Microsoft Azure, or even onto RStudio's cloud. The choice of how to deploy an app depends on the number of users, where users will access the app, the computational power available, the sensitivity of the data, the need for password authentication, and other considerations.

In any case, these are details that can be worked out after building something that suits the lab's needs.

What Can You Actually Do?

In my laboratory at St. Paul's Hospital in Vancouver, British Columbia, Canada, we have used R applications (without a web interface) and R Shiny (with a web interface) to tackle our rapid software development needs. For example, we have a quality control (QC) review app which taps a structured query language (SQL) database of our QC results for all instruments connected to our laboratory information system (LIS). This permits us to either produce PDF reports for all QC materials on all devices at once or to select which QC we want to see and view it onscreen interactively.

We have also undertaken several data automation tasks such as the

Hazards and Pitfalls

A warning: When building software for others to use, the developer becomes the de facto fallback person when there is an unexpected problem—and there always is. For example, power outages can occur, or the app may stop working when updating to a new version of R or Python, or if the formatting of the input data unexpectedly changes. If you are the code author, and your lab develops dependence on the tool, then it's best to make sure that there are contingencies and fallback strategies when you are unavailable. This is why, when there are larger user bases, it's recommended that the app be maintained by a team of people who can troubleshoot if there is a problem.

The Final Product

The initial learning curve for learning a scripting language may be tough, but through practice and determination, you can become proficient and see opportunities to streamline workflows in your laboratory. And, as a bonus, people will thank you for getting rid of those repetitive, mundane, and error-prone tasks.

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The Sample

Machine Learning Boosts Synthetic Cannabinoid Screening

Researchers have proposed a new synthetic cannabinoid screening tool based on changes in the metabolome that uses a machine learning algorithm to process the large amount of data produced by high-resolution mass spectrometry (HRMS) (Clin Chem 2022; doi: 10.1093/clinchem/hvac045).

Synthetic cannabinoids often lead to stronger adverse effects than natural cannabis, and they are growing in number. European researchers reported 11 new synthetic cannabinoids in 2020, and the compounds recently have made up a major portion of new psychoactive substances seized by law enforcement in the European Union.

Making the problem more challenging, the diversity of molecular structures poses a problem for labs. Qualitative screenings using immunoassays typically are conducted prior to a more lengthy quantification with liquid chromatography-mass spectrometry. But immunoassays often lack analytical sensitivity and specificity for new synthetic cannabinoids. New screening strategies are needed to preselect samples for quantitative measurements, the researchers noted.

In their study, the researchers measured 474 human urine samples with an untargeted metabolomics liquid chromatography–quadrupole time-of-flight-HRMS method. They preprocessed the data using Progenesis QI software. Following feature engineering, the researchers optimized a random forest model in the R computer programming language using a 10-fold cross-validation method and a training set. During random forest optimization, the researchers determined 49 features, 200 trees, and 7 variables at each branching node as most predictive. The optimized model accuracy was 88.1%, with 83.0% clinical sensitivity, 92.7% clinical specificity, 91.3% positive predictive value, and 85.6% negative predictive value. The test set predicted positive and negative samples with a mean accuracy of 88.0%, while the verification set showed the model could detect cannabinoid-specific changes in the metabolome.

Although their approach outperforms other screening methods, the researchers suggested using machine learning models in combination with other available methods. Deploying the method in a daily routine and expanding sample pools will lead to more confidence in the model's performance, they added.

TEST DISTINGUISHES BACTERIAL FROM VIRAL RESPIRATORY INFECTIONS

A point-of-care test can distinguish bacterial from viral respiratory infection with high negative predictive value (NPV) and may improve antibiotic stewardship and patient outcomes, researchers reported (JAMA Netw Open 2022; doi: 10.1001/jamanetworkopen.2022.7299).

Bacterial and viral causes of acute respiratory illness (ARI) are difficult to clinically distinguish, resulting in inappropriate use of antibacterial therapy. In response, the researchers developed a test that discriminates bacterial from viral infection in less than 1 hour by measuring the host's gene expression response. The host response bacterial/viral (HR-B/V) test, developed in collaboration with BioFire Diagnostics,

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The researchers validated the performance of the research-use-only HR-B/V test among 616 children and adults with febrile ARI of 7 or fewer days' duration in 10 U.S. emergency departments. The researchers reported performance characteristics for the HR-B/V test compared with clinical adjudication as either bacterial or viral infection or categorized into 4 likelihood groups: very likely viral, likely viral, very likely bacterial, and likely bacterial. They also compared HR-B/V results with procalcitonin measurement.

The HR-B/V test had 89.8% sensitivity, 82.1% specificity, and 97.9% NPV for bacterial infection, a performance significantly better than procalcitonin measurement. Procalcitonin measurement had sensitivity of 28.6%, specificity of 87.0%, and NPV of 87.6%. When stratified into likelihood groups, the HR-B/V test had an NPV of 98.9% for bacterial infection in the viral very likely group and a positive predictive value of 63.4% for bacterial infection in the bacterial very likely group. The HR-B/V test correctly identified 30 of 33 participants, or 90.9%, with acute COVID-19 as having a viral infection.

The findings suggest that an accurate point-of-care host response test with high NPV might offer an opportunity to improve antibiotic stewardship and patient outcomes, according to the researchers.

HDL AND GLUCOSE LEVELS IN YOUNGER ADULTS ASSOCIATED WITH ALZHEIMER'S DISEASE

A recent report for the first time shows that low high-density lipoprotein (HDL) and elevated glucose levels measured as early as age 35 are associated with Alzheimer's disease (AD) later in life. These findings suggest that careful management of cholesterol and glucose levels beginning in early adulthood can lower AD risk. (Alzheimers Dement 2022; doi: 10.1002/alz.12641).

Little is known about whether AD risk is associated with exposure to vascular factors in early adulthood. The researchers studied the influence of vascular risk factors on incident AD measured longitudinally for an average of more than 30 years in Framingham Heart Study Offspring Cohort participants.

The researchers evaluated effect of vascular risk exposure on incident AD based on single time-point measurements from early (ages 35–50), middle (ages 51–60), and late adulthood (ages 61–70). Their goal was to explore the appropriate timing of vascular screening and interventions necessary to maximize benefits to cognitive and brain health.

A 15 mg/dL increase in high density lipoprotein (HDL) cholesterol was associated with decreased AD risk during early and middle adulthood. In addition, a 15 mg/dL increase in glucose measured during middle adulthood was associated with 14.5% increased AD risk. These calculations remained significant after adjusting for treatment.

The findings suggest that an intervention targeting cholesterol and glucose management starting in early adulthood can help maximize cognitive health in later life, the researchers wrote.

They called for a better understanding of the molecular mechanisms underlying these associations. At the same time, additional vascular and metabolic factors may not be AD-specific and may be of similar size or even larger for other forms of dementia, so studies of other cohorts containing much larger samples of non-AD dementias and long follow-up periods are necessary. Further studies should also enhance findings and generalize them to populations of non-European ancestry, the researchers commented.

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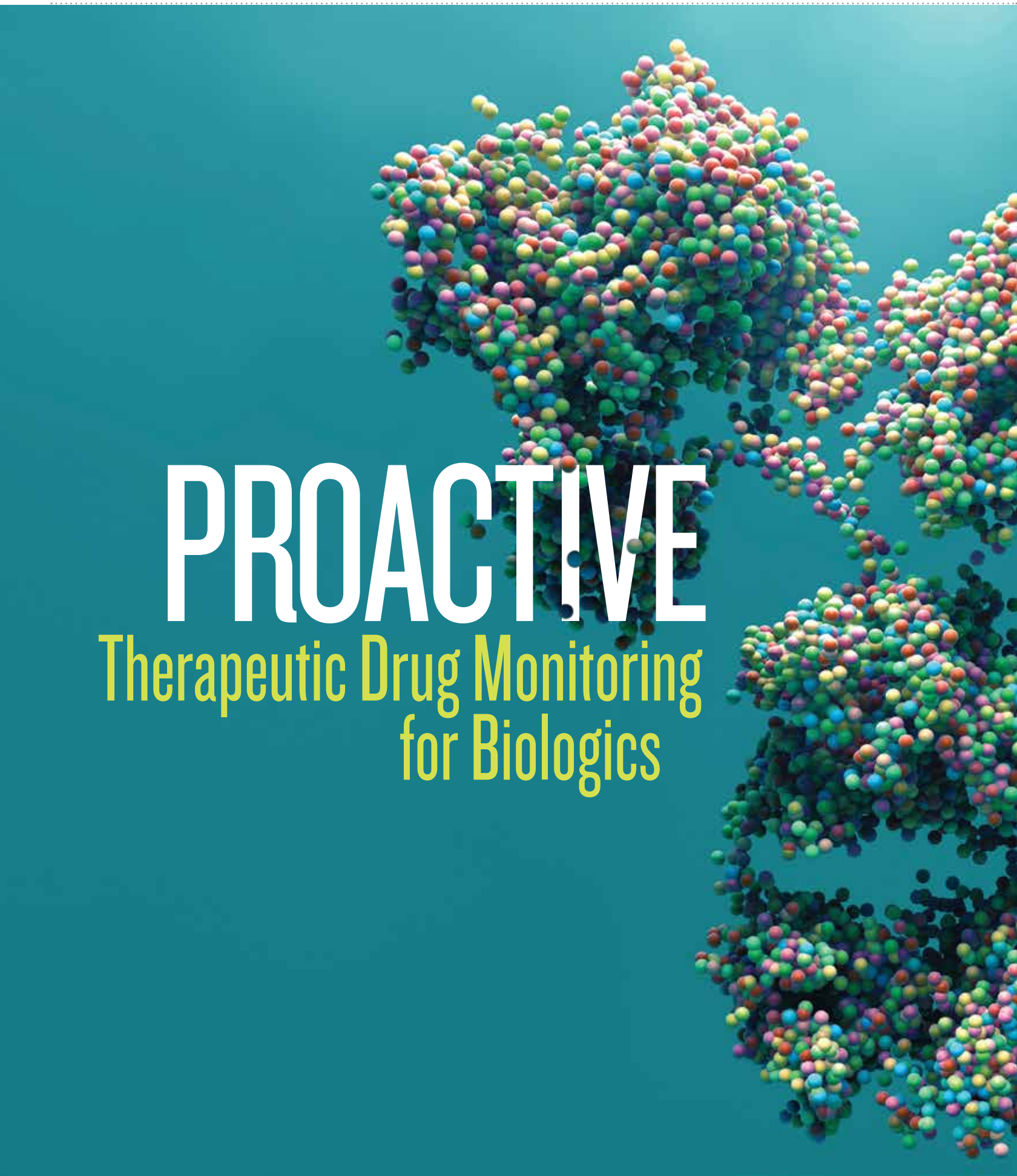

PROACTIVE

Therapeutic Drug Monitoring for Biologics

BY DEBORAH LEVENSON

Tumor necrosis factor (TNF) inhibitors and other biologic agents have improved outcomes for common chronic immune-mediated inflammatory diseases such as ulcerative colitis and Crohn's disease. But treatment failures after initial response are common, and they often result in organ damage and disability.

To prevent this, some clinicians try therapeutic drug monitoring (TDM). Reactive TDM involves measuring serum drug levels and the presence of anti-drug antibodies (ADAs) in response to evidence of active disease. In contrast, proactive TDM aims to optimize drug concentrations through scheduled assessments of serum drug levels and ADAs. While reactive TDM is included in clinical guidelines, multiple studies have found no benefit for proactive TDM.

The recent Norwegian Drug Monitoring (NORDRUM) trial, however, shows that proactive TDM for maintenance infliximab better sustains control of multiple immune-mediated inflammatory diseases than standard therapy (JAMA 2021;326:2375-84). "This paper is the first to show you can improve patient outcomes by doing proactive TDM," said Maria Alice Willrich, PhD, DABCC, FAACC, consultant and associate professor of laboratory medicine and pathology at Mayo Clinic in Rochester, Minnesota. If findings are replicated, labs could see increased demand for this biologics testing.

Experts say proactive TDM involves tackling several factors, including choice of quantitative assay, trough level testing, and difficulty measuring ADAs, which are associated with increased risk of infusion reactions and decreased duration of response.

NEW DATA IN FOCUS

The recent study details the second NORDRUM trial of proactive TDM. The first trial examined proactive TDM during infliximab induction and found it did not significantly improve remission rates over 30 weeks (JAMA 2021;325:1744-54). The more recent paper examined rates of sustained control during maintenance therapy in 458 patients with autoimmune diseases at 20 hospitals in Norway. These conditions were ulcerative colitis, Crohn's disease, rheumatoid arthritis, spondylarthritis, psoriatic arthritis, and psoriasis. The proactive TDM group had dose and interval adjustments based on an algorithm of serum drug levels and ADAs measured by immunoassay. The standard therapy was based on clinician judgement and discretion.

The sustained disease control rate was 73.6% in the proactive TDM group, compared with 55.9% in the standard therapy group. The estimated hazard ratio of disease worsening was 2.1 for standard therapy, compared with TDM. Fifteen percent of standard therapy patients and 9.2% of TDM patients developed significant levels of ADAs, defined as 50 µg/L or more. Rates for discontinuing infliximab and adverse events were similar in both groups.

A new study shows promise for this approach, but more research is needed to convince skeptics.

"We recommend proactive TDM at least for infliximab in maintenance phase. We're not sure if it's a beneficial approach for other drugs. It should be tested in proper trials before making it standard of care," said study coauthor Nils Bolstad, PhD, senior consultant and attending physician at Oslo University Hospital. He noted that proactive TDM already is a popular approach for Crohn's disease, ulcerative colitis, and certain rheumatological and dermatological conditions in Norway, which he said has the necessary lab services widely available at low cost.

The second NORDRUM trial's findings are not applicable beyond TDM for maintenance therapy with infliximab to other biologics, noted an editorial by Zachary S. Wallace, MD, MSc, and Jeffrey A. Sparks, MD, MMSc.

In an interview, Wallace called for further study of proactive TDM during maintenance of remission with infliximab in specific disease subgroups

and TDM involving other biological disease-modifying antirheumatic drugs.

ANOTHER VIEW

While reactive TDM is recommended in multiple national and international inflammatory bowel diseases (IBD) guidelines, only those from the Australian Inflammatory Bowel Diseases Consensus Working Group and the U.S.-based gastroenterology research group BRIDGe currently recommend the proactive approach. No rheumatology organization has taken a position on TDM, perhaps because its clinicians have more treatment options and can detect diseases' damage more easily, Willrich noted.

Hans Herfarth, MD, PhD, professor of medicine and codirector of the UNC Multidisciplinary IBD Center at the University of North Carolina in Chapel Hill, does not believe the second NORDRUM paper will spur more proactive TDM for infliximab and other biologics. He noted the paper showed no difference in infliximab trough levels between the two study arms and involved a population with a mixture of autoimmune diseases.

While the study showed no differences in mean and median trough levels in the two study arms, the proactive TDM group had less variation in infliximab levels, which "were more focused in the assumed therapeutic range," Bolstad said.

Herfarth remarked that a recent study comparing proactive and reactive TDM demonstrated no significant differences in drug persistence or overall maintenance of clinical remission (J Crohns Colitis 2022;16:199-206). Others that compared reactive TDM to dosing based on clinical symptoms or biomarkers found the proactive approach did not improve remission rates (Gastroenterology 2018;154:1343-51; Gastroenterology 2015;148:1320-9).

The pediatric PAILOT (Pediatric Crohn's Disease Adalimumab Level-based Optimization Treatment Trial) reported lower frequency of mild flares and less steroid exposure in its proactive TDM arm over 1 year, compared with its reactive TDM arm, but no difference in drug persistence or overall clinical remission (Gastroenterology 2019;157:985-96).

However, certain subgroups of patients on anti-TNF therapy may benefit from proactive TDM, Herfarth said. These include patients with an HLA-DQ1*05 allele that confers risk of developing low anti-TNF levels or ADAs, patients on a second anti-TNF therapy after loss of response to the first one, or patients on anti-TNF therapy in combination with thiopurines or methotrexate, who de-escalate to anti-TNF monotherapy.

USING TDM

Willrich suggested ways labs can encourage proper utilization of TDM tests. These include taking trough samples, providing timely test results to enable patient management decisions shortly after the draw for reactive TDM, offering interpretation to clinicians, and using reflex testing approaches when appropriate.

> The sustained disease control rate was 73.6% in the proactive TDM group vs. 55.9% in the standard therapy group.

Willrich added that all U.S. tests for drug quantitation and ADAs are lab developed and require high complexity environments. While drug quantitation can be done via immunoassays or mass spectrometry, she prefers mass spectrometry. Unlike immunoassays, mass spec does not require creating an antidrug monoclonal antibody to be used as a capture or detection antibody as an additional reagent. For large labs that have the proper instrumentation and a high test volume, mass spec can be a cost-effective approach if they have access to the drug as a calibrator.

Europe has CE-marked ELISAs, so ELISA testing for drug quantitation is more common there, Willrich said. She also noted that ELISAs are easier to automate and compare very well if there is access to the drug as a calibrator. For smaller U.S. labs, label-free immunoassay strategies such as surface plasmon resonance and interferometry with similar accuracy claims may be an option for both drug quantitation and ADAs. Label-free technologies detect the change of physical parameters caused by antibody–antigen interaction rather than the signal from a reporter, resulting in real-time immunometric measurement.

Bolstad prefers immunoassays to mass spec, which requires anti-idiotype antibody or the drug target to isolate the active/unbound drug, lest the test detect inactive drug either bound to the drug target or neutralized by an anti-drug antibody.

Comparing ADA assays is very difficult because of variation in patients and lack of reference materials, Willrich and Bolstad agreed. Each lab uses different standards and units, so only qualitative comparison of ADA tests is possible. Bolstad recommends ADA assays that measure only antibodies that neutralize the drug.

In an interview, Wallace urged laboratorians to think about how to achieve a quick return of results to guide clinician decisions about infliximab because clinicians want to act on TDM test results quickly and then adjust the dose of the next infusion. Meeting this goal requires coordination between labs and decisions about how to interpret the results of drug levels measured at certain time points in a patient's treatment cycle.

While Wallace also noted that providers may want to assess a level at a random point during a treatment cycle and might need help interpreting results, Willrich said that non-trough data assessment for biologics is different from and far more complex than for small molecule drugs that undergo liver and kidney metabolism.

Laboratorians must keep in close dialogue with clinicians using TDM of biologics and think about their complexities, Bolstad said. "Remember that biologics are different from most drugs. They are big, complicated molecules and are associated with adverse reactions, side effects, and complications related to measurements in the lab. Know the properties and limitations of assays in detail."

Deborah Levenson is a freelance writer in College Park, Maryland.
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Improving Lipid Worldwide

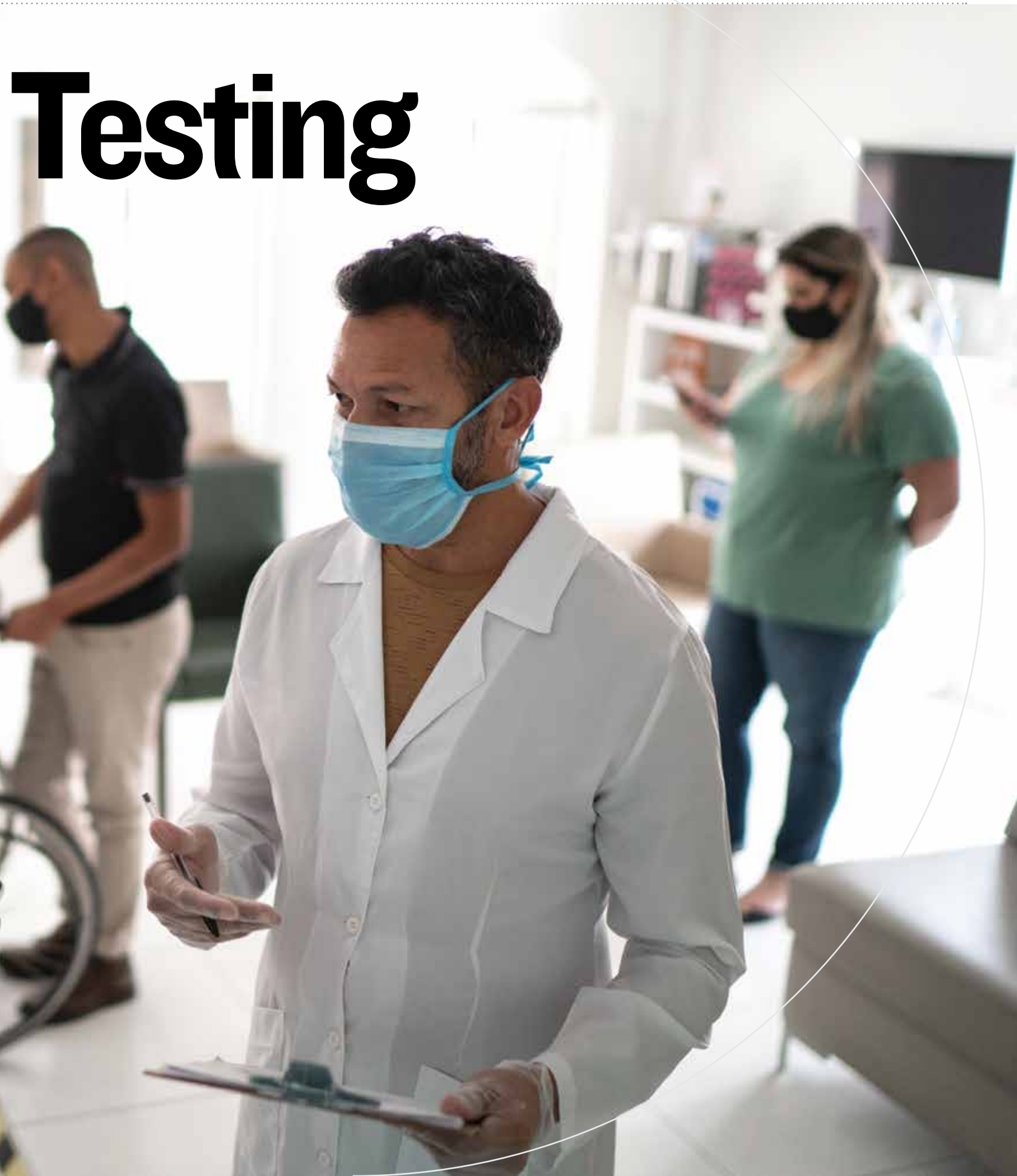
A novel partnership between AACC and CDC relies on point-of-care testing to improve global health.

BY SARAH MICHAUD

Cardiovascular disease (CVD), including heart disease and stroke, is the leading cause of death globally, and more than three-quarters of deaths are in low- and middle-income countries. Early detection, typically through lipid screening, is critical in preventing complications and deaths, especially in underserved areas. However, access to reliable lipid screening varies greatly.

In 2020, AACC launched a partnership with the Centers for Disease Control and Prevention (CDC) and the CDC Foundation to reduce the high mortality rate from CVD in resource-limited countries by expanding access to quality point-of-care (POC) lipid screening. The AACC-CDC collaboration focuses on training clinical laboratorians to administer and manage a POC lipid screening program in their communities.

Testing



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"Point-of-care testing devices are a very successful model for delivering clinical laboratory services because their portability lets you bring the lab to the patient," said James Nichols, PhD, DABCC, FAACC, professor of pathology at Vanderbilt University Medical Center in Nashville, and an AACC member who worked on designing the training curriculum. "But in financially strapped regions the quality of that testing, including technician training, lags behind what's accepted in advanced economy countries."

LIPID SCREENING AND POC TECHNOLOGY

Lipid screening plays a critical role in early CVD detection. A lipid screen performed by a clinical laboratorian can identify individuals at high risk of developing CVD, prompting them to get additional testing with their physician.

However, in low- and middle-income countries, well-equipped and well-organized laboratories often exist alongside those with out-of-date instruments and technicians who have not received adequate training. And some areas do not have access to laboratory testing at all.

"As a result, CVD detection can be very late in the course of the disease, and people can die at a younger age, often in their most productive years," said Hubert Vesper, PhD, director of clinical standardization programs for CDC. "Identifying those at highest risk of CVD and ensuring they receive appropriate treatment can prevent premature deaths."

AACC and CDC are working together with local laboratory medicine societies to improve both access and quality. Ultimately, the goal is to identify people at high risk of developing CVD and channel them further into the healthcare system where they can have their risk investigated before they develop serious health problems.

DESIGNING A CUSTOM CURRICULUM

AACC's point-of-care testing subject matter experts and representatives from CDC worked together to design the POC lipid screening curriculum, with the Philippines as the first site for deployment.

The curriculum has three main parts: training on quality management for POC lipid testing, training on country-specific rules and regulations for POC testing, and manufacturer-led training on how to use the actual device.

"We designed the training modules to have a strong focus on total quality management and on practical exercises," Nichols said. This includes quality management for testing as well as for acquiring and storing reagents and ensuring patient and physician satisfaction. The original modules for this part of the program include live, 2-day on-site training for laboratorians by two AACC lecturers with expertise in cardiology, POC testing, and quality control and assurance.

Also integral to the program is engagement with local subject matter experts. The AACC-CDC team joined with local experts through the Philippine Association of Medical Technologists (PAMET) to tailor the content to the country. "We want a program that is the best fit, that considers feedback from local expertise combined with our programmatic expertise," said Bill Clarke, PhD, DABCC, FAACC, director of clinical toxicology and professor of pathology at Johns Hopkins Hospital in Baltimore. Clarke worked with Nichols on developing the curriculum.

The PAMET partnership is led by the organization's past president Leila Lany Florento, PhD. "We all know that point-of-care testing has had a great impact on the clinical laboratory. The technology is helpful not only because it is cost-effective and fast—it also guides doctors on what to do next," said Florento. "The use of this point-of-care device will better identify which patients need more diagnostic investigation."

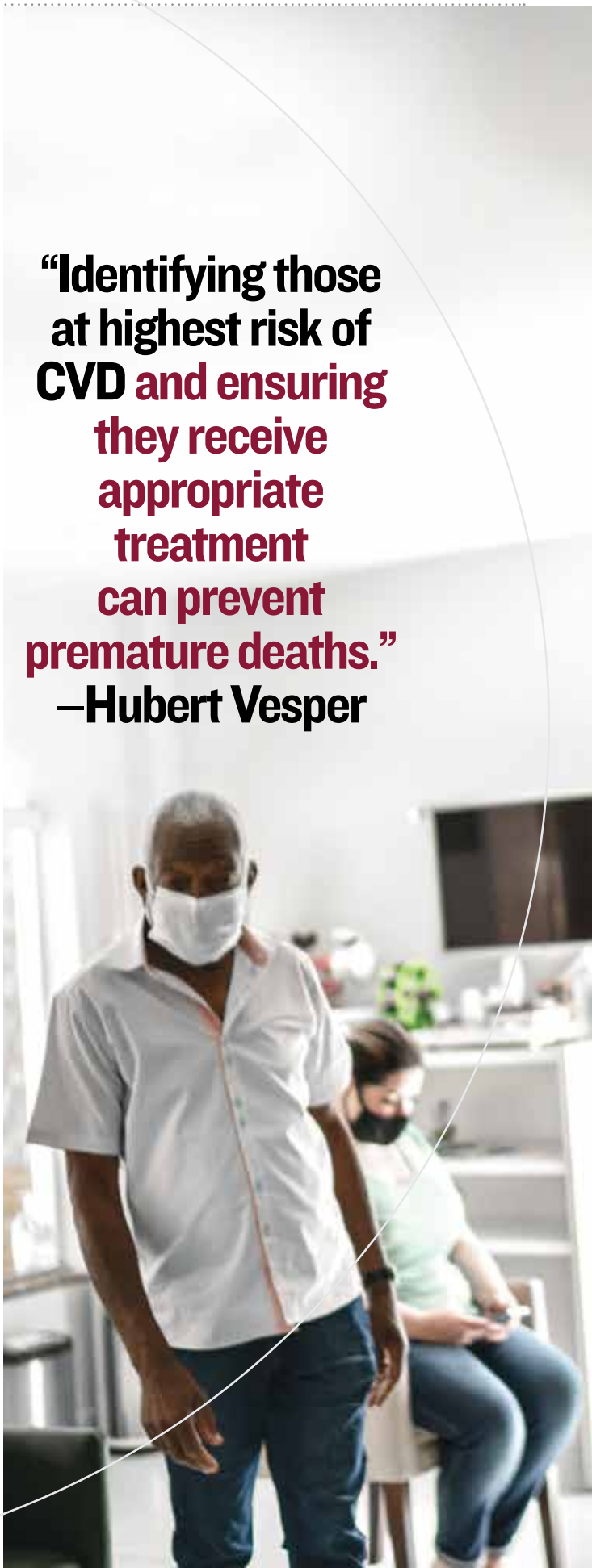
Florento and her PAMET colleagues chose the South Luzon region as a starting point for the program, but they plan to use the materials and train additional laboratory practitioners in other regions of the country in the future.

Program assessment is scheduled to take place 2–3 months post-training.

WITH COVID-19, TRAINING GOES VIRTUAL

The goal of the pilot phase of the POC lipid screening program, which

"Identifying those at highest risk of CVD and ensuring they receive appropriate treatment can prevent premature deaths."
—Hubert Vesper



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began in early 2020, was to train 20 laboratorians in the Philippines. However, like many plans for 2020, COVID-19 threw that agenda out the window.

The pandemic halted travel, making in-person training impossible, so the Philippines team adapted the training modules to virtual platforms. In hindsight, this may make the training modules easier to share and implement in areas where live instruction, for whatever reason, is not an option.

The U.S.-based training team will travel to the Philippines and visit several participants in their healthcare settings to assess their use of the device and device performance.

NEXT STOP, BOLIVIA

An AACC team is working concurrently to prepare a POC lipid screening program for Santa Cruz, Bolivia, with national clinical chemistry society partner La Sociedad Boliviana de Bioquímica Clínica (SOBOBIOCLI). One of the people leading this effort is Veronica Luzzi, PhD, DABCC, FAACC, section chief and medical director of the Tricore Research Institute in Albuquerque, New Mexico. The Bolivia program will use some of the virtual training modules developed by the Philippines team.

"The training the laboratorians will receive is very important, because lack of training and education may lead to inadequate use of the devices and perhaps inappropriate patient treatment," Luzzi said. "Our group is going to be teaching laboratory professionals how to maintain a quality program for monitoring the use of the POC devices, as well as testing accuracy and risk management."

The Bolivia program is aiming to start an in-person training workshop by mid-September 2022.

LEVERAGING ADVANTAGES OF POC TESTING

POC testing devices are known for offering low cost, portable testing. But in this case the benefits go beyond mere convenience. "As the testing volumes increase, we expect that the clinical laboratory specialists that go through this training program will be facilitating or overseeing the testing. That's why we are spending so much time on training," said Clarke. "We want to share with them our experience in not just the testing protocol, but also in how to ensure quality in testing and in patient and physician satisfaction in less controlled environments outside the hospital or clinical lab."

Looking beyond the AACC-CDC collaboration, advancements in POC technology are creating more opportunities for better patient outcomes in all healthcare settings. "A similar strategy could be used here in the United States," Nichols said, "to help address disparities in access to care that occur because of race and economic status."

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The AACC Global Lab Quality Initiative

AACC uses its influence and resources to promote international coordination around sharing best practices for laboratory medicine. Through the Global Lab Quality Initiative (GLQI), AACC aims to advance the practice and profession of clinical laboratory science and its application to healthcare, especially in countries with critical need. The lipid screening program is just the latest effort to capitalize on the leadership and experience of GLQI. Formerly known as the Emerging Countries Program, GLQI was designed to provide educational programming that reflects the needs of laboratory professionals worldwide.

GLQI Project Teams
AACC has several working groups devoted to providing critical advice and oversight in the planning and implementation of international educational projects:

- **Subcommittee on Global Affairs:**
  Barbara Goldsmith, PhD, DABCC, FAACC (chair)
- **Africa Working Group:**
  Olajumoke Oladipo, MBBS, DABCC, FAACC (chair)
- **Asia-Pacific Working Group:**
  Victoria Zhang, PhD, DABCC, FAACC (chair)
- **Latin American Working Group:**
  Veronica Luzzi, PhD, DABCC, FAACC (chair)
- **Newborn Screening Program:**
  Michael Bennett, PhD, DABCC, FAACC (lead) and
  Olajumoke Oladipo, MBBS, DABCC, FAACC (lead)
- **Improving Lipids Testing Capacity Worldwide:**
  William Clarke, PhD, DABCC, FAACC, and James H. Nichols, PhD, DABCC, FAACC, (year 1 faculty); Jose C. Jara-Aguirre, MD, and Verónica I. Luzzi, PhD, DABCC, FAACC (year 2 faculty); Hubert Vesper, PhD (adviser)

2022 AACC ANNUAL SCIENTIFIC MEETING+ CLINICAL LAB EXPO

JULY 24-28 / CHICAGO, IL / USA

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We are beyond excited to welcome you to Chicago for the 2022 AACC Annual Scientific Meeting & Clinical Lab Expo.

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AACC

Erwin Garcia, PhD
Diagnostics R&D Scientist II, Labcorp

Get Ready for the 2022 AACC Annual Scientific Meeting & Clinical Lab Expo

AACC will return this July to Chicago, one of our members' favorite cities in which to experience the premier gathering of laboratory medicine professionals from across the world.

Developed by accomplished AACC members on the Annual Meeting Organizing Committee, the 2022 scientific program is designed to prepare attendees for the technologies of the future—and to solve the pressing problems of today. Cutting-edge scientific sessions and lively roundtables promise something for everyone in the field.

On offer are more than 250 educational opportunities in a variety of formats spanning the breadth of laboratory medicine—from plenaries featuring today's scientific luminaries to lazer-focused workshops that boost essential practical skills.

Explore the program, browse exhibitors, get hotel and travel details, and register at meeting.aacc.org

Discover the AACC Clinical Lab Expo

More than 700 companies will be exhibiting in Chicago, with their most knowledgeable experts on hand to help attendees make the most of the latest innovations in laboratory medicine.

Beyond the exhibits, companies will offer lecture series presentations and unique workshops revealing the latest from their R&D, manufacturing, product development, and other areas of expertise.

Attendees can start planning their visit now and search exhibitors online, homing in on testing categories and other criteria, at meeting.aacc.org/clinical-lab-expo.

Thought-Provoking Plenary Lectures

Biomedical Informatics Strategies to Enhance Individualized Predictive Models

SUNDAY, JULY 24

Lucila Ohno-Machado, MBA, MD, PhD

Ohno-Machado will introduce how AI models are developed, tested, and validated. She also will elucidate performance measures that may help select these models for routine use.

Multiplexed & Exponentially Improving Technologies

MONDAY, JULY 25

George Church, PhD
2022 Wallace H. Coulter Lectureship Awardee

Church will explore the advances and implications of multiplexed sequencing and imaging that can identify small but crucial differences in DNA, RNA, proteins, and more.

Applications of Human Brain Organoid Technology

TUESDAY, JULY 26

Alysson R. Muotri, PhD

Muotri will reveal how developing a "human brain in a dish" can illuminate an organ that is still poorly understood due to the inaccessibility of its developmental stages in the uterus.

Building Trust in a Time of Turmoil

WEDNESDAY, JULY 27

Thomas H. Lee, MSc, MD

Lee will describe the importance of building trust among patients and among the healthcare workforce, and which strategies are most effective.

Guiding Clinical Decisions with Molecular Information Provided by Direct Mass Spectrometry Technologies

THURSDAY, JULY 28

Livia Schiavinato Eberlin, PhD

Eberlin will reveal innovations in the development and application of direct mass spectrometry techniques used in clinical microbiology labs, clinical pathology labs, and the operating room.

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Explore Pathways in Science and Leadership

AACC designed these pathways to help attendees chart a course based on their unique needs and interests first. But be sure to look for sessions that might be outside your comfort zone to refresh—and stretch—your skills. The following pathways highlight select sessions in core and emerging areas of laboratory medicine.

MOBILIZING DATA ANALYTICS

Let Me Show You the Data! A Showcase of Clinical Laboratory Dashboards

Transforming Laboratory Medicine through Mobile Health Technologies

Optimizing Laboratory Workflows Using Information System Tools: Leveraging Middleware, Health Information, and Laboratory Information Systems to Enhance Patient Care

AACC Healthcare Forum: How to Transform Laboratory Medicine with Data Interoperability

Bad, Better, Best: Putting Machine Learning Models to the Test

Machine Learning 101: Opening Opportunities for Laboratory Stewardship

TRANSFORMING POPULATION HEALTH AND EQUITY

Do Pediatric Reference Intervals Reflect the Development of Healthy Children?

Laboratory Implementation of Recommendations from the NKF-ASN Task Force Reassessing the Inclusion of Race in Diagnosing Kidney Diseases

Molecular Diagnostic Approaches to Navigating Healthcare Obstacles in Intersex and Transgender Patients

Population Genomics Health and Precision Medicine

At the Heart of Sex and Gender

Laboratory Testing for the Assessment of Preterm Delivery: A Summary of the AACC Academy Guidance Document

ACCELERATING MOLECULAR DIAGNOSTICS

Defining the Value of Next Generation Sequencing in Clinical Microbiology

Practical Challenges with Implementation of Diagnostic Algorithms for Infectious Disease

Genomic Prescribing: Implementation of Pharmacogenomic Testing and Results Delivery Programs

Clinical Chemistry Journal: Hot Topics in Molecular Diagnostics

Selecting Suitable Indicators to Monitor the Pre- and Post-Analytical Performance of Genomics Assays

SNP! BAM! NEO! Using Proficiency Testing Data to Unlock Your Molecular Lab's Superpowers

ELEVATING POINT-OF-CARE TESTING

Ten Hut! Fall in for the Essential Elements of a Point-of-Care Testing Boot Camp

Understanding the Current Expansion of Molecular Point-of-Care Testing

Point-of-Care Testing: Meeting Patient Needs in New Ways

AACC Guidance on the Use of Point-of-Care Testing in Fertility and Reproduction

Addressing Preanalytical Issues for Blood Collection and Testing Outside Conventional Locations

Laboratory and Clinical Medicine Consultative Case Interpretations Involving High Sensitivity Cardiac Troponin Testing

LEVELING-UP LABORATORY LEADERSHIP

Laboratory Medicine's Role in Creating Equitable Clinical Laboratories: A Global Call to Action

Becoming an Ally and Advocate: A Panel Discussion for Diversity, Equity, and Inclusion in Laboratory Medicine

Leadership: Wherever You Go, There You Are

The Clinical Laboratory Workforce: Essential Before, Critical Now, and a Blueprint for a Stronger Future

Valid Vital LDTs: Current State of Regulation Legislation of Laboratory-Developed Tests

Chemistry Confessions: Constructive Conflict Resolution with Case Studies

ADVANCING CLINICAL TOXICOLOGY

Drug Screening and Confirmatory Testing in Clinical Practice: Practical Interpretive Guidance and Public Health Consideration

Testing Strategies for Detecting Pediatric Drug Exposure: A Case Based Discussion

Unusual Toxicology: Interpreting Complex Cases Involving Urine, Umbilical Cord, Meconium, and Hair Samples

Cannabis and Driving: Biomarkers, Performance, and Officer Observation

Psychedelics in Medicine: Macroeconomics, Microdoses, and the Laboratory Perception

The Toxicology Tool Kit: An Interactive, Case-Based Approach to Toxicology Investigations

From top left: Laurence Dutton, SeventyFour, Adene Sanchez, nito100, visualspace, bluecinema / iStock

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FOCUS ON MOLECULAR DIAGNOSTICS

An interview with Robin Patel, MD

How Should We Assess PCR Accuracy?

BY JEN A. MILLER

PCR may have entered the general lexicon during the pandemic, but it's not a new technology. In fact, PCR tests have been used in clinical diagnostics for more than 30 years. Today, PCR technology has been refined to improve its accuracy and workflow. Now real-time PCR (RT-PCR) can be validated not only for detection but quantification, and a new approach called digital PCR (dPCR) even offers direct, absolute quantification of an analyte (Figure 1). So what role will PCR play in the future, both in and out of the COVID-19 spotlight?

CLN spoke to Robin Patel, MD, a professor of medicine, professor of microbiology, the Elizabeth P. and Robert E. Allen Professor of Individualized Medicine, and director of the Infectious Diseases Research Laboratory at the Mayo Clinic in Rochester, Minnesota, about how PCR tests have evolved, how they're being used right now (with sometimes surprising results)—and how it's everyone's job to make sure clinical testing is best serving patients.

PCR testing has been around for more than 30 years. How has accuracy and specificity changed?

At Mayo Clinic, we have been using PCR routinely in microbiology diagnostics since the 1990s. Initially, to detect amplified DNA, we would perform gel electrophoresis followed by a Southern blot. That worked, but was tedious, and interpreting Southern blots can be tricky at times. We performed Southern blot assays to add specificity, and a little sensitivity, but of course optimizing specificity was dependent on probe design. In the early years, there were some laboratories, especially research laboratories, that might have been basing analysis on size of amplified DNA alone, but on the clinical side, we always used Southern blots for specificity.

We transitioned to real-time PCR (RT-PCR) around the turn of the century. That change was advantageous for workflow — it is a lot faster and much less tedious than running a gel and Southern blot. And there is a huge improvement for contamination control.

Validation is needed to analytically assess specificity, and is just as important today as it was 3 decades ago.

There are different ways of approaching specificity in an RT-PCR assay. We incorporated probes into our assays to allow for specific detection of amplified DNA rather than generic amplified DNA. We could have used a non-specific dye to detect amplified DNA, but that would not tell us much about whether we had amplified exactly what we were looking for.

In my view, specificity, whether for an old school PCR assay or RT-PCR, comes down to assay design and validation; validation is needed to analytically assess specificity, and is just as important today as it was 3 decades ago.

Test developers need to consider what might cross react in the assay and be falsely detected. From a microbiologist's point of view, such an ask can be daunting because there are many microbes we haven't yet characterized, named, or sequenced. On one level, the developer has to think about the disease they are trying to diagnose and on another, the microbes — be they pathogens or non-pathogenic microorganisms — that might be present at the site being sampled.

Interestingly, non-specificity can be helpful, if easily recognized. For example, we've had scenarios where we've designed assays to detect particular microorganisms but discovered novel microorganisms that hadn't been known to cause human disease using our assays. We discovered them through the non-specificity of the assays, but we were able to easily recognize what was happening because of our assay design. Since we were careful in how we designed our assays, it was possible to see that there was something being detected that was not what the assays were specifically designed for.

That is obviously not the goal, but it does tell you that we live in a world where we are still learning about—and discovering—microorganisms. Some of them are likely to be pathogens we do not yet understand.

How should clinical laboratories choose between quantitative and qualitative PCR?

This depends on the disease being diagnosed and what the need is for patient care. While quantitative PCR (qPCR) assays are often used for microbial detection, they are typically not validated for quantitative

detection. That's because there are very few microorganisms we have a strong need to quantify and also very few clinically validated quantitative assays. An example of a regularly used quantitative test is HIV viral load measurement; this testing helps guide treatment. Conversely, for many microorganisms, such as *Mycobacterium tuberculosis* complex, for example, patients are either infected with the organism or not, and having a little bit of that organism is no different, technically speaking, than having a lot of it. It would be like being a little bit pregnant.

In the future, could qPCR assays become more useful in diagnosing other kinds of diseases?

Quantifying accurately and precisely using diagnostic assays in clinical microbiology is harder than people think. Truly quantitative assays usually rely on blood-based specimens because the denominator is relatively straightforward: a volume of blood (or plasma) is standard.

At the Mayo Clinic, many PCR assays we use are performed on non-blood specimen-types, such as body fluids, urine, or tissues. For these specimens, quantifying a denominator is more challenging than the situation for blood, and fraught with variability. Beyond the technical challenge of being able to quantify microorganisms in clinical specimens, the clinical question being answered with such quantification would need definition.

There is also the question of the ideal limit of detection of a qPCR assay. It depends on the microorganism being detected. With microorganisms like *Mycobacterium tuberculosis* complex, the laboratory needs to have the most sensitive assay possible. But there might be other scenarios where the laboratory is looking for microorganisms that could be part of the normal microbiome. In such scenarios, clinical significance may be based on the relative quantity detected.

It all depends on what the laboratory is trying to accomplish with the assay. One approach is not necessarily better than another for all applications.

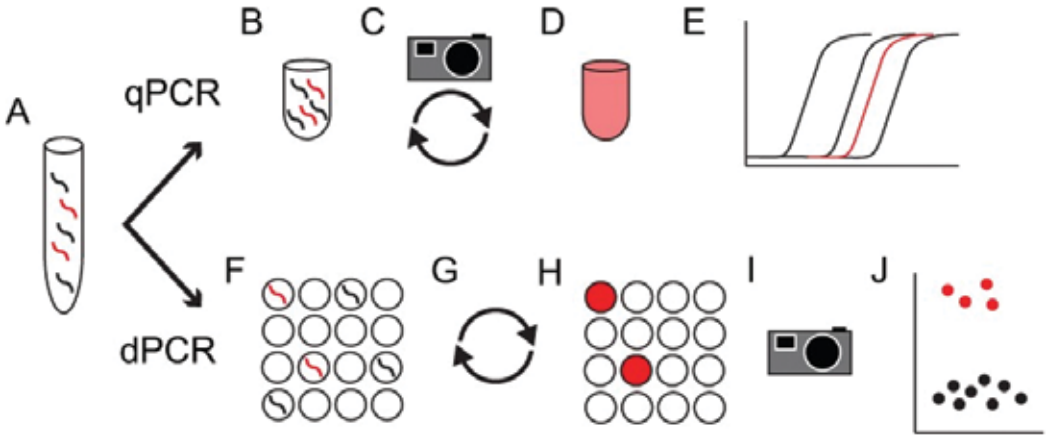
Where do you still see opportunities for laboratory medicine professionals to educate clinicians about the nuances of reliability and accuracy of PCR tests?

We need to better understand clinical utility of the assays we have and define and develop the future assays we need. In the end, it is everyone's responsibility — that is, the laboratory and test-ordering healthcare providers — to make sure our patients receive the appropriate testing they need, and don't receive inappropriate testing they don't need.

It is also a shared responsibility that, when patients have testing performed, their results are appropriately reported and acted on. In that sense it is not "education" of clinicians, but the responsibility of the collaborative team to assure the best patient care possible. It is not an us versus them situation.

So, with that context, a simpler answer to your question would be: every day, every minute, all of the time.

F1 **Comparing qPCR and dPCR**



(A) A specimen contains a mixture of nucleic acids, a subset of which corresponds to the template of interest (red). (B) In qPCR, a single reaction mixture containing a heterogeneous mixture of template and nontemplate molecules is prepared. (C) The PCR reaction is subjected to thermocycling, with detection of a fluorescent reporter (intercalating agent or probe) that marks the specific amplification of the target of interest occurring after each cycle. After an end point is reached (D), the relative or absolute concentration of the target of interest is subsequently inferred relative to an internal or external calibrator that is amplified in parallel (E). (F) During digital PCR (dPCR), the specimen is combined with PCR reagents and then subdivided into individual partitions such that on average each contains fewer than a single copy of the template molecule of interest. The array of partitions is subjected to thermocycling (G) until an end point is reached (H), after which partitions are ascertained for a fluorescent reporter that indicates the successful amplification of the specified target. (J) Quantification of the partitions that are positive versus negative for amplification allows the absolute concentration of original target molecules to be inferred using Poisson statistics.

Source: Clin Chem 2020;66(1):117-123

FOCUS ON MOLECULAR DIAGNOSTICS

An interview with Esther Babady, PhD

How Is the Menu of Molecular Diagnostics Expanding After COVID-19?

BY JEN A. MILLER

Molecular testing has been launched into the stratosphere because of the COVID-19 pandemic. Clinical laboratories around the world have invested billions of dollars not only in test kits for SARS-CoV-2, but in new instruments, staff, and other resources to support the enormous volume of testing required.

According to COVID-19 Response Advisors, monthly capacity for molecular SARS-CoV-2 testing in the U.S. was estimated to be 128 million in May 2022, although about a quarter of that includes point-of-care and over-the-counter molecular systems (Figure 1).

The new focus on molecular capability also has spurred innovation, as laboratorians determine what other areas could benefit from a molecular testing capacity boost, while also figuring out what to do with instruments bought to satisfy the demands of peak pandemic testing.

CLN talked to Esther Babady, PhD, chief of clinical microbiology service at Memorial Sloan Kettering about what she sees.

The pandemic has put so much emphasis on developing PCR testing. How will this change the types of tests and instruments clinical laboratories consider going forward?

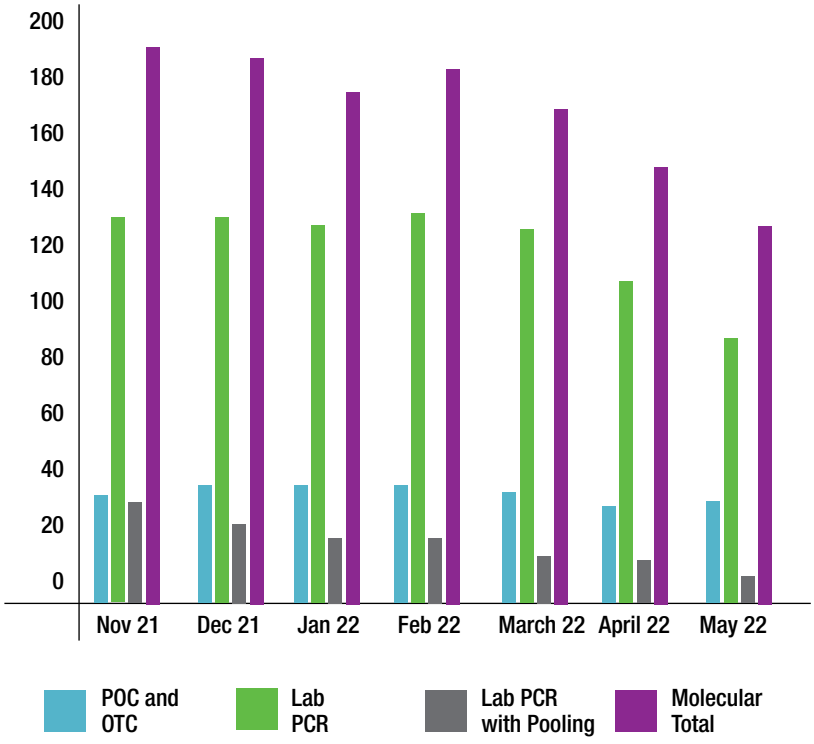
The pandemic has brought knowledge of advanced, high complexity testing into everyday life. Now people outside medicine talk about PCR testing like it's something everyone should understand.

This awareness has opened up a future for performing more testing, particularly infectious disease testing, at home. Before the pandemic, it would have blown my mind that in some cases molecular testing would be simplified to the point that a layperson could do it at home. This new reality is going to create a new set of challenges, but that door is now open, and we have to figure out how we walk through it.

What kinds of challenges do you mean?

The demand for SARS-CoV-2 tests has shown some of the limitations with molecular testing. One of the most controversial discussions around COVID-19 and molecular testing is cycle threshold, or CT, value and being able to understand viral load. CT values aim to capture information not only about how much virus is present in a sample

F1 **Monthly SARS-CoV-2 Testing Capacity Estimates**



In Millions of Tests. Source: COVID-19 Response Advisors

but sometimes to infer how infectious a person might be.

And the issue becomes that just detecting nucleic acids is not going to be enough to make at-home molecular tests as useful as we might want them to be. We need to figure out which molecular marker—or something else—will identify when a person is actually infectious.

In the pandemic, we discovered both the promise and the limitations of current PCR testing: We figured out that we can make things simple and reliable enough for patients to perform them at home, but now we're left with questions on how to make things a bit more advanced in order to capture the information we really want about who is infectious and who is not.

In the pandemic, we discovered both the promise and the limitations of current PCR testing

What are some smart ways that laboratories can use built-up capacity for SARS-CoV-2 testing after the pandemic recedes?

At the beginning of the pandemic, when we were all looking for platforms for testing, I had in the back of my mind, "What are we going to do once we don't need all of these?" Well, with continuing waves of the virus, we still need all these instruments right now. But it's still the case that we'll have all this new capacity for molecular testing. The question is: what else can you do?

Perhaps now there is more incentive for manufacturers to develop IVD assays that labs can use on these platforms. It's something that will take time to move through the FDA process. Meanwhile, for laboratories that have acquired these platforms, developing tests in-house that traditionally they were sending out to reference laboratories is one option.

Laboratories are all different. They are going to have to be creative to make sure this instrumentation is still beneficial and properly used. I think it's positive that this opens up new discussions about bringing new tests to hospitals' in-house laboratories, as well as laboratories themselves becoming more molecular-focused.

Yet, we know that this pandemic is so unpredictable. One minute we have low case counts and think we can move on to other things. And then, boom, another wave. For now, we're certainly not getting rid of any of these instruments.

How did the experience with molecular testing during the pandemic change the way laboratories are thinking about automation?

I think this also goes back to the question of, now that we have all these platforms, what are laboratories going to do with them? We hadn't planned to automate as much in microbiology, where we had only a few assays that ran on some of the automated platforms. We performed a lot of laboratory-developed tests that had been very manual.

With the pandemic, that became such a challenge, because we didn't have the front-end automation—beyond just automating the extraction and PCR—that was much more common in the clinical chemistry laboratory. It introduced a new element for us when we think about molecular testing and automation.

How can this experience offer ways for labs to improve patient care in the future with molecular testing?

One of the ways this is going to improve patient care is related to the fact that we now have molecular at-home testing, which means that we can make it faster in clinical point-of-care settings, too.

Molecular tests used to require a 24–48-hour turnaround time. Then manufacturers came out with rapid moderately complex testing platforms for the laboratory with a 1–3 hour turnaround, depending on the test.

During the pandemic, we've taken the leap to frequent use of point-of-care molecular testing, even in clinics or for patients presenting in the emergency department. I expect we're going to be seeing a lot more tests on the menu of point-of-care molecular platforms. They're more sensitive than antigen tests, and point-of-care testing avoids sending some of the more routine testing back to the laboratory.

This would improve patient care just because the clinician and the patient get an answer much more quickly.

Where specifically do you think these improvements are going to be?

Before COVID-19, we had already started to see a couple of assays that focused on flu and respiratory syncytial virus. We had antigen tests, but they're not necessarily the most sensitive. Same for streptococcal pharyngitis. Now a PCR assay can be performed in the emergency department on the same platforms on which SARS-CoV-2 tests were developed.

FDA has also approved molecular tests for some sexually transmitted diseases, so patients can test themselves from the comfort of their homes.

Do you see any other changes to how PCR tests will be used from now on?

Until COVID-19, medicine was not as focused on how a virus changes, or how pathogens evolve. We've now learned that we need to improve how we monitor variants and mutations. Even with flu, we are essentially offering a yes/no answer, only adding whether the patient has influenza A or influenza B, or maybe particular genotype. However, we know that the flu virus develops mutations that make it resistant to antiviral therapy.

We need better tools to monitor mutations for pathogens other than SARS-CoV-2—and to be able to act on that information quickly. That means having tools to perform genotyping more readily for other respiratory viruses that are circulating.

Regulatory Roundup

FDA Aims to Increase Racial and Ethnic Diversity in Clinical Trials

The Food and Drug Administration (FDA) has issued new draft guidance to the industry for developing plans to enroll more participants from underrepresented racial and ethnic populations in the U.S. into clinical trials. This expands on the agency's previous guidances for the industry to improve clinical trial diversity. This latest draft guidance recommends that sponsors of medical products develop and submit a Race and Ethnicity Diversity Plan to the agency early in clinical development, based on a framework outlined in the guidance.

This new guidance was developed by the Oncology Center of Excellence's Project Equity, which aims to ensure that the data submitted to FDA for approval of oncology medical products adequately reflects the demographic representation of participants for whom the medical products are intended. As this guidance applies to all medical products, the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health contributed to its formulation. Additionally, to support the goals of the guidance, the Office of Minority Health and Health Equity has created the "Diversity in Clinical Trials Initiative," which includes an ongoing public education and outreach campaign to help break down some of the barriers preventing diverse groups from participating in clinical trials.

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ABBOTT GETS FDA OK FOR SEXUALLY TRANSMITTED INFECTIONS TEST

The Food and Drug Administration has cleared Abbott's Alinity m STI assay, a multiplex test that simultaneously detects and differentiates between four common sexually transmitted infections (STIs). The test detects *Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis,* and *Mycoplasma genitalium*. It requires one swab sample or a urine sample collected in a healthcare setting by either a clinician or by the patient. It runs on Abbott's Alinity m system, a high-volume, PCR-based instrument that can run up to 1,080 tests in a 24-hour period. Other assays available for use on the Alinity m system in the U.S. include SARS-CoV-2, Resp-4-Plex (for SARS-CoV-2, influenza A, influenza B, and respiratory syncytial virus), HCV (for hepatitis C), HBV (for hepatitis B), and HIV-1.

FDA GRANTS BREAKTHROUGH DEVICE DESIGNATION TO SIEMENS' MULTIPLE SCLEROSIS TEST

Siemens Healthineers has received Breakthrough Device Designation from the Food and Drug Administration (FDA) for the Advia Centaur serum Neurofilament Light Chain (sNfL) assay, which was developed in collaboration with Novartis Pharma. The Advia Centaur sNfL quantitatively measures NfL in human serum and plasma and is

intended to be used in conjunction with clinical, imaging, and laboratory findings to help determine whether adult patients with relapsing multiple sclerosis are at low or high risk for multiple sclerosis disease activity. NfL is a biomarker for nerve cell injury measured in cerebral spinal fluid and blood. Research has shown that blood NfL levels change in a variety of serious neurological conditions, including multiple sclerosis, and can be related to disease activity and disability outcomes.

By earning Breakthrough Device Designation for this test, Siemens will now be able to get additional FDA feedback as the company works to validate the test and submit it for premarket approval. Following submission, the Advia Centaur sNfL will also be eligible for expedited review.

BAEBIES EARNS CE MARK FOR SARS-COV-2 POINT-OF-CARE TEST

The CE mark has been granted to Baebies for its Finder SARS-CoV-2 point-of-care test, which uses reverse transcription PCR (RT-PCR) to detect the SARS-CoV-2 virus. The test identifies SARS-CoV-2 RNA in nasopharyngeal and nasal swab specimens in 17 minutes or less, versus conventional RT-PCR tests, the results of which are typically reported after 24 hours. Its operation is fully controlled by software, enabling users to perform the test without specialized training.

The Finder SARS-CoV-2 test runs on single-use disposable cartridges on the Finder 1.5 platform, which features a compact, toaster-sized instrument with a mini tablet for user interface. The platform leverages Baebies' core digital microfluidics technology to streamline and miniaturize the RT-PCR process, producing lab quality results in near-patient settings. Specifically, this digital microfluidics technology uses electrical control to move discrete droplets on the disposable cartridge. Because the technology operates on low droplet volume, it enables rapid heating and cooling via heaters and sensors located directly on the cartridge.

CE MARK GIVEN TO QIAGEN FOR HSV 1/2 TEST

Qiagen has received the CE mark for its NeuMoDx HSV 1/2 Quant assay, which quantifies and differentiates between herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) DNA. This assay uses Qiagen's automated, three-step NeuMoDx solution, which extracts DNA from blood or urine to isolate the target nucleic acids and then conduct real-time PCR to target conserved sequences in the HSV genome.

This approval supports Qiagen's strategy to expand the menu of tests available for use on the NeuMoDx 96 and 288 molecular systems, which already feature 15 CE-marked tests. Additional assays on these platforms for which Qiagen hopes to get the CE mark in 2022 include a human herpesvirus 6 assay, reformulated assays for Epstein-Barr virus, and a combined respiratory panel test that detects influenza A, influenza B, respiratory syncytial virus, and SARS-CoV-2 virus.

NY STATE AUTHORIZES KSL DIAGNOSTICS' COVID-19 IMMUNITY INDEX

KSL Diagnostics has received New York State Department of Health emergency use authorization for the COVID-19 Immune Index, a blood test designed to detect an individual's immune response to SARS-CoV-2 and assess that person's risk of getting infected. According to the company, this test could help physicians and patients to determine appropriate timing for booster vaccine doses and to make other informed decisions related to potential SARS-CoV-2 exposure.

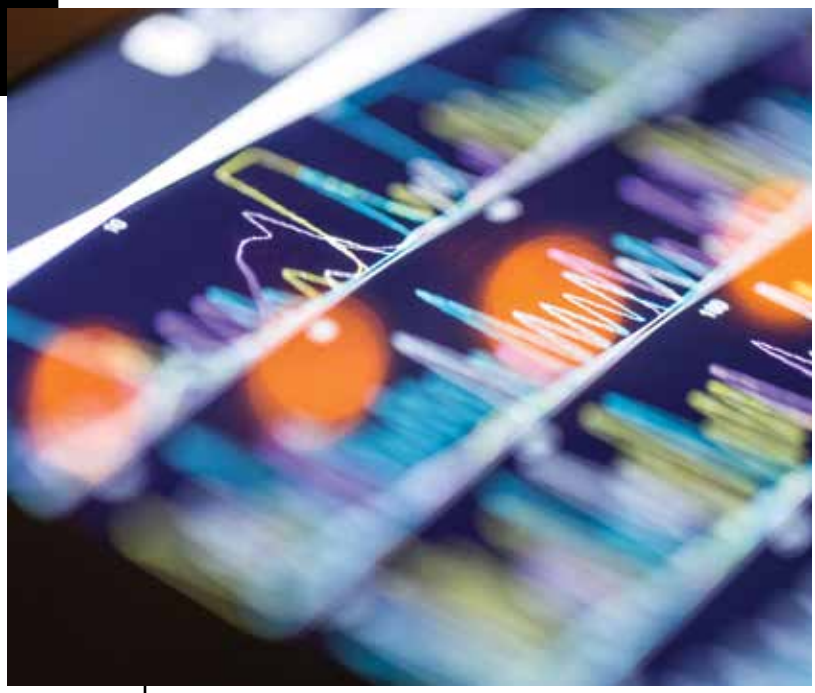
In order to develop the test, KSL completed studies on the relevance of circulating antibodies in vaccinated individuals in collaboration with researchers at the University at Buffalo in New York. These studies used a plaque reduction neutralization test, the gold standard for assessing virus deactivation, to determine the optimal neutralizing antibody titers required to block virus entry into host cells. Researchers then correlated these results with KSL's antibody assays, demonstrating stratification of immunity. For example, 100% neutralization of the virus was seen at IgG levels of 20 and above, suggesting adequate immunity. IgG levels from 10–20 reduced effective virus neutralization by 25%, while IgG levels below 10 indicated considerably decreased neutralization, suggesting ineffective immunity.

Industry Playbook

Companies Partner to Detect Emerging SARS-CoV-2 Variants

Thermo Fisher Scientific, the National Institutes of Health (NIH), Helix, and Rosalind announced a collaboration aimed to develop a new genotyping method to advance the identification of variants for SARS-CoV-2. Specifically, the companies will work with the NIH's Rapid Acceleration of Diagnostics (RADx) Initiative.

Currently, next-generation sequencing is the most common method used to detect new variants, with about 5% of randomly selected SARS-CoV-2 positive samples in the U.S. being tested for variant types. This method can take up to 21 days from a positive result before variant data is available in public repositories. In comparison, the new method, using polymerase chain reaction-based genotyping, could increase the number of positive samples used for testing and provide variant identification in only 2–3 days. If a sample does not get classified into a known variant, it then gets categorized as a potential identifier for a new or emerging variant.



Through the partnership, Rosalind's cloud-based data analytics platform will allow researchers to select and validate specific biomarkers for SARS-CoV-2 variants. The companies can use the platform as a centralized resource for analyzing data in a real-time dashboard format.

"With a public tracking dashboard, this automated analysis, classification, and real-time genotyping reporting provides a snapshot of the most current strains circulating the country and provides us with valuable information to respond more quickly," said Rosalind CEO Tim Wesselman.

CELLTREAT ACQUIRES VISTALAB TO TACKLE SUPPLY SHORTAGES

With ongoing supply shortages in laboratories across the U.S., CellTreat announced acquisition of VistaLab Technologies to combine laboratory product manufacturing to a single source and expand its network of consumers. The companies aim to design new products that significantly improve productivity, workflow, and ergonomics on the lab bench.

Through the acquisition, CellTreat will obtain new product designs from VistaLab to provide better offerings to labs. In addition, the acquisition not only will increase product supply but also will improve turnaround times that supply shortages have caused in labs, the companies said.

"By joining forces, we will be able to further innovation in the industry and provide better offerings, distribution, and support to the laboratory research market. We see this as a win-win for both companies, for our mutual customers, and in the long run, for the market overall," said Dick Scordato, CEO of VistaLab.

ELYPTA STUDY FINDS EARLY CANCER SIGNS IN GLYCOSAMINOGLYCANS

Elypta, a Swedish molecular diagnostics company, announced its second clinical study that focuses on the complete profile of human glycosaminoglycans (GAGomes) as

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metabolic biomarkers for multicancer early detection. The study targets adults 55–80 years of age with a high risk of developing cancer due to significant smoking history.

The study will analyze patient blood samples collected from the Yorkshire Lung Screening Trial Biomarker substudy as well as corresponding patient data collected from the Yorkshire Lung Screening Trial and the Yorkshire Kidney Screening Trial. Elypta's liquid biopsy process has shown improved performance for early cancer detection over other methods that use biomarkers based on circulating tumor DNA, according to the company.

Research shared by Elypta during the American Society of Clinical Oncology conference in June 2021 revealed that GAGomes can detect one-third of all stage 1 cancers across 14 types, including lung and kidney cancer. In part one of the multicancer early detection study, Elypta aimed to detect early signs of cancer in adults who showed no symptoms nor had any recent history of cancer.

ILLUMINA, HANNOVER MEDICAL SCHOOL AIM TO ADVANCE WGS FOR CHILDREN

Illumina and Hannover Medical School have joined forces to advance the use of whole-genome sequencing (WGS) in critically ill children suspected of having a genetic or rare disease.

Through the agreement, the partners aim to accelerate earlier diagnoses and treatment after using WGS in the neonatal and pediatric intensive care units. Ultimately, the companies aim to evaluate the efficacy of rapid WGS (rWGS), which requires faster turnaround times for results leading to timely diagnosis and care.

The study will include testing on approximately 100 children while also including data from parents when possible. Under the terms of the agreement, Illumina will provide reagents for the library preparation of DNA and sequencing reagents for the WGS samples.

According to the companies, recent studies on rWGS in Canada, the U.K., and the U.S. have shown it to be of great clinical value for pediatric precision medicine due to its high diagnostic rate, short time to diagnosis, and cost efficiency.

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ATCC EXPANDS BIOINFORMATICS PLATFORM WITH QIAGEN

American Type Culture Collection (ATCC) announced a partnership with Qiagen to expand its bioinformatics platform. Under the agreement, Qiagen will provide ATCC with sequencing data from its collection of human and animal cell lines and biological materials.

Through Qiagen's bioinformatics unit, Qiagen Digital Insights, the companies will create a database that develops and delivers high-value digital biology content for the biotechnology and pharmaceutical industries. The partners hope to advance the use of authenticated biological data sets to uncover new disease pathways and discover novel therapeutic targets.

According to the companies, the use of cell lines allows researchers to better understand underlying processes of normal and disease biology including cancer. ATCC will produce fully authenticated transcriptome and whole-exome sequencing datasets from human and animal cell lines. The datasets will include multiple biological and technical replicates that will help establish a baseline for a wide range of cell lines under typical cell culture conditions. Users will also be able to request datasets to be included in the database in the future.

"This first-of-its-kind arrangement will allow ATCC to provide data provenance that is traceable, standardized, and authenticated to its original source," said Raymond H. Cypess, DVM, PhD, chairman and CEO of ATCC. "We are embracing this digital biotechnology to be able to share our expertise in advancing authentication to the research community."

Index to Advertisers

Ask The Expert

When Binding Proteins Interfere With Immunoassays

EXPERT
By Anastasia Gant Kanegusuku, PhD

Why are abnormal binding protein concentrations an issue for immunoassays?

A: Immunoassay detection relies on noncovalent binding interactions between the receptor and the target analyte. These interactions are equilibrium reactions, and the results that are obtained are snapshots of one moment in the equilibrium process of very complex sample mixtures with potentially high inter-individual variability.

Most antibodies used as receptors in immunoassays have binding affinities (Ka) ranging from 108–1010 L/mol. For many analytes, this level of binding selectivity is excellent. For small molecule hormones that are transported by specific binding globulins, however, this level of binding selectivity may not be adequate, especially when concentrations of binding globulins are abnormal. This is because specific binding proteins such as thyroxine-, corticosteroid-, and sex hormone-binding globulins (TBG, CBG, SHBG) and vitamin D binding protein (DBP) also have Kas for their target hormones (e.g., thyroxine, cortisol, estradiol, testosterone, and vitamin D) ranging from 108–1010 L/mol (JBMR Plus 2020; doi: 10.1002/jbm4.10418).

Which assays are affected by abnormal concentrations of binding proteins?

In general, there is consensus that total hormone levels can fluctuate due to abnormally high or low binding protein concentrations. However, a high or low concentration of total hormone may not necessarily mean that there is an excess or a deficiency of biologically active, or free hormone, that is available to the tissue. For this reason, free hormone levels for analytes such as cortisol, thyroxine, triiodothyronine, testosterone, and vitamin D are also important to measure. Unfortunately, researchers have shown that the measurement of free hormone by immunoassay, particularly free thyroxine, is affected by both nonspecific (albumin) and specific binding protein concentrations (TBG) in comparison with a reference liquid chromatography-tandem mass spectrometry (LC-MS/MS) method, which does not exhibit a bias due to binding protein concentrations (Clin Chem 2011; doi: 10.1373/clinchem.2010.154088).

There are many occasions when the measurement of total hormone can be used to confirm a diagnosis or monitor a patient's treatment. Immunoassay measurements of total hormones are considered less susceptible to binding protein concentrations, because they typically include additional reagents such as acid to denature binding proteins, or ligands with higher binding affinities to displace the native target hormone. However, total hormone measurements by immunoassay also still can be affected by abnormal concentrations of binding globulins. For example, one study found immunoassay measurements of total cortisol to be falsely low compared with LC-MS/MS measurements in patients with abnormally high concentrations of CBG (Clin Endocrinol (Oxf) 2013; doi: 10.1111/cen.12039).

Which major patient populations are affected by abnormal binding protein concentrations?

The following patient populations have conditions or treatments that can lead to abnormal binding protein concentrations: patients who are pregnant, patients receiving estrogen treatment or taking oral contraceptives, patients with liver diseases, and patients with compromised renal function.

What can be done to ensure accurate laboratory results for these patients?

There are several strategies that both clinical and laboratory teams can take to ensure accurate measurements for patients with abnormal levels of binding proteins. Initially, if laboratory measurements do not agree with the clinical presentation of the patient, the analyte-specific binding globulin can be measured to rule out bias due to abnormal concentrations of binding proteins. If possible, the sample can be analyzed by the gold standard method, LC-MS/MS, which removes binding proteins by precipitation or, in the case of free hormone measurements, physically separates the bound from the free fraction via equilibrium dialysis or ultracentrifugation. If measurement by LC-MS/MS is not feasible, the clinical and laboratory teams can collaborate to define appropriate reference intervals for specific patient populations.

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