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CLN Clinical Laboratory News

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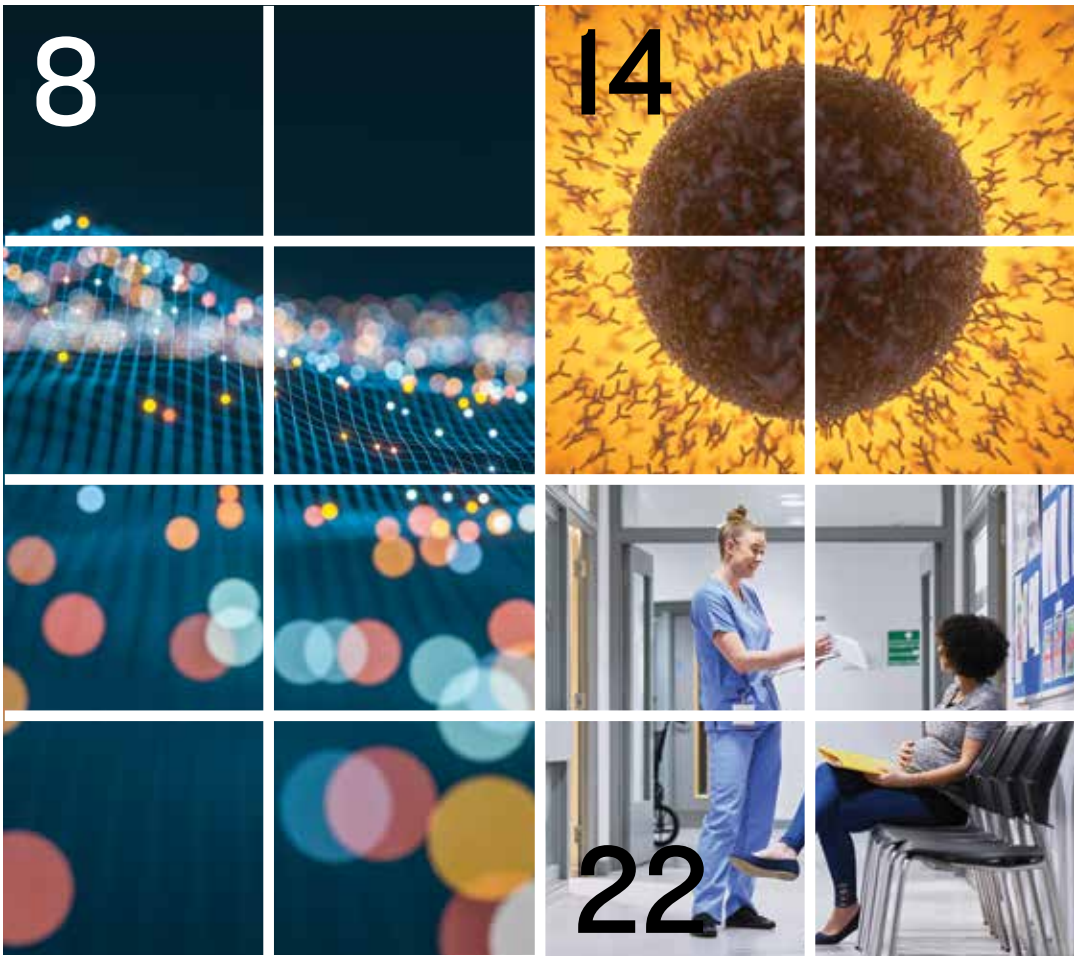

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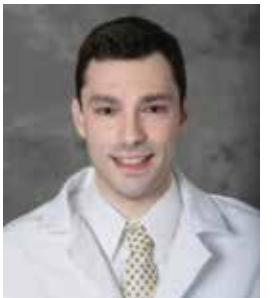

"Our study demonstrated that laboratory staff are at low risk of incurring a harmful exposure from most of the [radioactive] samples received in our lab. Risk is difficult to truly assess, though."
p40

Federal Insider

LDT Regulation Back in the Spotlight

Lawmakers are not done looking for a solution to the dispute over regulation of laboratory-developed tests (LDTs), an issue where most industry observers expect President Joe Biden's administration to have a different approach than his predecessor. Senator Rand Paul of Kentucky has reintroduced the VITAL Act, which would formally place LDT regulation solely under CLIA and separate it from Food and Drug Administration (FDA) oversight. AACC has endorsed the bill.

A very different, but similarly named bill called the VALID Act died in the 116th Congress, but Bloomberg Law reports that Democrats in the House expect to reintroduce it this year. Contrary to the VITAL Act, the VALID Act would define new powers for FDA to regulate LDTs. When first introduced in 2020, the bill was criticized by AACC for promoting duplicative, costly federal regulations that would decrease patient access.

AACC recently wrote to Health and Human Services Secretary Xavier Becerra seeking dialogue on the issue and emphasized that a burdensome, overlapping regulatory structure under FDA, like that of the VALID Act, would force many hospital laboratories to discontinue needed testing. "The creation of a one size fits all regulatory approach would likely harm, rather than improve patient care," the letter said.

HHS INKS VENTURE CAPITAL DEAL TO TACKLE FUTURE PANDEMICS

The Department of Health and Human Services (HHS) is launching a new public-private partnership for pandemic diagnostics, drugs, and vaccines that enables the government to fund new technology alongside private firms using venture capital practices.

Called the BARDA Ventures program, the Biomedical Advanced Research and Development Authority (BARDA) is partnering with the nonprofit organization Global Health Investment Corporation (GHIC) to accelerate development and commercialization of the new technologies. BARDA will spend a minimum of $50 million over 5 years, with potential for up to $500 million over 10 years. To bring in private capital, GHIC will launch a global health security fund with matching dollars from other investors. While BARDA has long collaborated with private companies, the Ventures program will be the first such partnership allowing direct linkage with the investment community.

If successful, profitable investments will compound to BARDA's benefit: As companies generate investment returns, proceeds from BARDA Ventures funding will be returned to GHIC for reinvestment in BARDA Ventures.

"Pathogens and health security threats constantly evolve and change. To effectively combat them," said BARDA Director Gary Disbrow, PhD. "We need new and innovative ways to tap into the most novel and impactful ideas in the entrepreneurial community. BARDA Ventures will rise to the challenge by engaging that community and leveraging both public and private funds to change the way we prepare for health security threats of the future."

BIDEN'S CMS CHIEF RENEWS FOCUS ON EXPANDING ACA

President Biden's pick for Centers for Medicare and Medicaid Services (CMS) administrator, Chiquita Brooks-LaSure, will oversee a host of consequential programs, including Medicare's influential coverage and payment policies, and the government's health insurance marketplace. She's a former policy official who guided the Affordable Care Act (ACA) through Congress, working for the House Ways and Means Committee. She's also served as the director of coverage policy for the agency.

Brooks-LaSure is already making clear how the administration will work to support and expand the ACA. She told Kaiser Health News that near the top of the list is dealing with the so-called Medicaid gap—a situation faced by people who cannot afford an ACA marketplace plan, but who live in one of the 21 states that has not expanded Medicaid to cover more low-income residents.

In addition, she'll face another problem that she hopes to turn into an opportunity: The Medicare trust fund will run out of money in 2026. Brooks-LaSure says she will work with Congress to fix the funding shortfall and also strengthen benefits.

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Bench Matters

Basics of Researching, Selecting, and Implementing New POCT Devices

By Kathleen David, MT (ASCP)

Technology is advancing by leaps and bounds, and manufacturers release new point-of-care testing (POCT) devices almost daily. As news of a novel technology spreads, requests from hospitals, provider offices, urgent care sites, and other locations increase. Likewise, when the public becomes aware of the possibilities of faster testing, people start to expect that when they visit their provider or any other healthcare site, they'll be able to get results and necessary treatment immediately. With emerging POCT devices, the days of hospital-based glucose and urine dipstick testing being the only tests available at patient bedside are in the past.

Researching New Technology

There are multiple ways to discover new POCT devices. Clinical laboratory-focused magazines such as *CLN*, organizations such as AACC and the American Society for Clinical Laboratory Science, and social media sites such as LinkedIn are a few sources that can provide information on the latest POC devices. It's important for clinical laboratorians to keep up with news about testing devices and kits that might be almost ready for launch, as well as potential new methodologies coming in the future.

Laboratorians must also keep abreast of the need for testing on the clinical side. Investigating a POCT device that won't answer a clinical question or support better patient outcomes does little good, and the very best technology or device won't be useful if no one wants to adopt it. For instance, you might have discovered the best device to detect malaria, but if that disease isn't endemic in your area, healthcare sites won't bring the device onboard.

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Is It Approved for Patient Testing?

Once I'm aware of a new device or test that I might want to implement, it's important to do as much research as possible, starting with looking into the device's FDA authorization status and CLIA designation. For use in a clinic, a device must be CLIA waived, while use in a hospital or urgent care site might require a moderate complexity designation. The COVID-19 pandemic added a new complication, which is that both laboratories and near-patient sites are using newly developed tests under FDA emergency use authorization (EUA). This EUA process has an impact on a test's CLIA designation. If a device is listed for use in a POC setting, it is considered waived; however, if the EUA doesn't specify that the test can be used at the point-of-care, then the laboratory must validate it as a moderate complexity test.

Things to Consider

Once I've decided that the device or test will meet a clinical need, and there are requests for use from clinics, there are multiple considerations to address. Will the device fit into the space available? Is there an electrical plug available, or can one be installed? Is the environment suited for the device (for example, does the device need to be in a "dirty" area)? Is a printer or other ancillary device needed? Does the device have barcode capability built in, or will a separate barcode device be needed? Ensuring all requirements for a device are met is important to having a beneficial outcome.

If It's Not Connected, I Can't Use It

If the device is going into a hospital, urgent care, or physician office that is part of a system, I already have POCT connectivity for other devices. Interfacing POCT devices has many benefits: automatic transmission of results to the patient chart, elimination of manual entry errors, lockout of those not trained to use the device, and the ability to track and trend results and quality control (QC). This is one of the first questions I ask of any vendor presenting a new device.

The gold standard is bidirectional connectivity, where information is sent from the device (results, QC data) as well as to the device (operator information, new reagent lot information). This allows me to monitor devices even when they're located hours away from the office. Many new device manufacturers are developing cloud connections for their devices to monitor results and QC. This is useful for those sites that do not have connectivity for their POCT devices.

What Are the Next Steps?

Once I've decided that the device is approved for use and that it meets clinical needs, I start on the implementation. The clinical validation requirements will be different depending on complexity—moderate complexity devices have more requirements before they can be used, while waived devices need only follow manufacturer's instructions.

For moderate complexity devices, accuracy, precision, reportable range or analytical measurement range (AMR), and patient normal reference range need to be validated. Many manufacturers make validation kits for their devices/kits, and often the same validation kit can be used for both accuracy as well as AMR.

Since I am interfacing with the device, I need to do an IT validation, too. I connect the device to my test systems and run test patients samples to ensure that results are being reported accurately from the device through the middleware to the laboratory information system or electronic medical record. I make sure that the reference ranges and units are correct, and that any comments needed have been transmitted along with the results.

Before taking the device live, all operators who will use the device to test patient samples need training. Often, the vendor can assist with this. If many people need training, I use a train-the-trainer model, where the POCT team trains a few key people in the unit or clinic, who then train the rest of the staff.

Go Live

Once all these steps are complete, the device is ready to use for patient testing. I recommend a celebration and thanking all who helped, including the POCT team, IT team, vendor, and the unit or clinic staff.

Kathleen David, MT (ASCP), is manager of point-of-care testing at TriCore Reference Laboratories in Albuquerque, New Mexico.
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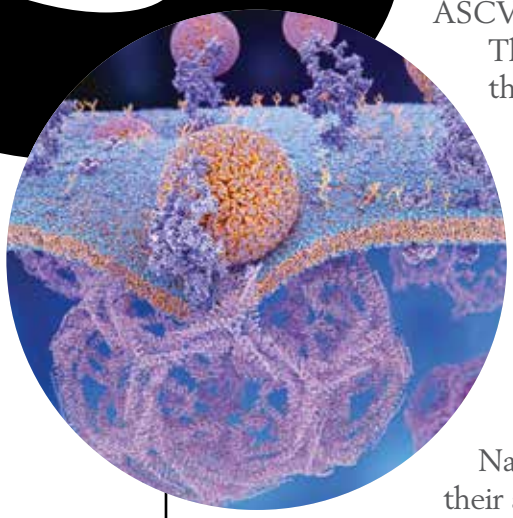
The Sample

Small Dense LDL Cholesterol May Help Predict Atherosclerotic Cardiovascular Disease Risk

A new equation for small dense low-density lipoprotein cholesterol (sdLDL-C), based on the standard lipid panel, may help improve atherosclerotic cardiovascular disease (ASCVD) risk stratification (Clin Chem 2021; doi.org/10.1093/clinchem/hvab048).

Because research has shown an association between sdLDL-C and ASCVD, the National Cholesterol Education Program has recognized sdLDL-C as an emerging risk factor. But its utility as an independent ASCVD risk factor has not been fully established. Measuring sdLDL-C also has been labor-intensive, and until recently, estimating it required additional tests. However, researchers have used a Food and Drug Administration-approved, fully automatic direct method for measuring sdLDL-C in recent studies that show it is a stronger risk factor for ASCVD than LDL-C.



The researchers describe a new sdLDL-C equation based only on results of the standard lipid panel, which includes total cholesterol, high density LDL-C, and triglycerides (TG). Based on observed relationships between different lipid concentrations and cholesterol on large buoyancy (lb) LDL-C and sdLDL-C, the equation uses two terms. The first (1.44 x LDL-C) accounts for individuals with high levels of LDL-C with more lbLDL-C. Larger LDL particles contain more cholesterol, the researchers note. The second term (0.14 X 1n(TG) x LDL-C) is an interaction term between LDL-C and TG. It accounts for a greater fraction of cholesterol in sdLDL than lbLDL as TG increases.

The researchers used sdLDL-C and lbLDL-C as risk enhancer tests in the National Heart and Nutrition Examination Survey (NHANES) and examined their association with ASCVD in the Multi-Ethnic Study of Atherosclerosis (MESA). The lbLDL-C equation was more accurate, with an R2 of 0.933 and slope of 0.94, compared to the sdLDL-C equation with an R2 of 0.745 and slope of 0.73. Using the 80th percentile concentration, 46 mg/dL, as a cutpoint, sdLDL-C identified in NHANES pointed to additional high risk patients not identified by other risk-enhancer tests based on TG, LDL-C, apolipoprotein B, and non-HDL-C. Univariate survival-curve analysis showed that estimated sdLDL-C was better than other risk-enhancer tests in predicting ASCVD events in MESA participants.

After multivariate adjustment for other known ASCVD risk factors, estimated sdLDL-C had the strongest association with ASCVD compared to other lipid parameters, including measurements of actual sdLDL-C.

NEW ASSAYS PROVIDE BETTER SPECIFICITY AND SELECTIVITY FOR ABETA1-42 AND ABETA1-40

Researchers have developed a highly specific blood test that could be used in studies of Alzheimer's disease therapies (Sci Rep 2021;11:9736). The assays measure full-length Abeta1-42 and Abeta1-40 peptides in amyloid plaques found in the brains of people with Alzheimer's disease. These peptides are used to monitor treatment response and are usually measured in cerebrospinal fluid or by positron emission tomography. Both tests are invasive and expensive.

Researchers aimed to validate the assays, called ready-to-use Amyblood tests, and explore their clinical value in a cohort of 43 patients and 42 controls who had also had cerebrospinal fluid (CSF) testing via the commercially available Quanterix Simoa trilex kit and Euroimmun ELISA assays. The researchers compared linearity and intra- and inter-assay percent coefficient of variation (%CV) among the three assays.

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Amyblood, Quanterix triplex, and ELISA showed similar linearity (96%–122%) and intra-assay %CV of 3.1% or less. Using Amyblood, the researchers measured a minor nonspecific signal of +2.4 pg/mL Abeta1-42 when incubated with 60 pg/mL Abeta1-40. Researchers saw a substantial nonspecific signal of +24.7 pg/mL Abetax-42 when measuring 40 pg/mL Abeta3-42 with the Quanterix triplex. Selectivity for Abeta1-42 at physiological Abeta1-42 and Abeta1-40 concentrations was 125% for Amyblood and 163% for Quanterix. Amyblood and Quanterix ratios and ELISA Abeta1-42 concentration differentiated samples from Alzheimer's disease patients and controls.

These validation data show that the Amyblood assays are suitable for measuring 1-42 and 1-40 amyloid isoforms in blood, the researchers wrote.

A next step in developing Amyblood assays is leveraging the multiplexing possibilities of Simoa technology to simultaneously detect multiple biomarkers and to reflect different aspects of Alzheimer's disease within one assay run. These measures would save time and resources, the researchers said.

TECHNIQUE MAY IMPROVE NEXT-GENERATION SEQUENCING AND INCREASE ITS USE

A new technology helps overcome the inefficiency and high error rates that have limited the clinical application of next-generation sequencing (NGS) techniques, according to a recent paper (Nat Biotechnol 2021; doi.org/10.1038/s41587-021-00900-z).

Despite improved baseline error rates in NGS technology, identifying and quantifying low-frequency mutations remains challenging. Meanwhile, NGS is not very useful for detecting rare mutations, especially in liquid biopsies. In response, researchers developed what they call the Safer Sequencing System (SaferSeqS). SaferSeqS allows efficient tagging of both DNA strands in each original molecule present in an individual's blood sample with a unique barcode. The double-stranded DNA molecule's structural redundancy allows the researchers to distinguish real mutations from errors, an approach called duplex sequencing. If both strands of a DNA molecule contain the same mutation, it is far more likely that the test has found a real mutation and not an error.

The researchers, who described SaferSeqS in a previously published study, built upon their technique by constructing a library via in situ generation of double-stranded molecular bar codes, and by adding target enrichment via anchored polymerase chain reaction (PCR) and in silico reconstruction of template molecules.

The researchers used this enhanced SafeSeqS assay to retest 74 blood samples from cancer patients with false negative results on CancerSEEK, a single multiplex PCR blood test that screens for eight common types of cancer. Using SaferSeqS, the researchers found previously undetectable mutations in 58% of the newly tested samples.

On the basis of both the current and previously published study, the researchers concluded that SaferSeqS reduces the error rate of existing mutation-detection approaches more than 100-fold. SaferSeqS is highly scalable, cost-effective, and amenable to high-throughput automation, the researchers added.

Modern

When developing reference intervals, clinical laboratories must consider what data sources and statistical methods to use, among other factors.

BY DUSTIN BUNCH, PHD, DABCC

Historically, clinical laboratories have referred to reference intervals (RI) as normal ranges and developed them using samples from a "normal or healthy" population. This approach to RI quickly encounters a stumbling block, however. Namely: How do we define who is normal?

In the modern age, we would define normal as biochemically normal, but this is a weak definition, as it uses circular logic.

Recognizing this shortcoming, the laboratory community adopted the term RI in place of normal range, and in 1987 the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) released a detailed definition for RI, which states that an RI is "the interval between and including the reference limit" created from a reference population (*1*). This more inclusive definition allows for the determination of an RI in a reference population composed of individuals who are not healthy, such as those with chronic conditions that seriously affect the RI, or patients who have a chronic elevation that could obscure an acute event. Since the shift from normal ranges to RI

Reference Intervals

occurred, different types of RI—known as continuous, common, and personalized—have also emerged, further fine-tuning the concept of RI as well as labs' ability to identify pathological test results.

RI take into consideration patient variables that clinicians are aware of, such as age and sex, as well as laboratory variables that clinicians are unlikely to know, such as which vendor and assay is used in a particular lab. RI play a critical role in patient care by enabling clinicians to interpret laboratory data accurately and to link that data to clinical action. Without the accompanying RI, a lab result is just a number. It is therefore essential for clinical laboratories to establish RI that are accurate and appropriate for their local patient populations.

To facilitate this, several professional organizations have published recommendations for performing RI studies, including the Clinical and Laboratory Standards Institute (CLSI) and IFCC. According to CLSI, RI can be determined through two processes: direct methods, which use patient samples and are considered the preferred approach, and indirect methods, which use data from the laboratory informatics system (LIS) or the electronic health record (EHR) (*2*).

DIRECT REFERENCE INTERVALS

Current guidance recommends developing RI that are both specific to the population that a clinical laboratory serves and to the assay that the lab is using. To do this with the direct method, labs should use samples from a "healthy" patient population. These samples can come from patients who were prospectively recruited, or they can be banked and/or residual patient samples. Labs can confirm the health status of RI study participants with direct questionnaires in the case of prospective recruitment and/or through chart review. The goal should be to collect a minimum of 120 data

Indirect methods require robust statistical methods to separate normal results from the pathological.

points for each partition, which is necessary for determining the 90% confidence interval around an RI (*2*). Partitions may include sex, age, Tanner stage, and menstrual cycle day, to name a few.

There are three common roadblocks to determining direct RI that labs typically encounter: Not being able to recruit enough people to fill each partition, the recruitment population not reflecting the population served by the clinical laboratory, and preanalytical factors failing to recapitulate those found in standard operations (*2*, *3*).

The first and second issues tend to be related to advertisement. Often the clinical laboratory advertises for RI study recruits within the confines of the hospital. This limits the possible study population to those who are on campus, however, and those on campus have a high probability of not fitting the inclusion criteria. They also might not reflect the whole population serviced by the clinical laboratory, as the lab might receive a large proportion of samples from ancillary locations in outlying areas. In fact, in my experience with performing RI recruitment, most responders tend to be related to the laboratory, which is a population that is usually very different from the service population in age, sex, and education levels. For pediatric populations, there is an additional barrier to recruitment in that the lab is required to get the consent of both the participating minor and their guardian, while for adults, only the consent of the individual participant is needed.

Since recruitment is so difficult, the clinical laboratory often wants to draw various blood tube types during the one encounter with a study participant. The personnel used for this encounter tend to be well-trained in blood draws and the correct order of blood tube draw. In addition, the samples are processed in the most ideal conditions (e.g., at an optimal temperature, time, etc.). In my experience, this creates the third major roadblock mentioned above and can lead to a deviation between the measured RI based on the collected population and routine samples.

As an example, the samples used for our lab's chromium RI determination were collected as the last tube during a seven-tube collection, allowing the chromium present on stainless-steel needles to wash out adequately. This yielded a lower RI than was experienced when a single tube was collected for routine chromium determination.

With these inherent disadvantages, why is this the preferred method for establishing RI? The major advantage of this method is the low probability of pathological samples being introduced into the RI data, which in turn means that the statistics required to calculate the RI are relatively straightforward and simple to perform.

INDIRECT REFERENCE INTERVALS

By using data from the LIS or EHR, laboratories performing indirect RI determinations can deal with many of the disadvantages of the direct method. Recruitment is simpler with the indirect method because the lab is starting with all available data. In fact, this method can make data available that would otherwise be uncollectable if an additional blood collection were required, especially in the pediatric population. Sample data inherently reflects the laboratory service population, and preanalytical factors represent standard operation. In addition, partition groups can be easier to fill, with some partitions having thousands of data points, though others might still be more limited in scope.

However, the indirect method does come with its own set of drawbacks. A major issue is that data sets from the LIS and EHR include intermixed pathological and normal results. To correct this, indirect methods require robust statistical methods to separate normal results from the pathological. Furthermore, with the indirect method, the time and effort used for sample collection with the direct method is shifted toward elucidating the appropriate exclusion criteria. The exclusion criteria need to incorporate clinical as well as institutional knowledge with considerations that include the source of data, how the assay is used, the instrument, and assay changes. Since the RI should be specific to the assay the lab uses, care should be taken to exclude data from previous assays.

The lab must also decide how much of the data to use—for instance, will the lab use all the data available or out patient data only? Inpatient data typically contains more pathological data than outpatient data, but specialty clinics and practices need to be considered, too. Another factor to consider when deciding what data and which system to use is the type of partition. For example, the LIS is typically not going to contain data on Tanner stages or menstrual cycle day. The EHR is more likely to house these data, but they are often not in discrete fields and will require more sophisticated techniques to extract.

One final consideration is that if an assay is used as a confirmatory test, then it probably isn't a good target for the indirect method because there is a high suspicion of a pathological process. This will reduce the healthy population signal and cause distortions even in robust statistical algorithms.

Even with all these caveats, the indirect method is useful for determining RI for many analytes in the clinical laboratory. A more detailed comparison of the pros and cons of the direct and indirect methods is available in a *Clinical Chemistry and Laboratory Medicine* review by Jones et al. (*4*).

STATISTICS FOR REFERENCE INTERVALS

CLSI's guidance has recommendations on the statistical methods labs should use in RI studies. These recommendations are mainly targeted toward data collected via direct rather than indirect methods, but CLSI also touches on the robust statistical methodologies recommended for indirect methods (*3*, *4*). For direct methods, parametric or transformed parametric statistical methods are recommended, with the caveat that labs should limit their use to analytes that demonstrate a Gaussian probability distribution. The preferred statistical method for determining the 2.5 and 97.5 percentiles of an RI is a simple nonparametric regression.

As for robust statistical methods, IFCC recommends that more research be done on these, and provides guidance on the data that should be collected for a complete

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BFR0001-3010-01

research analysis (*4*). These robust statistical methods can be achieved through consultation of biostatisticians, specialized statistical software, and/or statistical programming languages such as R (*5*, *6*).

There has been a surge in articles on indirect RI over the past 3 years, and these publications often supply the program code or application for the statistical method they used. Statistical methods for indirect RI are also frequently available in online code repositories like Github or on institutional websites. Thanks to this open-source code, laboratories across the world can determine RI using appropriate statistical methods with relative ease compared to previous years. Additionally, the availability of code for different statistical methods enables laboratorians with limited programming experience to compare them.

Labs should strive to gain a thorough understanding of any statistical method they use and of the assumption that method employs. Consultation with a statistician can also be useful when working with a new statistical method for the first time.

THE FUTURE OF RI

The three biggest concepts that are shaking up the RI world today are continuous, common, and personalized RI. Continuous RI do away with partitions and represent an incremental change in how RI have been determined historically. Currently, partitions create an artificial break in RI. If an analyte has a partition from 8–9 years old and from 10–11 years old, then the day a child turns 10, they move outside the RI for 8–9-year-olds even though the child hasn't actually changed much. Continuous RI adjust for this by using an equation that automatically accounts for the true age of the child. The biggest hurdle to implementing this type of RI is in the systems used for storing the data, the LIS and EHR. These systems only accept fixed values for RI rather than the dynamic intervals that would be required with continuous RI.

The next big concept shift is common RI. Common RI require three conditions to be met. First, there must be a reference method for the analyte in question. Secondly, assays must be traceable to the reference method. Finally, a multicenter RI study should be conducted with a common protocol. IFCC has performed studies such as this on a global scale for certain analytes with acceptable results (*7*).

The last and possibly most interesting new concept in the world of RI is the personalized RI. With standard RI, it's possible for a patient's analyte to traverse a large interval without being considered abnormal and getting flagged within the EHR. Personalized RI are therefore needed because there is sometimes less inherent variation in analyte concentration within individuals than in the general population from which standard RI are derived. Personalized RI create a smaller reference range for the individual than the population, which allows the EHR to flag and inform clinicians about subtle changes that may indicate a move toward a pathological state at an earlier stage of disease development (*8*).

CONCLUSION

With the advent of new RI concepts and larger datasets, the clinical laboratory community is moving into a new age for RI. Large multicenter RI studies are now available due to advances in computing power, greater adoption of EHRs, and newer robust statistical methods that can adapt to variations in datasets. As RI continue to evolve, however, their central tenet of supplying vital information to clinicians will not change.

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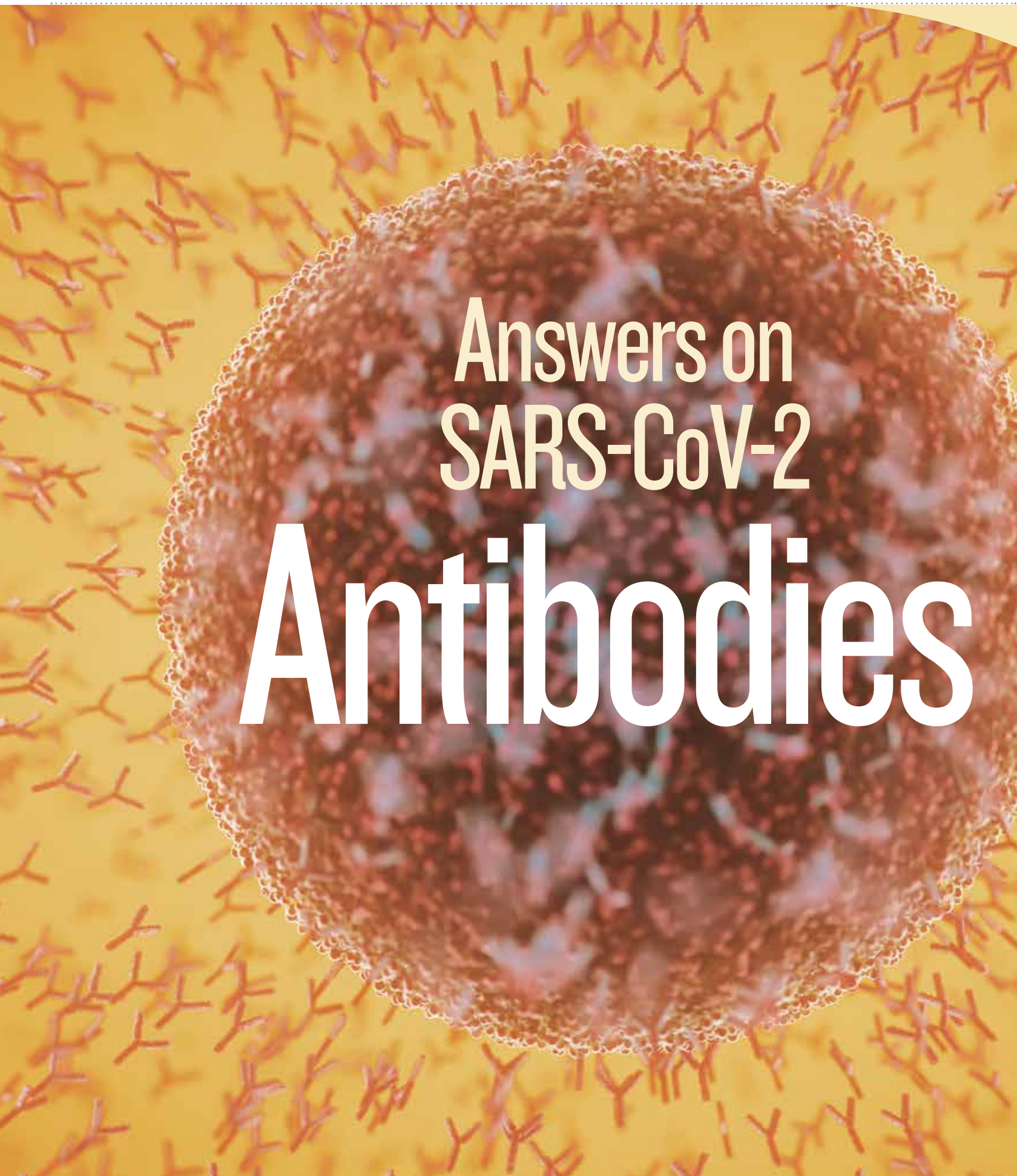
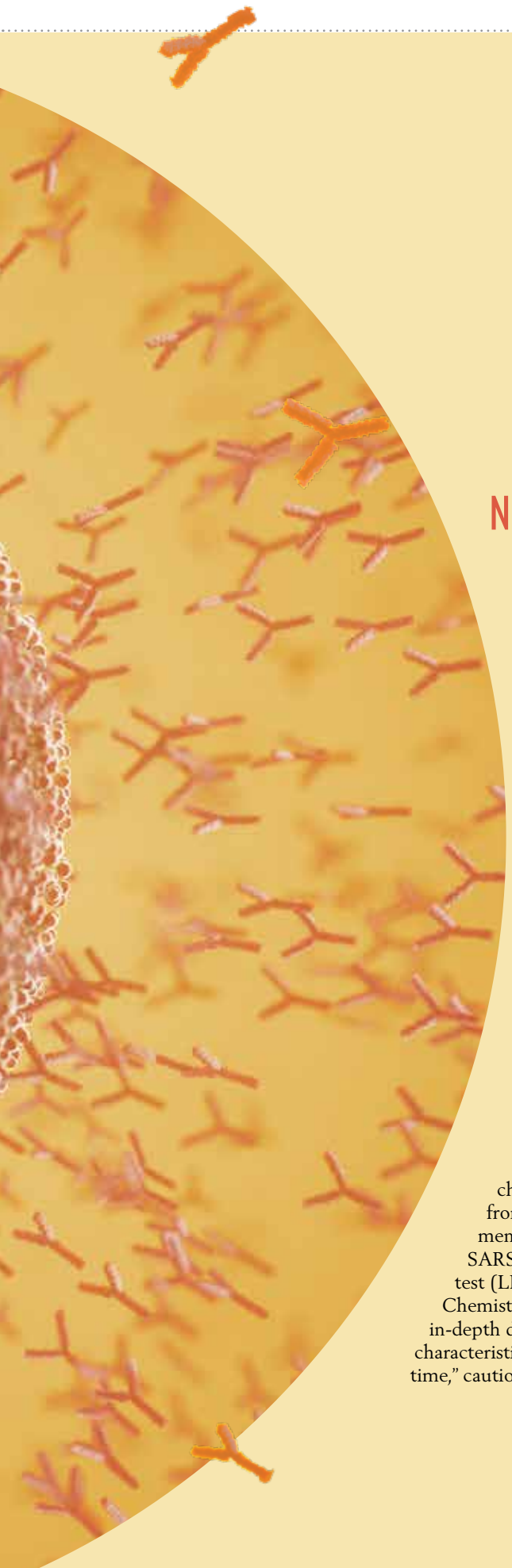


Answers on SARS-CoV-2 Antibodies



New guidance from AACC offers an anchor for clinical laboratorians amid constant questions and emerging data about serologic testing.

BY KAREN BLUM

As the COVID-19 pandemic evolved over the past year, so too did available antibody tests for SARS-CoV-2 and clinicians' understanding of how to use them. Throughout this time, AACC played an active role in helping the field to navigate challenges, forming a COVID-19 task force last spring to tackle ever-increasing questions on the utilities of serology testing, said Y. Victoria Zhang, PhD, MBA, vice chair for clinical enterprise strategy and director of clinical chemistry for the University of Rochester Medical Center, in New York. The group published initial recommendations in 2020 about the use and limitations of serology testing but felt there was a need for a more in-depth guideline.

This spring, the expert panel—including professionals from clinical chemistry, microbiology, and immunology laboratories, as well as specialists from in vitro diagnostics, industry, and regulatory agencies—released a document of practical recommendations for implementing and interpreting evolving SARS-CoV-2 emergency use authorization (EUA) and laboratory-developed test (LDT) serologic testing. The recommendations were published in Clinical Chemistry (Clin Chem 2021; doi:10.1093/clinchem/hvab051), with a longer, more in-depth document available on AACC's website, www.aacc.org. "The performance characteristics of these assays and their clinical utility continue to be defined in real-time," cautioned Zhang, the publication's lead author.

The document provides information about serologic assay design, antibody classes, and the kinetics of the humoral immune response, as well as verification and validation of both EUA and LDTs. It also discusses four indications for serologic testing: supporting the diagnosis of COVID-19 and related sequelae (e.g., multisystem inflammatory syndrome in children); identifying potential convalescent plasma donors and manufacturing of convalescent plasma; epidemiologic and seroprevalence studies; and vaccine efficacy studies.

"Though various organizations have published guidelines on clinical utilities of serology testing, ours is the first and most comprehensive document we know so far for the implementation of the tests, particularly EUA tests, in clinical laboratories," Zhang said. "We wanted this guideline to be a reference for our own labs and trainees for implementing EUA and LDT serology tests in-house. It is our intention to provide a full reference for laboratory professionals and healthcare workers to appropriately implement these assays in the clinical laboratory and interpret the results to serve their patient needs during this pandemic."

EVALUATING SARS-COV-2 SEROLOGY ASSAYS

The team went to work with the goal of providing better guidance for clinical laboratories on what to consider when bringing in a serologic test and how to validate and implement it, said coauthor Elitza Theel, PhD, director of the infectious diseases serology laboratory at Mayo Clinic and a professor of laboratory medicine and pathology. This included "everything from how serologic testing should be used, to how many samples to consider for accuracy studies, and what to think about for specificity studies, etc."

They also designed the document to serve as a useful resource for future disease outbreaks. "This probably won't be the last pandemic. There was Zika virus and dengue, so we designed this as a broader guidance for things to consider when implementing serologic assays for emerging pathogens in the future," Theel said.

Clinical laboratories can find multiple uses for the document, Zhang noted. It could be a reference guide for understanding the host immune response to SARS-CoV-2, antibody kinetics, and available EUA assays; or it could help laboratorians understand the clinical utilities and limitations of serology testing and gain insights into the nuances in implementing EUA or LDT serology testing.

Importantly, the authors say, serology tests are not recommended for diagnostic purposes for SARS-CoV-2 infection. But they could identify different types of antibodies, such as IgG and IgM, and antibodies for S and N proteins or neutralizing antibodies. There are a lot of vaccine-preventable diseases for which laboratories perform serologic testing, Theel said, but the key is first identifying a minimum antibody threshold or correlate of protective immunity for those pathogens.

"I can see serologic testing playing a much more prominent role for COVID-19, maybe to guide potential future boosters or revaccination policies," she said. "But until that happens, the role of serologic testing is going to be pretty minimal."

"I can see serologic testing playing a much more prominent role for COVID-19, maybe to guide potential future boosters or revaccination policies. But until that happens, the role of serologic testing is going to be pretty minimal."
—Elitza Theel, PhD

HOW TO HANDLE QUESTIONS ON UTILITY AND INTERPRETATION

The guidance is timely. Clinicians continue to look to laboratories for answers, Theel said, most commonly now questioning why their vaccinated patient tested antibody-negative, and what that means. "We start by saying, 'You don't need to test,' and 'Did you order the right test?' because with an assay ordered after vaccination, a patient's result is going to be negative unless they were previously infected," she said. "We also talk about whether [the patient is] immunosuppressed, because we are seeing that immunosuppressed individuals are not as reactive."

Clinicians also are using antibody testing to see if people have been infected without knowing or to confirm the course of disease for people that are known to be positive or to have been positive, said Robert Boorstein, MD, PhD, medical director for Lenco Diagnostic Laboratories in New York City, a large reference laboratory.

"One has reason to be somewhat optimistic that the number of new infections is going to continue to decrease in the U.S., so the need for monitoring current

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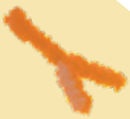
infection presumably is going to go down as well," Boorstein said. "As more people become vaccinated, the utility will largely be in helping determine how long vaccination lasts. The question is whether that information will be useful in aggregate, or for individual patients."



"There's not a lot that we can actually do with confidence based on a test result, whether it's negative or positive."
—Debra Poutsiaka

A major push in this area is determining the immune correlate, said Debra Poutsiaka, MD, PhD, an infectious disease physician and vice chief for clinical affairs for the Division of Geographic Medicine and Infectious Diseases at Tufts Medical Center, in Boston, who agrees with Theel. Serologic tests for now don't indicate whether a person is or is not protected from getting symptomatic or severe COVID-19, she said, making their clinical utility in some cases "essentially nil."

"There's not a lot that we can actually do with confidence based on a test result, whether it's negative or positive," Poutsiaka said, noting that her infectious disease colleagues rarely send samples for antibody testing for COVID-19. "That's mainly because there's no clinical action that should be dictated by the results of that test, because there is no data to back up a clinical action."

Multiple arms of the immune system can combat COVID-19, Poutsiaka added, and antibody testing is not going to identify some of these other means of protection. For example, there is an arm of the immune system called cellular immunity, which is separate from antibody-mediated immunity.

"Multiple studies have demonstrated that vaccines and natural infection generate cellular immunity against COVID-19, but this will not be measured by antibody tests," she said. "Right now, we're not close to having a global assessment of immune protection from COVID-19, so I think studies will be moving in that direction."

RESEARCH NEEDED TO STANDARDIZE ASSAYS, LINK RESULTS TO PROTECTION

As vaccination rates climb in the U.S., there is some interest in

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Hct

Hb

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K

Cl

TCO_2

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iMg

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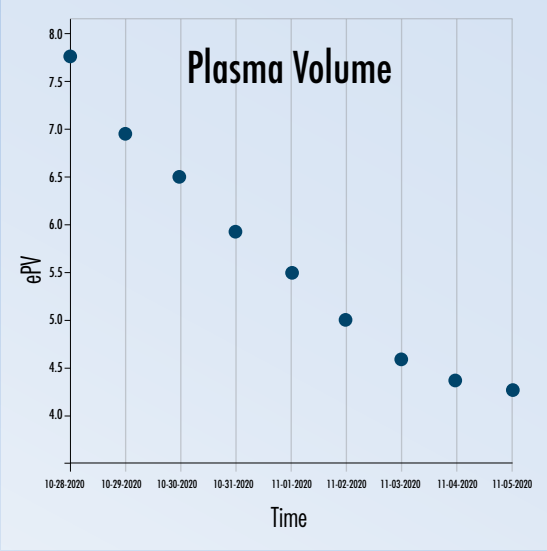

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1. Kalantari, I et al. Assessment of intravascular volume status and volume responsiveness in critically ill patients. Kidney Int, 2013.83(6): 1017-28.
2. Kobayashi, M et al. Estimated plasma volume status in heart failure: clinical implications and future directions. Clinical Research in Cardiology. Published online before print 6 Jan 2021.

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studying antibodies to the N protein, Boorstein said, and being able to distinguish between people who have been infected and those who have been vaccinated. Theel and Poutsiaka said there also is a need for standardization among assays—across institutions or even across countries—because it is difficult to know if antibodies found in one laboratory will translate to a patient at another location. A test, methodology, and patient population can differ among locations, Poutsiaka noted.

"Clinical tests we send out are essentially qualitative, and some are semiquantitative, but basically it's a yes or no," she said. "It's hard for us to know how yes is a yes, how positive is that yes, how high is the antibody level, and even if we knew that, we don't know yet if that translates into protection. That's the critical link—to get an idea of whether or not someone is protected against COVID-19 based on their antibody tests. That absolutely doesn't exist right now."

One recent study (Nat Med 2021; doi:10/1038/s41591-021-01377-8) pulled data on observed protection from seven current vaccines and convalescent cohorts and did some statistical modeling to try to determine how antibody levels would translate to protection against symptomatic and severe SARS-CoV-2 infection, Poutsiaka said. That's the type of work that will be "very valuable for providing a framework for how to standardize or think about measuring antibody levels, and how to figure out what's protective and what's not," she said.

Meanwhile, Zhang said, tests continue to evolve from qualitative to semiquantitative to quantitative: "The more information we can get from one test, the better we will understand the science, and understand the clinical utilities of serology testing in serving patient needs."

"Clinical tests we send out are essentially qualitative, and some are semi-quantitative, but basically it's a yes or no," she said.

Karen Blum is a freelance medical and science writer who lives in Owings Mills, Maryland.
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Predicting Preterm Birth

Clinical laboratorians must collaborate closely with obstetricians to ensure optimal utilization of current assays.

BY DEBORAH LEVENSON

Preterm birth (PTB) is the second most common cause of infant death in the United States and a major cause of costly—and sometimes lifelong—health and social problems. As a result, clinicians and laboratorians have a keen interest in detecting women at risk. A new AACC guideline does not recommend routinely measuring interleukin 6 (IL-6), placental alpha microglobulin 1 (PAMG-1), or fetal fibronectin (fFN) in pregnant women with symptoms consistent with preterm delivery. These biomarkers have low positive predictive values (PPVs) and provide limited utility in diagnostic algorithms most commonly used in the U.S., according to the guidance.

Despite the guideline's negative stance on the markers' routine use, its authors say labs should not issue unilateral decrees about these tests. "Decisions should be made with the obstetricians in a collaborative effort," said senior author Robert D. Nerenz, PhD, DABCC, assistant director, clinical chemistry and assistant professor of pathology and laboratory medicine at the Geisel School of Medicine and Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire.

PRETERM BIRTH: A NATIONAL PROBLEM

The precise mechanisms involved in PTB are not fully known, but proposed etiologies leading to PTB include fetal stress, inflammation, decidual hemorrhage, and pathological uterine distension, according to the guideline. Each of the tests measures a single protein associated with a specific PTB etiology: IL-6 for infection and inflammation, fFN for degradation of the extracellular matrix, and PAMG-1 for presence of amniotic fluid.

PTB can lead to low birth weight, respiratory distress, underdeveloped organs, neurodevelopmental disabilities, cognitive impairment, visual and hearing impairments, developmental coordination disorders, and behavioral and emotional difficulties.

U.S. clinicians may find it challenging to stop fFN testing because some guidelines recommend it.

After a period of declining PTBs, they accounted for 10% of all 2018 U.S. births and disproportionately affected racial and ethnic minorities, especially African Americans.

Some treatments may improve outcomes for babies of patients who present with signs and symptoms of premature labor. "However, 90% of these patients won't deliver preterm. It's useful to have tools to see who's genuinely at risk," said Phillip R. Bennett, MD, PhD, a PTB biomarker researcher and professor of obstetrics and gynecology at Queen Charlotte and Hammersmith Hospitals in London. He added, however, that some therapies may be harmful when symptoms are not related to PTB.

RECOMMENDATIONS ON PRETERM BIRTH BIOMARKERS

The guidelines say biomarkers are unlikely to provide much clinical value in populations with a pretest probability of less than 5%. "In a population with a low pretest probability, these markers don't have much clinical utility," Nerenz said. "While the three markers do have high negative predictive values, a negative result doesn't substantially change the diagnostic uncertainty, as most women in the population being evaluated will not deliver prematurely. To distinguish the small proportion of women who will give birth prematurely from a larger pool with similar signs and symptoms who will not, a test with a high PPV is needed."

Limiting biomarker testing to only high-risk women identified on the basis of cervical length or other characteristics will increase the pretest probability in the tested population and improve PPV, Nerenz added.

PAMG-1 may be useful in some cases. In populations with a pretest probability of 5%, a positive PAMG-1 result increases the post-test probability to about 20%–30% while a negative result leaves the post-test probability essentially unchanged, the guideline notes. However, PAMG-1 does not provide sufficient assurance to either rule in or rule out PTB within 7 days. In populations with a pretest probability of 20%–25%, however, a positive PAMG-1 result substantially increases the post-test probability to about 75%. In this patient population, a positive PAMG-1 result may identify women likely to deliver within 7 days.

fFN research in populations with a pretest probability of 3% shows a positive fFN result modestly increases the post-test probability to about 15%, while a negative result does not substantially reduce the post-test probability. Studies of fFN testing show it does not consistently improve clinical outcomes, as measured by reduced hospitalization rates, rates of PTB, or healthcare costs. fFN should not be measured in asymptomatic women due to its low specificity and PPV, according to the guideline.

Bennett noted a movement toward quantifying fFN values to give better predictive statistics and guide practice. The guideline says this tactic is promising but calls for studies to further demonstrate improved clinical outcomes.

In study populations with a pretest probability of 2%, a positive IL-6 result modestly increases the post-test probability to about 15%, while a negative result does not substantially reduce the post-test probability. IL-6 and fFN have similar diagnostic performance characteristics. IL-6 does not provide sufficient assurance to either rule in or rule out PTB within 7 days, the guideline says.

Some researchers have proposed using multimarker panels to more accurately predict women who will deliver prematurely. But multimarker panels evaluated to date do not improve diagnostic performance relative to single biomarkers, the guideline says.

TALKING TO CLINICIANS

Some U.S. clinicians may find it challenging to stop fFN testing because some guidelines recommend it. Additionally, malpractice is a consideration in obstetrics and gynecology practice, said guideline co-author Joely Straseski, PhD, MT(ASCP), DABCC, medical director of endocrinology and automatic core laboratories at ARUP and associate professor at the University of Utah School of Medicine in Salt Lake City.

AACC's new PTB testing guideline exists alongside others from the American College of Obstetricians and Gynecologists (ACOG), Society for Maternal-Fetal Medicine (SMFM), and the United Kingdom's National Institute for Health and Care Excellence (NICE). ACOG does not recommend routine use of fFN to stratify risk for preterm delivery, while SMFM recommends fFN for women presenting with symptoms of preterm labor prior to 34 weeks and transvaginal ultrasound demonstrating cervical length between 20–29 mm. NICE recommends testing fFN if a cervical length measure is not available or not acceptable.

Straseski sees the guideline as a conversation-starter for labs and obstetricians. The guideline can help clinicians understand that the three biomarkers "are not helpful for all women with symptoms of premature birth," plus the specific situations where they may be useful, she said.

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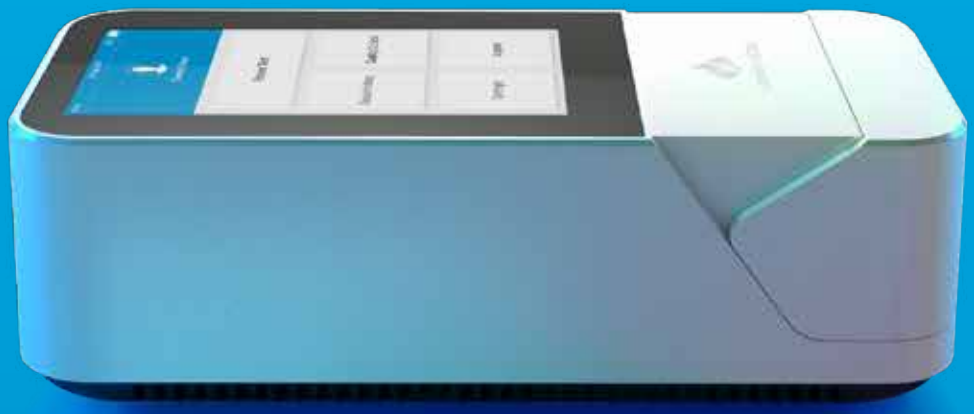

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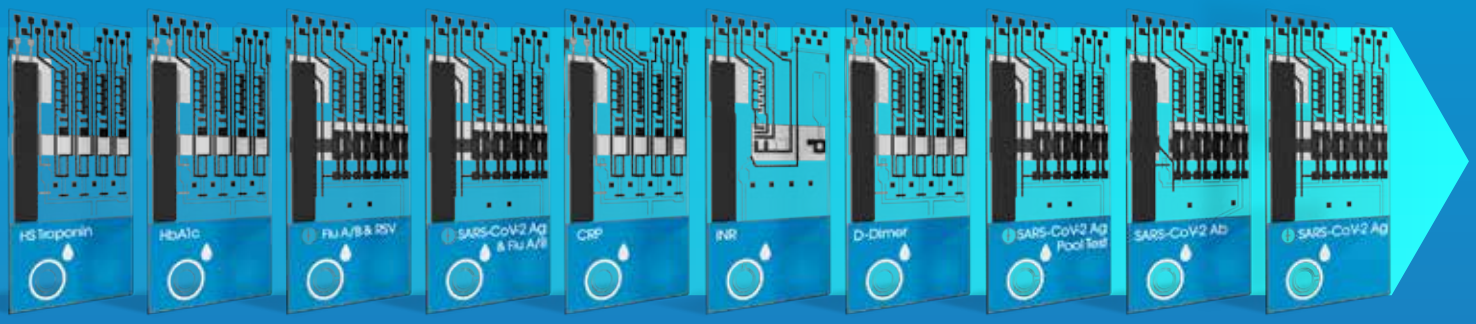

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Added Nerenz, "The guidance's goal is to make clinicians think critically about why they order these tests. Do they help make better clinical decisions? Are patient outcomes better?" He noted that his institution has dropped fFN.

Penn State Hershey Medical Center also stopped offering fFN after a test utilization review revealed that volume dropped to the point where the lab ran just two fFN tests in 2020, said Yusheng Zhu, PhD, DABCC, professor of pathology, laboratory medicine, and pharmacology and medical director of clinical chemistry and the automated testing laboratory at Penn State Hershey, where he also chairs the laboratory utilization committee.

In a discussion with his hospital's departments of obstetrics and gynecology and family and community medicine, Zhu shared a literature review that revealed a growing consensus about fFN's limited utility. He suggests that other clinical laboratorians focus similar discussions with clinicians on prevalence of PTB in an institution's patient population and clinician practice. Some laboratorians and clinicians may need to do their own research to determine the utility of preterm labor biomarkers in their institutions, he added.

LOOKING TO THE FUTURE

"We do need better biomarkers with higher PPVs," Nerenz noted. The search continues for other potential biomarkers to determine risk at various stages of pregnancy.

For example, Bennett studies first trimester circulating microRNA to predict PTB and cervical shortening in women at risk of preterm delivery. The hope is that early identification of PTB risk allows time to deliver outcome-modifying interventions.

Zhu pointed to other research examining multiplex biomarkers based on proteomics, metabolomics, and exosomics. Preliminary data on one such panel of novel protein markers in cervicovaginal fluid samples collected from asymptomatic women at gestational weeks 16–24 had sensitivity and specificity of 91% and 78%, respectively (Am J Obstet Gynecol MFM 2020;2:100084). Another study showed that cervicovaginal fluid microbiota metabolic profiling identified eight vaginal microbiota metabolites to predict preterm labor (Metabolites 2020;10:349). Other research focuses on proteins in plasma exosome.

Time will tell which of these and other potential biomarkers will be useful. "The biomarkers with the best potential have the better PPVs. That's the key, across the board," Straseski said.

Deborah Levenson is a freelance writer in College Park, Maryland.
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After a tumultuous year for healthcare, the laboratory medicine community is eager to come together at the AACC Annual Scientific Meeting & Clinical Lab Expo this September in Atlanta.

Whether it's in a workplace, a profession, or even the wider circles of local, national, and global affairs, there's probably never been a greater focus on the need for leadership. The COVID-19 pandemic has tested every person's—and every institution's—ability to deal with change, draw on their creative powers to solve problems, and understand the best way to strive for the common good.

By every measure, the clinical laboratory community has passed this test. By the time this issue of *CLN* goes to print, laboratories in the U.S. will have passed the 500 million mark for number of SARS-CoV-2 tests performed. This number itself is impressive. Even more remarkable is the fact that laboratories and their partners in the in vitro diagnostics industry stood up this testing from scratch and in the face of heretofore unimaginable barriers: congested supply chains, regulatory reversals and ambiguities, a decentralized healthcare system, and shortages of everything from swabs, tubes, and reagents to personnel.

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AACC is offering a unique opportunity for attendees to participate personally in important SARS-CoV-2 research.

While the scientific community continues to devote great efforts to understanding all aspects of SARS-CoV-2, a key question that has not yet been answered is how long the currently available vaccines will protect against the virus.

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Disclaimer: AACC collected 60 mL of blood from volunteer donors attending the AACC Annual Meeting in Atlanta, GA in order to establish the 99th percentile for cardiac troponin in a healthy population. After collection, the blood was processed on site, divided into equal sample sizes and then transported to CDC for storage at -80°C. Samples were de-identified and no test results will be provided to donors. Sets of donor samples are being offered to IVD manufacturers of cardiac troponin assays for purchase. AACC has undertaken this activity as part of its mission to further scientific research. THE DONOR SAMPLES ARE PROVIDED "AS IS". AACC DISCLAIMS ALL WARRANTIES INCLUDING IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE.

As the U.S. and some other countries reopen their economies on the strength of highly effective vaccines, those fortunate enough to live in these parts of the world have begun to look toward a post-pandemic world.

This might be the next big test of clinical laboratory professionals: How will you continue to lead and shape this new healthcare landscape—or will that be left to others? Even though the pandemic, and the changes it's wrought, are far from over, the opportunity to carry the mantle of leadership in our institutions and professions could close sooner than we think.

Since unleashing the technology, know-how, and professional grit to meet the testing needs during the pandemic, the broad field of diagnostics has found itself in the spotlight. Now is the time to look deeply at the potential for this new visibility—and its attendant collaborations, relationships, and credibility—to forge a widening circle of impact. Within and without the profession, people are ready for less transactional and more creative connections that will make a difference in global health.

This September in Atlanta, come to the meeting ready to share your own story of innovation and resilience, to hear those of others, and to find a fresh vision for the field of laboratory medicine. Your colleagues—whether they identify as academics, clinical laboratory scientists, researchers, or business professionals—are ready too.

THEMES IN FOCUS

Need to focus on a specific topic at the 2021 AACC Annual Scientific Meeting? Chart a course based on your needs and interests first, then add other sessions that might be outside your comfort zone to refresh your skills. The following pathways highlight select sessions in core and emerging areas of laboratory medicine.

COVID-19: Transitions, Lessons, and Data

The Role of Journalism in the Analysis and Dissemination of Pandemic-Related Data Through the Lens of the COVID Tracking Project

Understanding Adaptive Immune Response to SARS-CoV-2: Applications in Clinical Practice, Public Health, and Vaccine Studies

COVID-19: Vaccines and the Tango of Viral Evolution and Host Immune Responses

Implementation of Serological and Molecular Tools for COVID-19 Patient Management

Curating and Documenting Research During Chaos: Lessons from COVID-19 and Beyond

What COVID-19 Testing Hath Wrought: A Forecast for the Future of Virology Testing

Data Analytics and AI

Machine Learning Analysis of Laboratory Test Results Supports Clinical Decisionmaking and Patient Care

Artificial Intelligence in the Clinic: Strengths, Weaknesses, and Opportunities

Doing More with R: Create Your Own Automated Reports and Dashboards

Mind the App: Application Development as a Solution to Unmet Needs in Laboratory Workflows

How Artificial Intelligence and Machine Learning Will Help with Patient Diagnosis: Application to Autoimmune Testing

Data Aggregation and Integration in Laboratory Medicine: How to Build Prediction Models and Learn from Multinstitutional Data

Laboratory Leadership and Stewardship

Navigating Your Lab Through Change: Leadership, Innovation, and Crisis Management | SYCL Workshop

Women in Laboratory Medicine: A Panel Discussion on Diversity and Inclusion

Bringing Laboratory Testing Closer to the Patient: The Good, the Bad and the Ugly

A Look Inside a Clinical Chemist's Toolbox: Managing High Pressure Situations in the Clinical Laboratory

Providing Value Beyond Values: Leaving the Laboratory to Increase Laboratory Visibility and Enhance Patient Care

Healthcare Forum: The Changing Regulatory Environment

Molecular Medicine

Tackling Infectious Disease Testing and Interpretation from the Perspectives of the Core Clinical Laboratory and the Point-of-Care

Little Molecules that Pack a Big Punch: The Promise of Cell-Free DNA

What's New in Newborn Screening?

Next Generation Sequencing for Laboratorians: Understanding the Essentials

Laboratory Consultations in Genomic Medicine: Case-Based Learning

Cervical Cancer Screening: What Is New?

Population Health and Equity

Exploring Racial and Ethnic Health Disparities through a Laboratory Medicine Lens

Strategies for Enhancement of Laboratory Medicine in Africa

Connective Tissue Diseases, Lupus, and dsDNA Testing: Updates in Diagnosis and Testing

Laboratories Ally with Clinicians in Mitigating the Burden of Heart Disease from Childhood

Emerging Areas in Therapeutic Drug Monitoring: Antifungals, Direct Oral Anticoagulants, and Psychoactive Drugs

The Remarkable Journey from Bench to Bedside Changing Lives for Individuals with Cystic Fibrosis

Emerging Diagnostics

Case Studies in the Use of Emerging Technologies in Pediatric Laboratory Medicine

New Technologies and Innovations to Improve the Clinical Laboratory

AACC Disruptive Technology Award Competition

Novel Multiplex Proteomics Technologies for Biofluid Analysis: Looking Beyond Mass Spectrometry

Drug Checking: Using Mass Spectrometry and Novel Rapid Mobile Devices to Reduce Opioid Overdoses

Clinical Translation of Engineered Microsystems: From COVID-19 to Hematology and Hemostasis

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BY MICHAEL ASTION, MD, PHD, AND BRIAN R. JACKSON, MD

Moving Toward Patient-centered Laboratory Stewardship

Patient-centered care has become a popular term within the medical establishment. The commonly accepted definition provided by the Institute of Medicine is: "Providing care that is respectful of, and responsive to, individual patient preferences, needs and values, and ensuring that patient values guide all clinical decisions" (*1*).

From an ethical perspective, being patient-centered means respecting individuals' autonomy and values in all that we do. It means reimagining our systems and processes through patients' eyes and being willing to give up both convenience and control on the provider side when necessary. From a practical perspective, patient-centered care can improve the effectiveness of care by breaking down barriers to patient engagement and access.

In this article, we apply some of these patient-centered principles to laboratory stewardship, with a special focus on access to testing.

Patient-centered Stewardship

Given that healthcare organizations, including laboratories, are generally operated as businesses, any discussion of patient-centeredness must also address the relationship between healthcare corporations and the patients they serve. Just prior to the pandemic, one of us proposed the concept of "patient-centered capitalism," whereby the interests of patients would be explicitly prioritized over those of financial and other stakeholders within both the healthcare system and its suppliers. The idea, summarized, is that "…healthcare will find it easier than many other industries to find the right balance among its various groups. The doctrine of shareholder supremacy has a certain elegance in that it simplifies the decision about which group comes first: shareholders. Medical ethics and patient-centered capitalism offer an equally elegant solution: patients come first and all others, including shareholders, come second" (*2*).

Stewardship refers to the careful management of an essential resource. Traditionally, lab stewardship is defined as a set of activities, policies, and procedures that improve four elements of lab testing: test ordering, result retrieval, result interpretation, and financial fairness for patients and other stakeholders (*3*).

It stands that for laboratory stewardship to be patient-centered, the scope must include access on the part of the patient because the correct test is irrelevant if the patient is unable to complete the testing process.

Patient-centered Innovation

Table 2 lists examples of expanded physical access to testing. These include home testing, self-collection at home, mobile collection by healthcare professionals, and increased community collection and testing sites. These services were available, and slowly improving, before the pandemic, but the pandemic dramatically expanded them as a logical response to an international emergency. The economics of these services—for example, through reasonable reimbursement for SARS-CoV-2 testing—became more favorable during the pandemic, and this fueled innovation.

Patients throughout the United States clearly like the convenience that the pandemic necessitated. Health systems have responded by integrating improved access to lab testing into their scope of care, which now includes a significant telemedicine component. It follows that expanded

T1 **Expanding Laboratory Stewardship From Four to Five Domains to Enhance Patient-centeredness.**

Five Components of Laboratory Stewardship	Patient-centered Examples
Access to testing*	■ Drive-through SARS-CoV-2 testing. ■ Home-based collection.
Test order	■ Genetic counseling session to explain details and options at appropriate educational level. ■ Test order initiated as part of telemedicine visit.
Result retrieval	■ Mobile app to enable patient retrieval of results. ■ Patient access to their electronic medical record.
Result interpretation	■ Educational materials written in patient's language of choice. ■ Enhanced communication between patients and physicians, nurses, physician assistants, and genetic counselors through text, phone, and electronic medical record.
Financial fairness	■ Patient understands their out-of-pocket expenses before test is ordered and specimen collected. ■ Financial counseling to understand inclusion criteria for charity care. ■ Test pricing reflects the broader market value and does not exploit situational vulnerability.

*See Table 2 for more examples

LABORATORY STEWARDSHIP FOCUS

access to testing is likely to persist, and innovation will accelerate.

Self-collection is enabled by technologies that make it easier to collect and properly label any specimen, including dried blood spots, capillary blood, saliva, nasal or nasopharyngeal swabs, buccal swabs, urine, and stool. For example, the use of dried blood spots, ordered through telemedicine and self-collected at home, is feasible for chronic disease monitoring, and this usage expanded during the pandemic (*4*). Similarly, access to genetic testing has improved due to expanded use of saliva and buccal sample collection kits through home collection.

Mobile collection is enabled by a variety of technologies, and it is best if these technologies are redundant. For example, in some metropolitan areas, patients with smartphones can now order mobile phlebotomy services from an app that is analogous to Door Dash or Uber, and those without a smartphone can just call a phone number to request the service. Northwell Health, which launched an app-driven mobile phlebotomy service called LabFly in August 2019, scaled that service to more than 500 patients per day during the pandemic (*5*).

Self-collection, mobile collection, and alternative-site collection are not only more convenient for the patient, but they also have distinct clinical and public health advantages. During the pandemic, alternative collection sites have helped reduce infectious exposures for both healthcare workers and patients. They also have led to patients being tested who otherwise might not have been tested, a benefit that could apply to other tests as well.

Expanded Testing at Home

Home testing is most patient-centered when done in collaboration with care providers. This is particularly important for monitoring chronic conditions. If a broader menu of safe point-of-care instruments and collection devices were available at home, chronically ill patients could partner with their providers to establish a monitoring plan for a variety of useful testing such as therapeutic drug monitoring, markers of disease burden (e.g. viral loads), and biomarkers of organ function and damage. Patient-centered stewardship is enabled by manufacturers that develop reliable, broad-menu instruments that surpass regulatory requirements and are usable by a wide range of patients, while connecting to the patient's care providers and medical records.

Avoiding Excesses—Including Quackery

Improved access to testing is necessary but not sufficient to enhance patient-centered laboratory stewardship. Improved access only enables stewardship if the testing is medically necessary.

Removing barriers to access likely will expand the waste and abuse that have long plagued the laboratory industry (*6*). These include: overbundling of tests, quackery, and releasing tests for clinical use before there is reasonable, independent evidence of their clinical utility. Lack of evidence for clinical utility is particularly problematic regarding tests marketed directly to patients. For example, direct-to-consumer genetic testing aimed at guiding a patient's diet or exercise remains largely unproven in producing better outcomes.

Laboratory stewardship programs that put in safeguards to avoid these excesses, while expanding access to medically necessary testing, will be on the vanguard of improving patient-centered care.

T2 **Examples of Expanded Access to Laboratory Testing Prompted by the COVID-19 Pandemic**

Home self-collection	■ Saliva or buccal swab kits for genetic testing. ■ Dried blood spots with mail-based delivery to lab for a variety of analytes including therapeutic drugs, creatinine, and HbA1C. ■ Self-collected tests for SARS-CoV-2 with mail-based delivery.
Home collection by medical professional	■ Mobile phlebotomist available through smartphone app or phone call.
Home testing: Instruments and kits	■ Pulse oximeters for SARS-CoV-2 patients. ■ Glucometry with beta-hydroxybutyrate. ■ SARS-CoV-2 tests.
Expanded number of collection sites	■ Drive through SARS-CoV-2 testing. ■ Kiosks or collection tents for SARS-CoV-2 testing located in malls, parks, community centers, airports, commercial buildings, and houses of worship. ■ Test-only appointments in freestanding walk-in clinics, pharmacy-based clinics, and conventional urgent cares within health systems.

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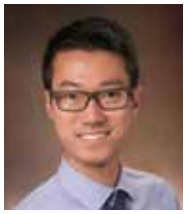

BY DERICK LIM, MS, SC(ASCP)CM, MLS(ASCP)CM, KHUSHBU PATEL, PHD, DABCC, AND TRACEY POLSKY, MD, PHD

HbA1c Access and Opportunity During the COVID-19 Pandemic

LABORATORY STEWARDSHIP FOCUS

Getting the right test to the right patient at the right time" is a common goal for medical and laboratory professionals working on laboratory stewardship. This mantra translates into ensuring that laboratory resources are optimized for patient-centered care.

To achieve this goal, laboratory professionals typically identify and address both underutilization and overutilization of laboratory resources. Overutilization of laboratory testing is a frequently targeted problem—and one that is easier to identify. However, underutilization is an equally important problem that often goes unnoticed, and therefore is tougher for stewardship programs to tackle. In fact, underuse is estimated to occur as frequently as overuse, if not more (*1*).

Test underuse can occur for many reasons. Providers may be unfamiliar with best practices, guidelines, or even available testing options. They may lack clinical decision support systems to help identify appropriate diagnostic testing. And patients may lack access to testing in a timely and convenient manner. To emphasize this latter point, the inability of patients to take time off work or school during normal business hours can be a major contributor to limiting physical access to testing.

COVID-19 Leads to New Underutilization Challenge

For most laboratories, analytic tools are not effectively designed to capture test underutilization. Identifying underuse often requires a close partnership between the laboratory and ordering providers to understand patterns of test ordering and assess the impact of these patterns on clinical management.

However, due to "medical distancing" resulting from the COVID-19 pandemic, laboratories were able to quickly identify areas of underutilization (*2*). One example is the measurement of hemoglobin A1c (HbA1c). Many diabetic patients at our institution have HbA1c measurements performed at the point-of-care during their clinic visit. However, early in the pandemic, many patients transitioned their routine care from in-person visits to telehealth visits. As a result, HbA1c testing was drastically affected for us, with point-of-care HbA1c testing volumes declining approximately 80% at the peak of the pandemic's first wave.

Out of necessity, the COVID-19 pandemic has paved the way for a new and different future.

International consensus guidelines recommend HbA1c measurements be performed every 3 months to assess and manage glycemic control in children, adolescents, and young adults with diabetes (*3*). With such a significant decline in volume for HbA1c testing performed at both the point-of-care setting and in the central laboratory, it became quite evident that many patients were not getting their HbA1c levels evaluated at the appropriate recommended interval.

Dealing with laboratory test underutilization and implementing an appropriate solution can be as challenging as identifying it. In our scenario of HbA1c underuse, our endocrinology colleagues promptly brought our attention to the problem. Test volume data from our laboratory's operations dashboards also unmistakably pointed to the issue. It was clear that to address it, we needed a solution that improved patients' access to testing. We needed a test that would allow patients to collect samples at home and send them to our laboratory for analysis.

To that end, we explored adding dried blood spots as an alternate specimen type to our existing central laboratory HbA1c assay. Fortunately, our colleagues at Seattle Children's Hospital had validated a dried blood spot assay for this purpose. They had already been offering a dried blood spot option for immunosuppressive therapeutic drug monitoring for transplant patients long before the pandemic, and they graciously provided us with support (*4*,*5*).

Rising to the Opportunity

Rapidly deploying resources to implement a new test during the pandemic was challenging. Validating a test and training staff on a major change in procedure in a timely

manner—in an understaffed and overworked laboratory—seemed insurmountable at the time. However, with the dedicated help of hardworking staff members, collaborators, and clinical colleagues, we were able to validate and implement our dried blood spot testing program for HbA1c in a matter of months of identifying the issue.

The most time-consuming aspect of the process turned out to be operationalizing the program, and not the actual validation of the dried blood spot HbA1c assay itself. We needed to quickly develop an intricate infrastructure to support a multistep process, which included identifying patients that would need the test in advance of a telemedicine visit, mailing the dried blood spot collection kit to the patient, the patient mailing the sample back to the lab, the lab tracking and receiving the dried blood spot sample, and creating a patient encounter in the electronic medical record so that results could be verified in time for the upcoming telemedicine visit.

Developing this workflow required close collaboration among the clinical and administrative staff at our diabetes clinic, information services, and sections of the clinical lab mailing the collection kits, performing the testing, and accessioning the mail-in samples. Much of the burden on creating this process fell on our central laboratory professionals, who had to operationalize a new process for mailing the collection kits and receiving the samples. Identifying patients whose insurance would cover this service was another implementation challenge, one we continue to work on with our hospital's financial services team, especially for patients who are covered by insurance with laboratory capitation.

Looking Ahead

The concept of telemedicine is not new to diabetes management. Several studies assessing the impact of telemedicine visits on diabetes management have shown better glycemic control through mean reduction in HbA1c levels. Telehealth use prior to the pandemic was mainly limited because of CMS restrictions, which were lifted in March 2020.

Out of necessity, the COVID-19 pandemic has paved the way for a new and different future; it has accelerated the adoption of technologies that were long overdue. Regardless of whether the surge in telemedicine visits continues postpandemic, implementation of a remote blood sampling program has unveiled opportunities for our laboratory to address aspects of laboratory test underutilization when access is a key driver. Expansion of our remote sample-collection program to other tests beyond HbA1c will enable us to reach patient populations with chronic conditions that need more convenient and accessible laboratory testing.

In the era of value-based healthcare, it is of utmost importance that laboratories collaborate with care providers to identify and devise solutions that make the most of these opportunities.

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Regulatory Roundup

FDA OKs 23andMe to Report Pharmacogenomic Variants Without Confirmatory Testing

The Food and Drug Administration (FDA) has granted 23andMe 510(k) clearance for a pharmacogenomics report for two medications: clopidogrel, which is prescribed for certain heart conditions, and citalopram, which is prescribed for depression. This 510(k) clearance modifies the labeling of the previously authorized 23andMe CYP2C19 Drug Metabolism Report, removing the need for confirmatory testing and allowing the company to provide interpretive drug information based on genetic factors for these specific medications.

Individuals with certain genetic variants that affect how the CYP2C19 enzyme metabolizes drugs may experience reduced efficacy with clopidogrel and citalopram. They may also have increased chances of side effects—some of which could lead to life-threatening adverse events, such as cardiac problems. With this new pharmacogenomics report, consumers can learn if they have variants of the *CYP2C19* gene or any other clinically validated pharmacogenomic associations consistent with the FDA-approved drug labels for these medications. Consumers can then share this information with their doctors to determine if any modifications to their medication regimes are needed.

In order to meet FDA requirements for this new clearance, 23andMe performed method comparison studies designed to increase the likelihood of obtaining rare *3 allele combinations and further mitigate the risk of false-positive and false-negative results. Through this, the company found that the accuracy of its pharmacogenetics report exceeds 99% concordance with Sanger sequencing.

CE MARK GRANTED TO BD HPV ASSAY FOR USE WITH AT-HOME SELF-COLLECTED SAMPLES

BD has earned the CE mark for a new at-home self-collection indication for the BD Onclarity HPV assay. This new indication enables patients to self-collect samples for human papillomavirus (HPV) screening using a BD diluent tube. Patients send their samples to a laboratory, where they're processed using the Onclarity HPV assay on either the BD Viper LT, which is in use globally, or the BD COR system, which is in use across Europe. In a single analysis, the BD Onclarity HPV assay detects and provides genotyping information for the following 14 HPV types: 16, 18, 31, 45, 51, 52, 33/58, 35/39/68, and 56/59/66.

Studies have shown that adding at-home collection as an option to cervical cancer screening programs increases participation. BD therefore hopes that the new indication for the Onclarity HPV assay will help address the public health challenge of reaching women who do not attend routine cervical cancer screening—a problem that has recently been compounded by the COVID-19 pandemic.

Sundry Photography / iStock

FDA AUTHORIZES NOWDIAGNOSTICS' RAPID, POINT-OF-CARE SARS-COV-2 ANTIBODY TEST

NowDiagnostics has received emergency use authorization (EUA) from the Food and Drug Administration for its point-of-care AdexusDx COVID-19 antibody test. Following this EUA, NowDiagnostics will offer this test across a variety of CLIA-waived healthcare settings, such as pharmacies, clinics, and hospital emergency rooms. The company is also conducting studies in order to make the technology behind the AdexusDx available for over-the-counter detection of SARS-CoV-2 antibodies. The test analyzes 40 µL of either fingerstick or venous whole blood, serum, or plasma. Using separation microfluidics and proprietary multilayer membranes, it separates plasma from whole blood automatically and displays results in 15 minutes. Performance of the AdexusDx does not require a phlebotomist, buffers, reagents, or additional equipment, making it suitable for large-scale testing as well as testing in remote or under-resourced areas.

NowDiagnostics developed this test with funding and technical support from the Biomedical Advanced Research and Development Authority, which is part of the U.S. Department of Health and Human Services.

FDA GIVES NOD TO PHOSPHORUS DIAGNOSTICS FOR AT-HOME SARS-COV-2 SALIVA TEST

Phosphorus Diagnostics has received Food and Drug Administration emergency use authorization for its SARS-CoV-2 saliva test featuring at-home sample collection. The test was developed at Phosphorus' CLIA laboratory in Secaucus, New Jersey and uses OraSure's OrageneDx (OGD-510) saliva collection device. Consumers can order the test online, and Phosphorus is also making the test available through partnerships between employers and healthcare providers with the goal of helping companies safely resume operations. After ordering the test, consumers will be directed to complete a medical questionnaire that will then be reviewed by an independent physician. Once the physician approves the order, Phosphorus will ship a sample collection kit to the consumer's home. The consumer can then collect a saliva sample without supervision and ship it back to the lab. Test results will be available within 72 hours after the laboratory receives the sample and will be accompanied by a consultation from medical personnel.

Nils Hasenau / iStock

FOUNDATIONONE CDX GETS FDA APPROVAL FOR USE AS BILE DUCT CANCER CO-DIAGNOSTIC

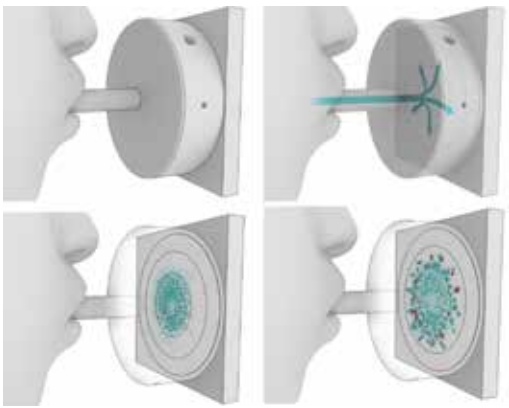
The Food and Drug Administration (FDA) has approved Foundation Medicine's FoundationOne CDx test for use as a companion diagnostic with the new bile duct cancer therapeutic infigratinib. Infigratinib, which is marketed as Truseltiq by QED Therapeutics, is a kinase inhibitor for adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (*FGFR2*) gene fusion or other rearrangement. Using formalin-fixed paraffin-embedded tissue specimens, FoundationOne CDx analyzes numerous guideline-recommended genes in solid tumors, including *FGFR2*, and can therefore identify patients who are most likely to benefit from infigratinib. The test has previously received FDA approval for use as a companion diagnostic with more than 20 other targeted therapies, including drugs for non-small cell lung cancer, melanoma, breast cancer, colorectal cancer, ovarian cancer, and prostate cancer. In addition to gene analysis, the test's results include microsatellite instability and tumor mutational burden to help inform immunotherapy decisions, and loss of heterozygosity for ovarian cancer patients.

Industry Playbook

Medivolve and Marvel Diagnostics Partner for Noninvasive SARS-CoV-2 Test

Medivolve and Marvel Diagnostics have partnered to advance Marvel Diagnostics' breath diagnostic technology, BlowFISH, as a noninvasive method of testing for the SARS-CoV-2 virus that causes COVID-19. Medivolve, a company solely focused on commercializing technology for the COVID-19 pandemic, announced a $1 million investment in BlowFISH in January 2021. With BlowFISH currently undergoing clinical trials, the companies aim to obtain emergency use authorization from the Food and Drug Administration.

Marvel Diagnostics developed the BlowFISH technology not only for SARS-CoV-2 testing purposes, but to improve testing methods for different respiratory illnesses, making testing more comfortable, convenient, and accessible, according to the company's cofounder, Pirouz Kavehpour, MD. With the BlowFISH technology, patients breathe into a whistle-like device that collects sample droplets from the patient's lungs and returns results in about 10 minutes. According to the partners, the technology will be used as an alternative to the nasal swab samples commonly used to test for the virus.



"Making testing more accessible to populations, such as children and the elderly, where it may be difficult to administer a nasopharyngeal swab test, will become important in our transition to resuming daily life in the 'new normal,'" said Medivolve CEO David Preiner. "Data obtained from BlowFISH powered testing will also further Medivolve's mission to use innovation and artificial intelligence to close the loop in health management for every American."

PHENOMIX AND MAYO CLINIC DETERMINE OBESITY RISK THROUGH PHENOTYPES

Phenomix Sciences and Mayo Clinic have signed an exclusive technology licensing agreement for a blood test that has the ability to detect four common phenotypes predicting obesity in patients.

Using one patient blood sample, the MyPhenome test developed by Mayo Clinic employs an artificial intelligence-based algorithm to analyze a patient's DNA as well as metabolomic and hormone markers related to obesity. The companies expect it to help clinicians provide earlier diagnosis and better anti-obesity treatment options, including drugs, devices, or surgeries, by analyzing the phenotypes identified from the test.

According to Phenomix, a patient can fall under four primary phenotypes they have classified as: hungry brain, a defect of satiation; hungry gut, a defect of satiety; emotional hunger, an emotional reward from eating; and slow burn, a defect in energy expenditure.

The test was developed based on a recent study led by Phenomix founders Andres Acosta, MD, and Michael Camilleri, MD, which concluded that knowing a patient's obesity phenotype allowed that patient to lose double the amount of weight after only 12 months of treatment. MyPhenome aims to launch the test before 2022.

FUJIFILM AND HELIO HEALTH COLLABORATE ON LIVER CANCER SCREENING

To improve early detection of liver cancer, Fujifilm Medical Systems and Helio Health are collaborating to market the Helio Liver test, a blood-based test that aims to diagnose liver cancer patients early for better treatment options. Through the partnership, the Helio Liver test will leverage Fujifilm's µTASWako i30 Immunological test system, a microfluidic-based clinical immunoanalyzer for in vitro diagnostic use.

The Helio Liver test works by collecting a 10-mL tube of a patient's blood sample, extracting cell free DNA, and performing a

Courtesy of Marvel Diagnostics

bisulfate conversion step to differentiate unmethylated versus methylated cytosines. The sample is then run on Fujifilm's µTASWako i30 Immunological test system to detect early biomarkers of liver cancer.

Over time, studies have shown that detecting liver cancer in the early stages results in a survival rate 12 times higher than if detected at a later stage. The companies hope that the Helio Liver test will simplify cancer screening by providing a convenient, noninvasive form of testing as opposed to the imaging tests, MRIs and ultrasounds, that are typically used.

The Helio Liver test is currently under regulatory review for registration by the China National Medical Products Administration. Through the partnership, Helio Health also aims to use Fujifilm's established network to market the test in the United States.

DERMTECH AND STANFORD STUDY SKIN CONDITION TEST

DermTech, a company that specializes in precision dermatology, announced a partnership with a team of researchers from the Stanford School of Medicine on a research study that aims to improve analysis of hidradenitis suppurativa (HS), a chronic skin condition made up of swollen lesions in the armpit, groin, anal, and breast regions of the body. The study, "A Study of Longitudinal Noninvasive Cytokine Monitoring in Patients With Hidradenitis Suppurativa," will be a 3-year evaluation to ultimately improve diagnostic turnaround times and provide better treatment options for HS.

Through the course of the study, researchers will utilize DermTech's noninvasive sample collection and precision genomics platform to identify and evaluate biomarkers in patients with HS. DermTech has developed a noninvasive skin genomics platform that collects RNA, DNA, and protein from a lesion through a "Smart Sticker." The sticker is first placed on the lesion, then analyzed to phenotypically characterize HS, identify potential subsets of HS, and assist clinicians in treatment decisions.

Previous studies have shown that because the direct cause of HS is unclear, it can take more than 7 years for an accurate diagnosis.

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BBI, ILLUMINA, GENEDX JOIN FORCES FOR WHOLE-GENOME SEQUENCING PROJECT

Brotman Baty Institute, Illumina, and GeneDx are teaming up on a project to improve detection of developmental differences in children through whole-genome sequencing (WGS).

Called SeqFirst, the 3-year project will begin by offering WGS to 100 children showing signs of developmental differences, and over the course of the study, researchers will continuously review the medical records of each participant. As part of the agreement, Illumina will provide advanced sequencing reagents for the study, while GeneDx will perform WGS. Through SeqFirst, the companies hope to emphasize the importance of early genetic sequencing for children with developmental disorders.

"WGS can dramatically reduce the time it takes to diagnose genetic conditions, which can improve patient outcomes," said Jeremy Preston, vice president for regional and segment marketing at Illumina. "We are proud to support the University of Washington and GeneDx and help families find the peace-of-mind that comes with a diagnosis for their child."

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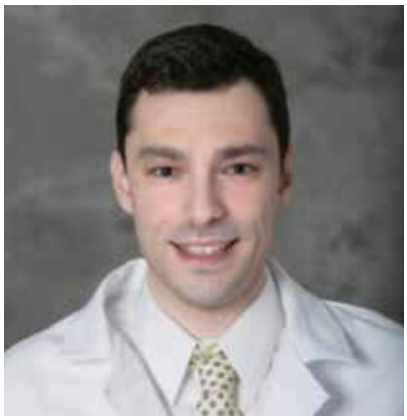
Ask The Expert

Radioactive Patient Samples in the Lab



EXPERT
Christopher G. Suciu, MD

You have been studying the radioactive specimens sent to your laboratory. What got you interested in this topic?

A: In the fall of 2019, our hospital core laboratory unexpectedly received specimens labeled as radioactive from a patient who was receiving an experimental radiopharmaceutical treatment. At that time, our laboratory was unprepared to handle radioactive specimens. In addition, because the laboratory did not perform radioimmunoassays, personnel had not received radiation safety training. This event led to an investigation of all radioactive specimens received in the laboratory.

Why are some patient specimens radioactive?

Major medical centers and cancer centers use numerous types of radiopharmaceuticals routinely for both diagnosis (generally lower doses) and treatment (generally higher doses). Ideally, patients receiving high doses of radiopharmaceuticals should have specimens drawn for laboratory testing prior to administration, but this is not always possible.

What types of radioactive materials are sent to your laboratory?

Over a nearly 2-year period, we calculated that over 11,000 patient blood, urine, stool, and other body fluid specimens were sent to our laboratory within 5 physical half-lives of nine different radionuclides being administered. The radionuclides primarily consisted of beta and gamma emitters. Beta particles have localized effects, and their ability to damage tissue allows them to be effective antineoplastic agents. However, thin materials such as plastic typically block them. Therefore, beta particles pose a greater risk to people from sources inside and on the surface of the body than from sources outside the body. In contrast, gamma rays can travel great distances and have the ability to penetrate materials that would block other radioactive particles. Therefore, gamma rays pose a risk to people even from sources outside the body.

Do you think this radioactivity poses a threat to laboratory employees?

Overall, our study demonstrated that laboratory staff are at low risk of incurring a harmful exposure from most of the samples received in our lab. Risk is difficult to truly assess, though. It depends on the radionuclide, how radiopharmaceuticals distribute in the body, the time between sample collection and receipt in the laboratory, and how specimens are handled. For instance, we found that if specimens are held at the top of the tube, no specimens can deliver a 2 mrem effective dose of gamma radiation in <5 minutes. However, if specimens are held firmly in the palm of the hand, many specimens could potentially deliver this dose in <2 minutes.

Furthermore, the index specimens that were sent to our laboratory labeled as radioactive had over 30 microCuries of iodine-131. This means these specimens contained enough radioactivity to exceed our institutional threshold and would have been considered a "major spill" if they were dropped in the lab. Specimens such as these present a real risk to laboratory personnel and need to be handled with extra caution and disposed of properly.

What recommendations do you have for laboratories regarding radioactive specimens?

We recommend that laboratories do the following: 1) Provide radiation safety training for all personnel. 2) Maintain open lines of communication with members of radiation safety and radiation oncology. This enables labs to stay informed about when they will get samples from patients who have received high doses of radiopharmaceuticals. 3) Develop protocols for the labeling and transport of specimens with significant radioactivity. 4) Develop protocols for tracking the receipt, processing, and disposal of specimens from patients who received large doses of radiopharmaceuticals. 5) Assess cumulative exposure to personnel and instruments with dosimeters. 6) Assess for potential environmental contamination with periodic wipe testing. 7) When possible, collect patient specimens before radioisotope administration or after at least 5 physical half-lives.

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The author thanks his Washington University colleagues Ann M. Gronowski, PhD, and Max Amurao, PhD, for their support investigating radioactivity in the clinical laboratory.

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