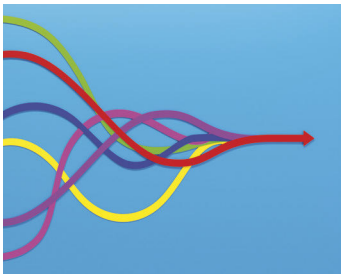
June 2020

CLN Clinical Laboratory News

An AACC Publication | Volume 46, Number 5

EXPANDING SARS-COV-2 TESTING CAPACITY



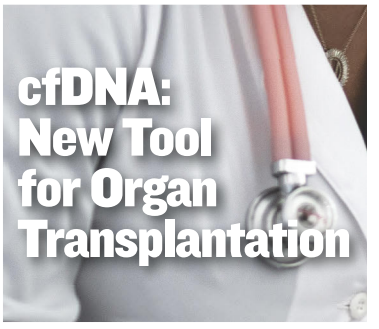
Study shows pooling samples can save kits, time

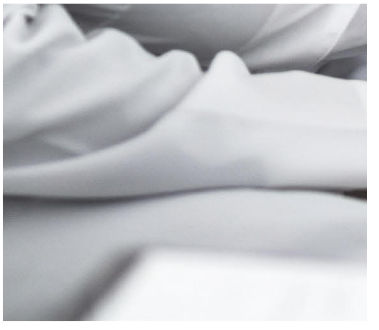
PAGE 6

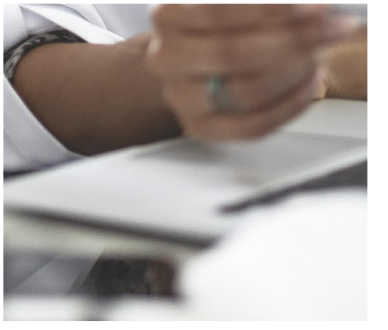
Building a Better DRUG TESTING SYSTEM

Raising the Bar for Specimen Labeling

cfDNA: New Tool for Organ Transplantation







AACC Better health through laboratory medicine.

Promega

Don’t settle for just a supplier. Find a custom manufacturing partner.

Your specifications. Your format.
Our scientists waiting to help.

Let’s TALK CUSTOM

cGMP Manufacturing

15 ISO CERTIFIED Locations

100+ GLOBAL IVD COMPANIES Supplied

Selecting a supplier for your molecular diagnostic applications can be a challenge—especially a supplier who can adapt to your specific needs. Work with a manufacturing partner you can be certain about. With our breadth of technologies and rapid response manufacturing, Promega is here to support your molecular testing needs.

Learn more here:
promega.com/CustomManufacturing

CLN Clinical Laboratory News
www.aacc.org

Clinical Laboratory News is published monthly (10 times per year—Jan/Feb., March, April, May, June, July/August, Sept., Oct., Nov., and Dec.) by the American Association for Clinical Chemistry. 900 Seventh St., NW, Suite 400, Washington, DC 20001. Phone: +1 202.835.8756 or +1 800.892.1400 Fax: +1 202.877.5093. POSTMASTER: Send address changes to AACC, 900 Seventh St. NW, Suite 400, Washington, DC 20001.

Design and Production Management
imagination.

Cover: FG Trade / Getty Images; MF3d / Getty Images

Features

Departments

Most, if not all digital microscopy systems feature remote review, which ... enables technologists to perform complete blood counts with differentials even when they aren't in the hematology area.
p32

Federal Insider

CMS Relaxes Rules Around COVID-19 Testing

The Centers for Medicare and Medicaid Services (CMS) continued its efforts to open up access for testing related to the novel coronavirus pandemic with a new set of waivers and rules around ordering and performing tests for COVID-19, the illness caused by the SARS-CoV-2 virus.

Notably, CMS will no longer require a written order from the treating physician or other practitioner for beneficiaries to get COVID-19 tests, nor for influenza tests meant to rule out other infections. The caveat: CMS still expects the person ordering the test to be authorized to do so under state law. Further complicating the picture, CMS rules also note that if a laboratory receives a test without a provider's order, the performing laboratory must "directly notify the patient of the results consistent with other applicable laws, as well as meet other applicable test result reporting requirements." In formulating policies around test ordering, laboratories will need to heed governors' executive orders and other rules that dictate how tests can be ordered on a state-by-state basis.

CMS also now will pay hospitals and practitioners to assess beneficiaries and collect laboratory samples for COVID-19 testing under a separate payment when that is the only service a patient receives. In addition, CMS will cover antibody-based tests authorized by the Food and Drug Administration (FDA). For its part, FDA recently tightened policies around serological tests for COVID-19, requiring developers to obtain emergency use authorizations, submit their validation data within 10 business days, and meet new test performance thresholds, including 90% sensitivity and 95% specificity.

Other CMS rule changes include: an allowance for alternate specimen collection devices and media to collect and transport COVID-19 samples; permission for laboratories within a hospital campus to hold a single CLIA certificate for multiple laboratory sites, such as parking lot testing; payment for specimens a technician collects at a patient's home, or for FDA-authorized self-collection kits used by the patient; and a clarification that pharmacists can both collect samples and, if their pharmacy has a CLIA license, perform certain tests.

NIH LAUNCHES $1.5 BILLION INNOVATION INITIATIVE FOR COVID-19 DIAGNOSTICS

The National Institutes of Health (NIH) announced a plan to speed development of tests for SARS-CoV-2 that will infuse $1.5 billion in federal stimulus funding into a new initiative called Rapid Acceleration of Diagnostics. The program aims to accelerate innovative technologies for rapid and widely accessible COVID-19 related testing, with the goal of making millions of accurate and easy-to-use tests per week available in the U.S. by the end of summer 2020.

NIH also said it will help move technologies more swiftly through the development pipeline toward commercialization. The plan calls for NIH to work closely with the Food and Drug Administration, the Centers for Disease Control and Prevention, and the Biomedical Advanced Research and Development Authority.

According to NIH, the initiative will complement research currently underway that is focused on prevention and treatment of COVID-19, including the recently announced Accelerating COVID-19 Therapeutic Interventions and Vaccines public-private partnership to coordinate the international pandemic research response.

"We need all innovators, from the basement to the boardroom, to come together to advance diagnostic technologies, no matter where they are in development," said NIH Director Francis Collins, MD, PhD.

Part of the new program will be competitive. NIH is asking scientists with rapid testing technology to enter a national COVID-19 testing challenge for a share of up to $500 million. The technologies will be put through a competition in a rapid, three-phase selection process to identify the best candidates for at-home or point-of-care tests for COVID-19. NIH will match finalists with technical, business, and manufacturing experts to increase the odds of success. If selected technologies are already relatively far along in development, NIH will put these on a separate track that focuses on rapid commercialization.

jpgfactory / Getty Images

MilliporeSigma

Focus on rewriting the future.

We're inspired by our customers' passion to drive science forward. That's why we take an innovative approach to our work, just like you do.

Milli-Q® lab water solutions are constantly raising the bar to simplify maintenance, reduce water consumption and streamline data management – so you can keep your focus on the future of your work, not your lab water.

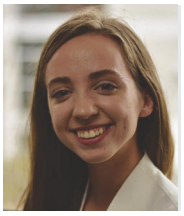
To find out more, visit:

SigmaAldrich.com/EmpoweringFocus

Milli-Q®
Lab Water Solutions

Bench Matters

Harnessing the Power of Big Data Analytics to Achieve Reference Interval Harmonization in Clinical Laboratories



Mary Kathryn Bohn, BS, PhD candidate

Khosrow Adeli, PhD, FCACB, DABCC

As clinical laboratorians, we know that the test results and reference intervals (RIs) reported to patient medical records should reflect the preanalytical, analytical, and postanalytical conditions at any given laboratory. However, most clinicians and patients are not aware that test results can vary depending on the method used. Moreover, laboratories operating within the same healthcare system, and even using the same analytical platform, might report different RIs for a given test. This lack of harmonization significantly increases the risk of inappropriate as well as inconsistent test result interpretation, potentially leading to erroneous or missed diagnoses and unnecessary interventions. In recent years, more patients having direct access to their medical data combined with tighter integration of healthcare networks has underscored why harmonization matters. As laboratory professionals, we play a leading role in advocating for and achieving harmonized patient care.

Harmonization in laboratory medicine involves the total testing process, from collecting samples to reporting and interpreting results. However, past harmonization efforts have mainly been limited to achieving method standardization in the analytical phase of testing.

GAINS FROM ASSAY STANDARDIZATION

Result comparability across healthcare centers depends on standardizing laboratory measurements and tracing them to common reference materials. Without standardization, harmonization of RIs would not be feasible or appropriate. Recent method standardization efforts have been successful for many analytes, including cholesterol, creatinine, glucose, hemoglobin A1c, and sodium. For these standardized assays, RI harmonization across laboratories is very possible and arguably critical to clinical service. RI harmonization is also possible for nonstandardized assays that demonstrate good concordance between analytical platforms.

Unfortunately, despite these improvements, different RIs continue to be used across laboratories. The delay in developing and implementing harmonized RIs lies mostly in the challenge of recruiting a large representative healthy population to establish RIs. This critical gap limits our ability to deliver uniform laboratory service across healthcare networks and urgently needs to be addressed.

A TREASURE TROVE OF DATA

As challenging as the journey to RI harmonizations has been, the big data era in which we now find ourselves poses new opportunities to achieve harmonization in laboratory medicine.

The principle of using extensive laboratory datasets to assist in clinical service is not new, but novel applications for using this treasure trove of information keep unfolding as new software and statistical programs are developed. In the context of harmonization, outpatient data extracted from the laboratory information systems (LIS) of multiple clinical laboratories can be extremely useful in assessing inter-laboratory differences and establishing harmonized RIs. For example, data for a given assay and time period can be extracted from the LIS of several laboratories, reflecting their unique preanalytical, analytical, and population demographics. RIs can then be established based on outpatient data for each center as well as all centers combined (i.e. harmonized) and compared against each other to determine whether RI harmonization is feasible.

A NEW METHOD

Many approaches for establishing RIs based on outpatient data have been described in the literature. Older graphical models such as the Hoffman and Bhattacharya methods have often been questioned due to their inherent subjectivity, while newer methods such as the Arzideh method reported by the German Society for Clinical Chemistry and Laboratory Medicine show greater promise (Clin Chem Lab Med 2007;45:1043–57). Specifically, this new automated approach statistically isolates the healthy population in an outpatient dataset to derive accurate and robust RIs, demonstrating remarkable comparability to health-associated data. It is also uniquely suited to harmonization, eliminating

Stígur Már Karlsson /Heimsmyndir / Getty Images

the need to recruit a large healthy population and allowing for robust assessment of large datasets representative of multiple analytical platforms and geographic regions.

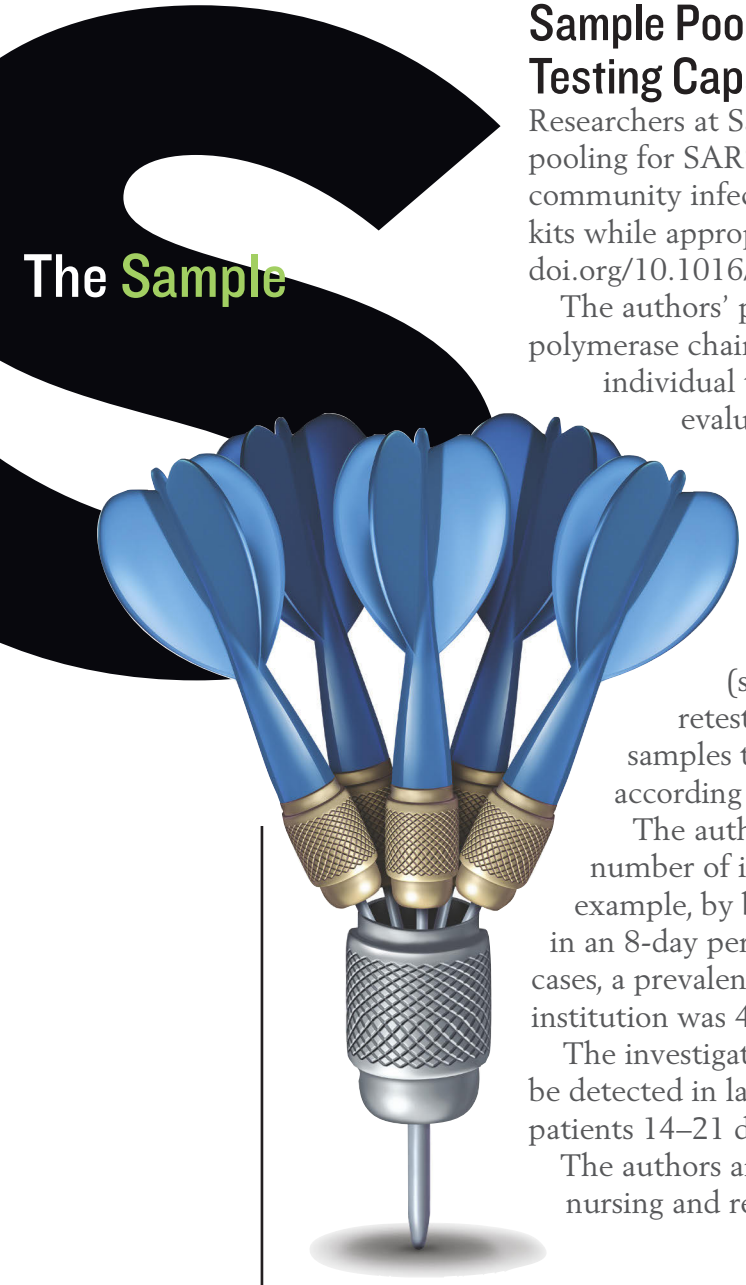
In our experience, we applied the Arzideh method to large outpatient datasets (up to 14 million results per test) extracted from community reference laboratory centers across Canada that use different analytical platforms for common laboratory tests (i.e. electrolytes, hepatic enzymes, and renal markers). When we applied this method to each center separately and to all centers combined, we observed only minimal differences in estimated reference limits. These findings highlight the use of big data in and the overall feasibility of harmonizing RIs in clinical laboratories for certain tests. We plan to expand this study to other analytes as well as verify established harmonized RIs using healthy adult samples.

As manufacturers' platforms become more standardized and novel data-driven tools emerge, the prospect of RI harmonization in laboratory medicine appears much closer. We urge laboratories to collaborate and consider using big data analytic tools like the Arzideh method to assess the feasibility of RI harmonization in their regions. Of course, for some assays, different methods generate vastly different results and harmonization is not feasible. In these cases, method-specific RIs should be considered and implemented across centers that use the same analytical platform/method. Conversely, if methods are traceable to a common reference standard, the feasibility of RI harmonization is higher and should be considered a priority for laboratories globally. Only then will harmonized patient care at the level of clinical laboratories be possible and ultimately result in enhanced patient safety and a higher quality of healthcare for all.

Mary Kathryn Bohn, BS, is a PhD candidate with the CALIPER Project at The Hospital for Sick Children and the University of Toronto in Ontario, Canada.
+EMAIL: marykathryn.bohn@sickkids.ca

Khosrow Adeli, PhD, FCACB, DABCC, is head and professor of clinical biochemistry and pediatric laboratory medicine and senior scientist in molecular medicine at The Hospital for Sick Children and University of Toronto in Ontario, Canada. He also serves as president-elect of the International Federation of Clinical Chemistry and Laboratory Medicine.
+EMAIL: khosrow.adeli@sickkids.ca

The Sample



Sample Pooling Effectively Expands SARS-CoV-2 Testing Capacity

Researchers at Saarland University in Saarbrücken, Germany, report that sample pooling for SARS-CoV-2 testing in asymptomatic individuals when the rate of community infection is low significantly expands testing capacity and saves test kits while appropriately detecting positive cases (Lancet Infect Disease 2020; doi.org/10.1016/S1473-3099(20)30362-5).

The authors' procedure involves pooling samples before reverse transcriptase-polymerase chain reaction (RT-PCR) amplification, then only conducting individual tests when the pooled sample yields positive results. They evaluated the effect of this approach on the sensitivity of RT-PCR by comparing cycle threshold (Ct) values of pools that tested positive with Ct values of individual samples that tested positive.

In pool sizes from 4 to 30 samples per pool, the Ct values of positive pools ranged from 22 to 29 for the E-gene (envelope protein) assay, and from 21 to 29 for the S-gene (spike protein) assay. The Ct values were lower for both assays in retested individual positive samples. In both pooled and individual samples the Ct values were below 30 and "easily categorized as positive," according to the authors.

The authors also successfully created sub-pools to further reduce the number of individual tests performed after a positive pool result. For example, by breaking 30-sample pools into 3 sub-pools of 10 samples each, in an 8-day period 1,191 samples required just 267 tests to detect 23 positive cases, a prevalence of 1.93% at a time when the rate of positive tests in their institution was 4.24%.

The investigators cautioned that borderline positive single samples might not be detected in large pools. This normally occurs in samples from convalescent patients 14–21 days after they become symptomatic.

The authors are now using this method to screen residents and staff in nursing and residential care homes in Saarland.

PREANALYTICS MATTER IN DIAGNOSING GESTATIONAL DIABETES MELLITUS

Researchers at Australian Capital Territory (ACT) Pathology demonstrated that preanalytical blood sample processing protocols have "critical importance" in accurately diagnosing gestational diabetes mellitus (GDM) (Diabetes Care 2020; doi.org/10.2337/dc20-0304). Their findings, comparing two large groups of women whose blood was processed under different procedures, confirm modeling predictions and prior small studies that investigated the effect of preanalytical procedures on GDM diagnoses.

Until 2017, preanalytical processing requirements for one-step, three-point 75-g oral glucose tolerance testing (OGTT) in much of Australia involved collecting the three samples (fasting, 1-hr, 2-hr) and sending them together to a lab for processing. In 2017, ACT Pathology implemented stricter protocols that required all samples to be centrifuged within 10 minutes of collection.

The authors compared the effect of this change by examining fasting, 1-hr, and 2-hr sample results in 7,509 women tested under the old protocol (January 2015 to May 2017), and 4,808 tested under the new protocol (June 2017 to October 2018).

They found that early centrifugation of samples led to a significant, almost double, increase in the GDM diagnosis rate, from 11.6% to 20.6%. GDM diagnosis rates based on values from fasting and 1-hr samples increased by 127% and

wildpixel / Getty Images

66%, respectively; the diagnosis rate based on 2-hr samples increased a statistically insignificant 15%. The mean fasting, 1-hr, and 2-hr values in mmol/L under the old protocol were 4.41, 6.99, and 6.05, respectively, versus 4.65, 7.33, and 6.21, respectively, under the new early centrifugation protocol.

"It is clear that the preanalytical blood sampling protocol for OGTTs during pregnancy needs attention and standardization," concluded the authors.

POLYGENIC RISK SCORE IDENTIFIES MEN AT ELEVATED RISK FOR ABDOMINAL AORTIC ANEURYSM

A polygenic risk score (PRS) based on 29 mutations identified more men at risk of abdominal aortic aneurysm (AAA) than would be identified under current screening recommendations. Extending current guidelines to include testing for those with high PRS "would significantly increase the yield of current screening," said the authors of a study presented at the American Heart Association's Vascular Discovery: From Genes to Medicine Scientific Sessions 2020 (Presentation 170).

Current AAA screening recommendations call for a one-time ultrasound in men ages 65–75 with a history of smoking. The survival rate once an AAA ruptures is only about 20%, so better identifying individuals at risk remains a priority.

The authors used electronic health data to identify participants with and without AAA in the Million Veteran Program (MVP), a national genomic research initiative. They tested 18 million genotyped and imputed DNA variants for association with AAA using logistic regression modeling, then used external datasets to replicate these findings. Finally, they tested and validated a series of AAA PRSs using an independent set of MVP participants.

From 7,642 AAA cases and 172,172 controls, the researchers identified 14 novel AAA loci implicating already established risk factors like lipids (*LPA*, *PCSK9*) and smoking (*CHRNA3*). A one standard deviation increase in the 29-variant PRS was associated with a 32% increased risk of AAA. Men older than age 50 with the 5% highest PRS had an AAA prevalence of 7.8%, which is higher than that observed in AAA screening trials upon which current guidelines were based.

The researchers acknowledged the need for more investigation to understand how well the PRS captures risk in diverse ethnic groups, as Caucasian men predominate in the MVP.

ADVANCING STANDARDS FOR SPECIMEN

LABELING AND TRACKING

Strategic use of data puts the high bar of a 0% error rate in sight

BY KIMBERLY SCOTT

A SARS-CoV-2 specimen labeling mix-up that resulted in an infected individual erroneously receiving a negative result highlights the very real consequences of errors that can occur during the pre-analytical phase of laboratory testing.

In February, the University of California San Diego (UCSD) Medical Center collected samples from four individuals who were in quarantine after returning from China and sent the specimens to the Centers for Disease Control and Prevention (CDC) for testing. Some confusion in differences between the two organizations' labeling systems resulted in miscommunication about the test results, with CDC incorrectly advising that all four patients tested negative for the virus, according to news reports.

As the four individuals were being transported from the UC San Diego Health hospital back to Marine Corps Air Station Miramar to wait out a 14-day government-mandated quarantine, word came that one of the individuals had in fact tested positive. That individual was then returned to the hospital and placed in isolation.

The episode underscores a finding that is becoming more relevant as clinical laboratories have rushed to offer testing for the new coronavirus and to come to terms with stressed supply chains and unusual sample collection procedures: that improving communication and collaboration with those outside labs remains the best strategy to ensure accuracy and protect patients.

Left: Andrew Brookes / Getty Images; Right: Greg Gibson

A REALITY CHECK ON LABELING STANDARDS

Clinical laboratories have been working for decades to overcome the problem of specimen labeling errors. Researchers estimate that more than 160,000 adverse patient events occur each year in the United States because of patient specimen identification errors involving clinical laboratories, while 11% of all transfusion deaths occur as a result of phlebotomists not properly identifying patients or mislabeling tubes of blood, according to an article in *The Journal of Applied Laboratory Medicine* (2017;2:244-58).

The Clinical and Laboratory Standards Institute (CLSI) in 2011 developed a standard to reduce the unacceptably high incidence of mislabeled specimens in clinical laboratories. The standard, "AUTO12–Specimen Labels: Content and Location, Fonts, and Label Orientation," specifies locations and formats for the required human-readable elements that must appear on the label for each clinical laboratory specimen. The standard also specifies rules for truncation for long patient names, the location and size of the bar code on each label, a list of the most commonly used variable elements that can appear on specimen labels, and the required orientation of labels on specimen tubes. That standard is still in effect.

The Joint Commission in 2014 acknowledged the issue of specimen identification errors and released two National Safety Goals to address this problem. The first goal called for healthcare providers to use two patient-specific identifiers, such as name and date of birth, to ensure each patient receives the correct medication or treatment. The second goal was to make sure the correct patient gets the correct blood when they get a transfusion.

But while standards are in place nationwide for specimen labeling and handling, the incidence of patient identification errors—including mislabeled and misidentified specimens—remains much too high, say experts. The best data on errors in U.S. laboratories comes from three separate College of American Pathologists (CAP) Q-Probe studies, in which the reported rates of mislabeled specimens were 0.39/1000 in 120 institutions (2006), 0.92/1000 in 147

clinical labs (2008), and 1.12% of blood bank specimens in 122 clinical labs (2010) (CLN 2014;4:12–13).

Over the past decade, laboratories have tried many interventions deemed to be effective in reducing specimen error rates. But how effective are they really? A 2016 study concluded that computer-generated identification systems and interdisciplinary cooperation can significantly reduce patient identification errors (PLoS One 2016;11:e0160821).

For the article in *The Journal of Applied Laboratory Medicine*, researchers conducted a review of published studies to determine which interventions resulted in substantial decreases in specimen labeling errors. Specifically, they evaluated the effectiveness of four categories of laboratory practices to reduce the incidence of specimen labeling errors involving blood or any other type of patient specimen. The four categories were: improved communication and collaboration between laboratory and healthcare professionals, education and training of healthcare staff responsible for specimen collection, audit and feedback of labeling errors and real-time event reporting, and implementation of new technology.

The authors concluded that improved communication and collaboration between laboratory and other healthcare professionals in the form of multidisciplinary teams was the top recommendation for decreasing specimen identification errors. While the other evaluated practices also led to a decrease in specimen labeling errors, the investigators couldn't make a recommendation in favor or against the effectiveness of those practices because of insufficient data.

Paramjit Sandhu, MD, an epidemiologist at CDC in Atlanta and author of the study, told *CLN* that despite CLSI standards and improvements in bar-coding, the rate of errors probably is even higher than what is known. "In general, published error rates are usually underreported because of inadequate detection methods and reluctance to publish or otherwise share errors," he said. "Accreditation organizations like The Joint Commission and CAP continually reinforce patient safety goals and standards. However, despite those efforts, labeling errors remain one of the leading types of preanalytical errors associated with ancillary services."

Andrew Brookes / Getty Images

Is it possible to get to a 0% error rate? According to Sandhu, a 0% error rate should be a goal, though he noted that specimen mislabeling can occur during multiple continually changing steps of the preanalytic phase of the total testing process. Errors can occur at the time of specimen collection, from an incorrect bar code read, or due to labeling mix-ups right before or after sample collection and during laboratory accessioning of a specimen.

UNIQUE CHALLENGES FOR POINT-OF-CARE TESTING

Point-of-care testing (POCT) is mostly automated and uses bar-coded patient identification and bar code scanners with a test device at or close to a patient, but that doesn't mean these systems are perfect. Typically, device manufacturers build in tools that detect certain preanalytic errors, said Brenda Suh-Lailam, PhD, DABCC, FAACC, director of clinical chemistry and point-of-care testing at the Ann and Robert H. Lurie Children's Hospital of Chicago.

"When preanalytic errors do happen, the system should render the test invalid," she explained. "The healthcare provider would need to recollect the sample and repeat the test."

Automation, bar-coding, and interfaces with electronic medical records (EMR) have helped reduce specimen collection labeling errors, but the potential for error in manual POC tests still exists, she added, especially if there is not an interface between the POCT device and the EMR. In addition, errors can occur in other parts of the preanalytic process, such as specimen collection and reagent storage.

While the goal may be to get to 0% labeling and identification errors, the human component means the possibility of an error probably will never be eliminated, said Suh-Lailam. "It's not foolproof," she said. "If you scan the wrong thing, you'll get the wrong information."

Ultimately, the extent to which a laboratory minimizes errors in labeling and specimen identification comes down to how closely the lab follows CLIA regulations and the CLSI standards, the amount of automation the lab employs, and the policies and procedures the lab has in place for its preanalytic processes.

"Because of the potential patient adverse consequences associated with mislabeled specimens such as transfusion-related death, medication errors, and misdiagnosis, every labeling error should be treated seriously," said Sandhu.

USING DATA TO DRIVE BETTER PRACTICES

If the standards have not changed, but the errors remain—what is the next step beyond improving communication to minimize errors in specimen labeling and handling? Some laboratories organize their efforts in this area according to the Six Sigma approach. David Rogers, senior operations director for support services at

ARUP Laboratories in Salt Lake City, explained ARUP's success with using Six Sigma to ensure that specimens are labeled, transported, and handled properly. ARUP also invests in keeping staff focused on detecting errors.

"We look for opportunities to improve each process," he said. "First, we identify the steps that go into a process, such as selecting the correct patient and printing the associated label, and then we establish checks for each step of the labeling process. We have built in detection processes on the front end and secondary detections within the individual testing labs on the back end."

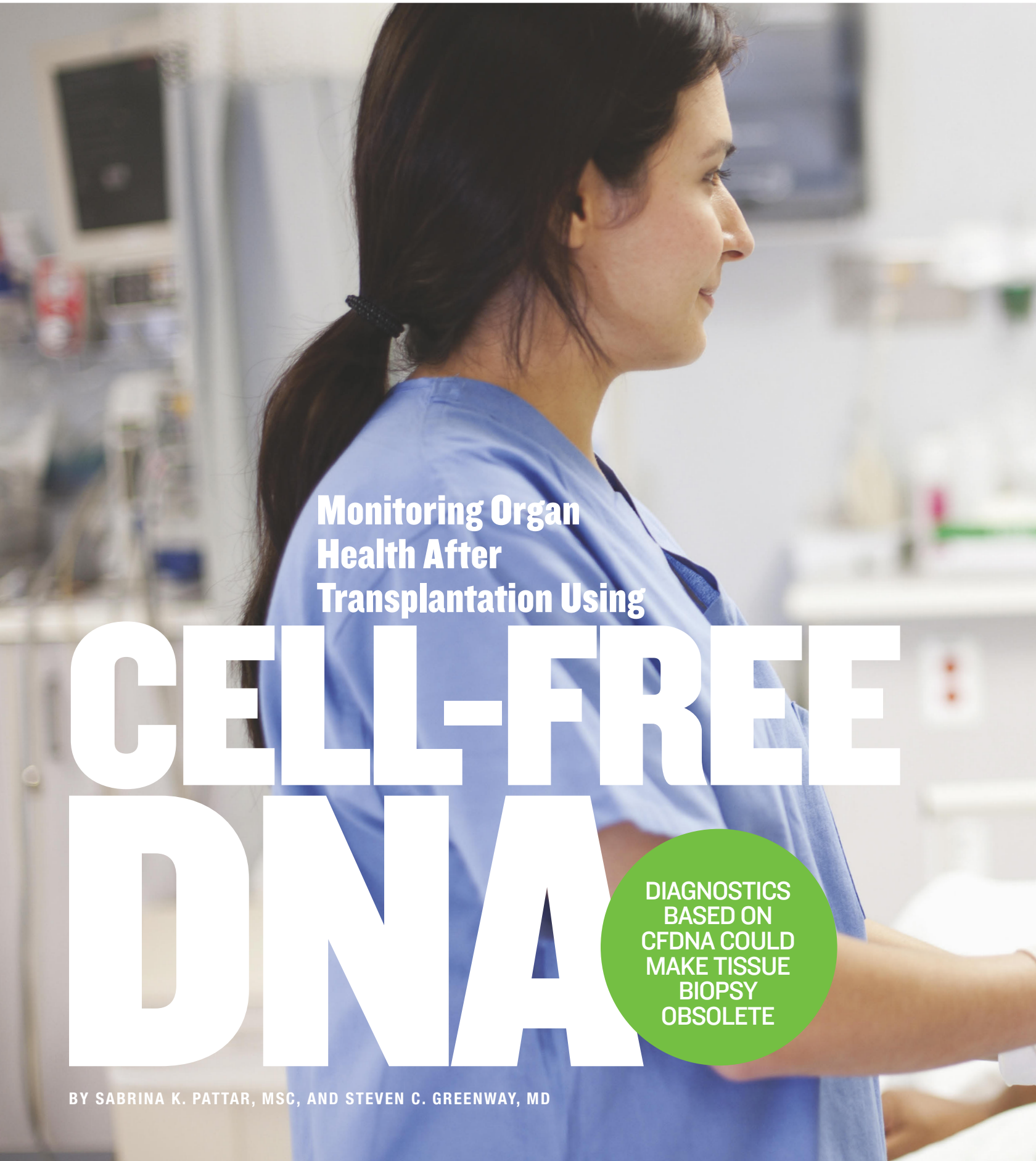
When ARUP receives a specimen, the processing staff use unique identifiers, such as a client's accession number or a medical record number (MRN), to query the system to ensure the correct label is printed. The system used in specimen processing defaults to query unique identifiers in order to eliminate risks associated with using patient names. Other processes involved require processing staff to electronically confirm orders to received specimens. Before a specimen is sent on for testing, at least four identifiers are double-checked during the labeling process. The most common are patient name, client accession or other container ID, MRN, collection date and time, and order. The labeled tube is then routed through an automated delivery system to the proper lab.

"We have a program that incentivizes our employees to find and report any labeling discrepancies," said Rogers. "We find it motivates our staff to check labels very carefully and, more importantly, report issues to facilitate optimal tracking and trending of the individual processes moving forward."

For tests that require complex collections and/or multiple specimens, such as adrenal function testing, additional secondary checks are required. For example, when two or more specimens are processed for these tests, a notification report goes to lab review staff and to support services. These individuals must certify and document electronically that they have reviewed the specimens and they are labeled correctly.

"In addition to implementing quality checks during the individual processing and labeling steps, we target additional processes and reviews where they are needed the most and where they will be most effective," explained Rogers. "That's what our data does for us. By engaging all staff in these efforts, and through effective tracking and trending, we have been able to pinpoint scenarios that inherently present higher risks, and we have identified staff whose specific task it is to secondarily review the associated specimens to ensure they are labeled correctly. Any lab can do this—it's all about effectively using the available data, not the size of the lab."

Kimberly Scott is a freelance writer who lives in Lewes, Delaware.
+EMAIL: kmscott2@verizon.net



Monitoring Organ Health After Transplantation Using

CELL-FREE DNA

DIAGNOSTICS BASED ON CFDNA COULD MAKE TISSUE BIOPSY OBSOLETE

BY SABRINA K. PATTAR, MSC, AND STEVEN C. GREENWAY, MD

Costly and invasive tissue biopsies to detect allograft rejection after transplantation have numerous limitations. Assays based on cell-free DNA (cfDNA)—circulating fragments of DNA released from cells, tissues, and organs as they undergo natural cell death—have been intensively studied recently and could ultimately improve our ability to detect rejection, implement earlier changes in management, and even enhance the long-term survival of transplanted organs.

CfDNA assays that circumvent the need for whole-genome sequencing (WGS) and the need for a priori knowledge of donor and/or recipient genotypes have powerful logistical advantages and are currently under clinical scrutiny. In addition, improving knowledge of the organ-specific kinetics of donor-derived cfDNA (dd-cfDNA) following transplantation has also helped optimize these assays. Laboratories also have introduced alternative methods for quantifying dd-cfDNA, such as digital droplet polymerase chain reaction (PCR) and organ-specific DNA methylation patterns. As such, the field of minimally invasive diagnostics based upon cfDNA is increasingly promising, one day potentially replacing traditional tissue biopsies.

THE ROLE OF CFDNA IN ORGAN REJECTION

Rejection, referring to injury of a donated organ caused by the recipient's immune system, can cause allograft dysfunction and even patient death. T-cell mediated acute cellular rejection (ACR) occurs most often within the first 6 months post-transplant (*1*). ACR involves accumulation of CD4+ and CD8+ T-cells in the interstitial space of the allograft as the recipient's immune system recognizes antigens on the donated organ as foreign. These T-cells initiate an immune cascade that ultimately leads to programmed cell death (apoptosis) of the targeted cells. As these cells die, genomic DNA is cleaved and fragments of dd-cfDNA, measuring approximately 140 base pairs (bp) in length, are released to join the pool of recipient cfDNA in the blood and ultimately excreted in the urine (*2*).

Circulating cfDNA has recently been leveraged as a diagnostic tool to replace invasive biopsies in other areas of medicine, including analyzing fetal DNA fragments within the maternal circulation

to identify genetic abnormalities in utero and sequencing circulating DNA released from tumor cells to identify cancer-related mutations. In both these cases as well as in transplantation, high-throughput sequencing that identifies and quantifies DNA sequence differences distinguishes between the two different populations of cfDNA derived from distinct sources (*2*). Three characteristics of cfDNA make it an excellent noninvasive candidate biomarker to detect rejection after solid organ transplantation: It can be obtained from a simple blood draw, its concentration accurately measured, and its nucleotide sequence easily identified. Using cfDNA as a biomarker for ACR is also advantageous since it is derived from the injured cells of the donated organ and therefore should represent a direct measure of cell death occurring in the allograft. Furthermore, cfDNA maintains all of the genetic features of the original genomic DNA, allowing the genetic material released from the donated organ to be differentiated from the cfDNA derived from cells of the recipient that are undergoing natural apoptosis (*3*).

Frequent and accurate monitoring of allograft health is essential for transplant recipients' long-term survival. For heart transplantation (HT), endomyocardial biopsy (EMB) is the current gold standard for detecting ACR (*4*). However, EMBs are costly with significant limitations, many of which are common to all organ biopsies (*5-7*). Moreover, the invasive nature of EMBs puts HT patients at risk for complications (*6,8,9*). Unfortunately, currently available noninvasive methods including echocardiography or magnetic resonance imaging (MRI) lack sufficient specificity and sensitivity to reliably detect rejection (*10-13*). Blood-based biomarkers, such as cfDNA, represent a promising alternative that could be readily implemented into clinical practice (*14-17*).

Levels of cfDNA fluctuate for multiple reasons including infection, surgery, trauma, or even exhaustive exercise.

KINETICS OF CFDNA DURING QUIESCENCE AND REJECTION

Since cfDNA originates from the naturally occurring process of apoptosis, all individuals have detectable levels of cfDNA in their blood (*18*). For healthy individuals, the majority of circulating cfDNA comes from hematopoietic cells that have undergone natural death related to cellular turnover. Levels of cfDNA fluctuate for multiple reasons including infection, surgery, trauma, or even exhaustive exercise (*2,19*). Therefore, developing a cfDNA-based assay to detect rejection requires assessing the expected kinetics of dd-cfDNA release into the recipient's circulation post-transplant. This consideration is especially important since the release of dd-cfDNA over time post-transplant is organ-specific (*20-22*).

For example, at 1 day post-HT the average level of dd-cfDNA is 3.8 ± 2.3% (*20*). However, by 7 days the level of dd-cfDNA has declined rapidly and remains consistently low (<1%). During an episode of acute rejection in the heart, the level of dd-cfDNA was found to increase to 4%–5% from a baseline of about 0.06% observed during quiescence. The kinetics of dd-cfDNA observed in the circulation of HT recipients was similar to that observed after renal transplantation (*22*).

In contrast, recipients of bilateral lung transplants were found to have an average dd-cfDNA fraction of 26 ± 14% on the first postoperative day. Furthermore, the reduction in dd-cfDNA was characterized by levels of dd-cfDNA that declined rapidly within the first week but then slowed and generally remained at 1%–3% (*21*). However, similar to heart and kidney transplants during an episode of acute rejection, the level of dd-cfDNA increased significantly, climbing to an average of 14%–15%.

Differences in tissue mass and rates of cellular turnover account for this variability in the levels of dd-cfDNA released early post-transplant and during quiescence. For example, differences in circulating dd-cfDNA levels in quiescent bilateral and single-lung transplants can be explained by the difference in cellular turnover, being 107 vs. 58 cells/second, respectively (*21*). By contrast, in a quiescent transplanted heart, the cellular turnover rate is only 8 cells/second (*21-23*). Thus, an understanding of the expected levels of dd-cfDNA associated with a given solid organ is essential to facilitate development of organ-specific assays that detect rejection. Once the kinetics of cfDNA release for a particular organ are understood, several methods exist for quantifying the relative amount of dd-cfDNA.

STRATEGIES TO DISTINGUISH RECIPIENT- VS. DONOR-DERIVED CFDNA

Donor-Recipient Sex-Mismatch

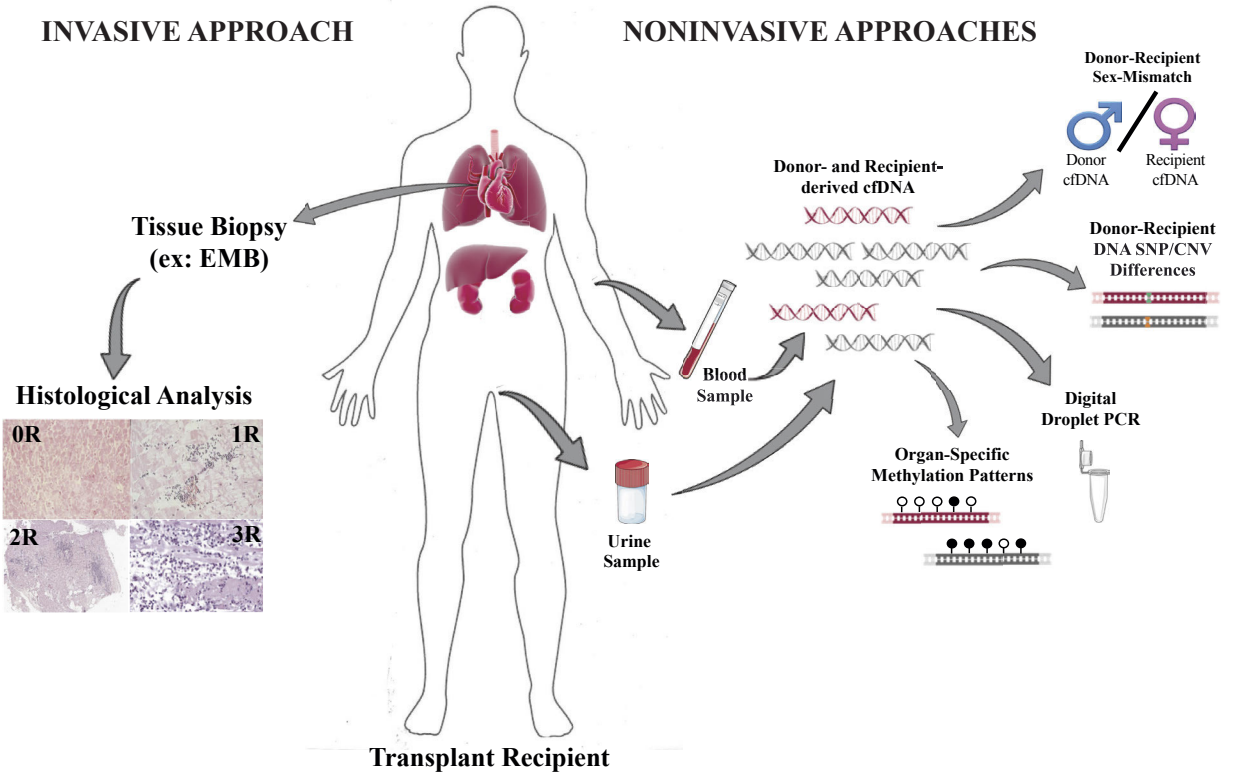
For organ transplants in which the donor is male and the recipient is female, laboratories can leverage this sex mismatch to calculate dd-cfDNA levels from within the recipient's total cfDNA pool (*17*). Researchers first demonstrated the feasibility of this approach in urine samples taken from female renal transplant recipients who had received a kidney from male donors and when they experienced rejection demonstrated elevated levels of dd-cfDNA in their urine that specifically contained regions found on the Y chromosome (*17*). Although this approach allows for confident diagnosis of rejection in the allograft, sex-mismatch between the donor and recipient is relatively infrequent and not universally applicable.

Donor-Recipient DNA Sequence Differences

An organ transplant can also be regarded as a genome transplant, as the cells within a transplanted organ contain the genetic information of its donor. As such, the concept of genome transplant dynamics (GTD) relies on the presence of genetic differences between the donor and recipient at a particular locus, which then can be leveraged to identify the origin of the circulating cfDNA (*20-24*). Ideally, the recipient would be homozygous for a single base (for example, AA) and at the same locus the donor would be homozygous for a different base (for example, GG).

Previous Page: ER Productions Limited / Getty Images

F1 Detecting Rejection



Methods to detect rejection following solid organ transplantation include invasive and non- or minimally invasive assays. Levels of donor-derived cfDNA can be quantified in blood or urine based on genetic or epigenetic differences. EMB, endomyocardial biopsy. Modified from Pattar and Greenway (7).

Given the genetic heterogeneity between individuals, tens of thousands of potentially informative loci across the genome can be interrogated using high-throughput sequencing to distinguish dd-cfDNA from recipient cfDNA (*20*,*24*). This concept was first illustrated using banked samples from cardiac donors to obtain a priori donor genotypes for each donor-recipient pairing. After extracting and sequencing cfDNA from each recipient, the fraction of donor-specific molecules was determined. In samples taken during or immediately preceding a biopsy-proven rejection event, the proportion of donor-specific single nucleotide polymorphisms (SNPs) was found to have increased from <1% to >3%–4% (*24*).

This early retrospective study has now been validated prospectively. Adult and pediatric heart and lung transplant recipients were recruited and genotypes for each donor-recipient pair were obtained through WGS with an average of 53,423 informative SNP markers identified (*20*). Overall, early detection of acute rejection was superior to that of AlloMap, the first Food and Drug Administration-approved non-invasive approach to detecting ACR after HT based on transcriptome analysis (*25*).

Research also has shown that WGS not only provides information about a graft but also a patient's virome and overall state of immunosuppression. This represents a potentially great advantage unobtainable by other assays (*26-28*).

However, WGS faces challenges that could prevent it from being implemented routinely in clinical practice. For example, while a recipient's genetic information can be easily obtained, this is not always true for a donor. Moreover, WGS is costly, labor intensive, and time-consuming.

An alternative method employs a panel of genotyped polymorphic SNPs identified within the pool of extracted cfDNA thereby eliminating the need for a priori knowledge of a donor's specific genotype (*29*). Unlike kidney and liver transplants, which often occur between closely related individuals, the donor-recipient pairs for heart and lung transplants typically are not related. GTD requires genotyping of both the transplant recipient and donor. However, in practice, donor genotype information is often unavailable. Here, we address this issue by developing an algorithm that estimates dd-cfDNA levels in the absence of a donor genotype. Our algorithm predicts heart and lung allograft rejection with an accuracy that is similar to conventional GTD. We furthermore refined the algorithm to handle closely related recipients and donors, a scenario that is common in bone marrow and kidney transplantation. We show that it is possible to estimate dd-cfDNA in bone marrow transplant patients

who are unrelated or who are siblings of the donors, using a hidden Markov model. Therefore, algorithms have been developed for heart and lung transplants which assume that the donor's genotype occurs at the same frequency as the general population. Based on these frequencies and comparison to the known genotype of the recipient, the fraction of dd-cfDNA can be reliably estimated from the total pool of cfDNA isolated from a recipient's plasma sample.

In the case of lung transplantation, this single-genome model, when compared to the methodology using both donor and recipient genotypes, was found to provide comparable fractions of dd-cfDNA. However, when researchers applied this same algorithm to HT, the estimated levels of dd-cfDNA were not as strongly correlated as in lung transplants. This might be related to the lower absolute amounts of dd-cfDNA present after HT. This is another example of organ-specific cfDNA kinetics that can influence assay results and must be taken into account (*30*).

In the case of renal transplantation, prospective studies have been conducted to ascertain the utility of dd-cfDNA levels, identified using known donor-specific SNPs, as a viable marker for rejection. In one such study, 384 kidney recipients were recruited from 14 clinical sites to provide blood samples at scheduled intervals and at times of clinically indicated biopsies (*31*). Overall, the study focused on the correlation between the histology in 107 biopsy specimens from 102 patients and the levels of dd-cfDNA found in matched plasma samples. More specifically, 27 biopsy samples from 27 patients with active rejection were obtained along with 80 biopsy samples from 75 patients without active rejection.

In this study, active rejection included acute antibody-mediated rejection (AMR), chronic AMR, and ACR. The assay used in this study employed a 1% cutoff for the fraction of dd-cfDNA to indicate the presence or absence of active rejection and was found to have 85% specificity (95% CI, 79%–91%) and 59% sensitivity (95% CI, 44%–74%). The sensitivity of this assay was greater for discriminating between active and absent AMR, as the use of a cutoff of 1% dd-cfDNA was found to have an 83% specificity (95% CI, 78%–89%) and 81% sensitivity (95% CI, 67%–100%). Notably, in both cases, the sensitivity declined substantially when the fraction of dd-cfDNA exceeded 3%.

To improve specificity and sensitivity of a non-invasive cfDNA-based assay to detect rejection following renal transplantation, investigators also have surveyed the absolute amount of dd-cfDNA (*32-33*). By interrogating the absolute amount of dd-cfDNA, one can eliminate the artificial changes in the fraction of dd-cfDNA due to increases in total cfDNA levels caused by non-rejection events, such as infection, trauma, or exercise, potentially creating a more accurate assay.

To investigate this possibility, one study employed 32 informative copy number variants (CNVs) based on population frequencies, as opposed to relative proportions of donor and recipient SNPs at given loci (*32*). All CNVs not present within a recipient's genome but present within the extracted cfDNA were therefore assumed to represent dd-cfDNA.

Interestingly, while the specificity and sensitivity improved overall with the use of absolute dd-cfDNA levels, this assay also had a greater capacity to distinguish between the presence and absence of active AMR, as opposed to cases of active ACR. In addition, serum creatinine levels were not sufficient in discriminating between active rejection and quiescence, likely because it is more indicative of glomerular function as opposed to kidney tissue damage (*31-33*).

Another study explored the absolute levels of dd-cfDNA in kidney transplant recipients related to levels of tacrolimus, an immunosuppressant (*33*). Here, the researchers found that the absolute amount of dd-cfDNA was substantially higher in patients with lower tacrolimus levels (<8 μg/L) in comparison to those with higher drug levels. These data suggest that dd-cfDNA levels also have the potential to detect allograft injury resulting from inadequate immunosuppression.

Algorithms have been developed for heart and lung transplants which assume that the donor's genotype occurs at the same frequency as the general population.

Laboratories also have proposed alternatives to WGS. Our group explored targeted sequencing of 124 highly polymorphic (minor allele frequency [MAF] >0.4) SNPs using a commercially available panel, next-generation sequencing, and a novel algorithm (*34*). This approach significantly reduced the total amount of sequencing required, decreasing costs and assay time, and enabling rapid analysis. However, since this assay relies upon differences in MAF between individuals, it would not be robust for closely related donor–recipient pairs, such as seen in living-related kidney donation. It remains to be validated for detecting moderate or greater rejection events.

Laboratories also have explored using polymorphic SNPs to quantify dd-cfDNA combined with the technology of digital droplet PCR (*30,35-37*). Using 41 highly polymorphic SNPs, stable kidney and HT recipients showed dd-cfDNA fractions of 2%–3% with stable liver transplant recipients having a level of 7% (*35*).

For a discussion of organ-specific methylation patterns in cfDNA, see a supplementary section in the online version of the article on www.aacc.org/publications/cln.

CONCLUSIONS

The use of a costly and invasive tissue biopsy to detect allograft rejection

has significant limitations. As such, a minimally invasive assay that can directly and accurately assess the health of the entire transplanted organ represents a holy grail in solid organ transplantation.

The use of cfDNA after transplantation has shown some initial promise, but further study and validation is required to improve our understanding of both the basic biology of cfDNA as well as its behavior post-transplant. At this time, it is clear that important organ-specific differences exist, and patterns of cfDNA release may also differ depending on the type of rejection event. However, cfDNA represents one of the most promising technologies yet developed to complement or even ultimately replace the tissue biopsy.

Sabrina Pattar, MSc, is a graduate student in the department of biochemistry and molecular biology in the Cumming School of Medicine at the University of Calgary in Calgary, Alberta, Canada.

Steven Greenway, MD, is an assistant professor in the department of biochemistry and molecular biology at the Cumming School of Medicine at the University of Calgary and a pediatric cardiologist at Alberta Children's Hospital in Calgary, Alberta, Canada.
+EMAIL: scgreenw@ucalgary.ca

REFERENCES

1. Cornell LD, Smith RN, Colvin RB. Kidney Transplantation: Mechanisms of Rejection and Acceptance. Annu Rev Pathol Mech Dis 2008;3: 189–220.
2. Lehmann-Werman R, Neiman D, Zemmour H, et al. Identification of tissue-specific cell death using methylation patterns of circulating DNA. Proc Natl Acad Sci USA 2016; 113:E1826–34.
3. Naesens M, Sarwal MM. Molecular diagnostics in transplantation. Nat Rev Nephrol 2010;6:614–28.
4. Sakakibara S, Konno, S. Endomyocardial Biopsy. Jpn Heart J 1962;3:537–43.
5. Khan T, Selvakumar D, Trivedi S, et al. The value of endomyocardial biopsy in diagnosis and guiding therapy. Pathology 2017;49:750–6.
6. McMinn J F, Lang NN, McPhadden A, et al. Biomarkers of acute rejection following cardiac transplantation. Biomark Med 2014;8:815–32.
7. Pattar, SK, Greenway, SC. Circulating nucleic acids as biomarkers for allograft injury after solid organ transplantation: current state-of-the-art. Transplant Research and Risk Management 2019;11:17–27.
8. Baraldi-Junkins C, Levin HR, Kasper EK, et al. Complications of endomyocardial biopsy in heart transplant patients. J. Heart Lung Transplant 1993;12:63–7.
9. Mason JW. Techniques for right and left ventricular endomyocardial biopsy. Am J Cardiol 1978;41: 887–92.
10. Kindel SJ, Hsu HH, Hussain T, et al. Multimodality Noninvasive Imaging in the Monitoring of Pediatric Heart Transplantation. J Am Soc Echocardiogr 2017;30:859–70.
11. Lunze FI, Colan SD, Gauvreau K, et al. Tissue Doppler imaging for rejection surveillance in pediatric heart transplant recipients. J Heart Lung Transplant 2013;32:1027–33.
12. Greenway SC, Dallaire F, Kantor PF, et al. Magnetic resonance imaging of the transplanted pediatric heart as a potential predictor of rejection. World J Transplant 2016;6:751–8.
13. Butler CR, Savu A, Bakal JA, et al. Correlation of cardiovascular magnetic resonance imaging findings and endomyocardial biopsy results in patients undergoing screening for heart transplant rejection. J Heart Lung Transplant 2015;34:643–50.
14. Strimbu K, Tavel JA. What are biomarkers? Curr Opin HIV AIDS 2010;5:463–6.
15. Huo Q, Zhou M, Cooper DKC, et al. Circulating miRNA or circulating DNA-Potential biomarkers for organ transplant rejection. Xenotransplantation 2018;e12444.
16. Duong Van Huyen JP, Tible M, Gay A,et al. MicroRNAs as non-invasive biomarkers of heart transplant rejection. Eur Heart J 2014;35:3194–202.
17. Sigdel TK, Vitalone MJ, Tran TQ, et al. A Rapid Noninvasive Assay for the Detection of Renal Transplant Injury. Transplantation 2013;96:97–101.
18. Yamani, M. H. & Taylor, D. O. Heart Transplantation. In Current Clinical Medicine 180–186 (Elsevier, 2010). doi:10.1016/ B978-1-4160-6643-9.00027-8.
19. Atamaniuk J, Vidotto C, Tschan H, et al. Increased Concentrations of Cell-Free Plasma DNA after Exhaustive Exercise. Clin Chem 2004;50:1668–70.
20. De Vlaminck I, Valantine HA, Snyder TM, et al. Circulating cell-free DNA enables noninvasive diagnosis of heart transplant rejection. Sci Transl Med 2014;6:241ra77.
21. De Vlaminck I, Martin L, Kertesz M, et al. Noninvasive monitoring of infection and rejection after lung transplantation. Proc Natl Acad Sci U S A. 2015;2015;112:13336–41.
22. Gielis EM, Beirnaert C, Dendooven A, et al. Plasma donor-derived cell-free DNA kinetics after kidney transplantation using a single tube multiplex PCR assay. PLoS One 2018;13:e0208207.
23. Bergmann O, Bhardwaj RD, Bernard S, et al. Evidence for cardiomyocyte renewal in humans. Science 2009;324:98–102.
24. Snyder TM, Khush KK, Valantine HA, et al. Universal noninvasive detection of solid organ transplant rejection. Proc Natl Acad Sci U S A. 2011;108:6229–34.
25. Pham MX, Teuteberg JJ, Kfoury AG, et al. Gene-Expression Profiling for Rejection Surveillance after Cardiac Transplantation. N Engl J Med 2010;. 362:1890–900 (2010).
26. Lorio MA, Rosa R, Suarez JF, et al. Influence of immune activation on the risk of allograft rejection in human immunodeficiency virus-infected kidney transplant recipients. Transpl Immunol 2016;38:40–3.
27. Simonetta F, Pradier A, Masouridi-Levrat S, et al. Torque Teno Virus Load and Acute Rejection After Orthotopic Liver Transplantation. Transplantation 2017;101:e219–21.
28. Mendez-Eirin E, Barge-Caballero E, Paniagua-Martin M, et al. Impact of Cytomegalovirus Infection on Long-Term Heart Transplant Outcome. J Heart Lung Transplant 2017; 36:S89.
29. Sharon E, Shi H, Kharbanda S 4 et al. Quantification of transplant-derived circulating cell-free DNA in absence of a donor genotype. PLOS Comput Biol 2017;13:e1005629.
30. Schütz E, Fischer A, Beck J, et al. Graft-derived cell-free DNA, a noninvasive early rejection and

graft damage marker in liver transplantation: A prospective, observational, multicenter cohort study. PLoS Med 2017;14:e1002286.
31. Bloom RD, Bromberg JS, Poggio ED, et al. Cell-Free DNA and active rejection in kidney allografts. J Am Soc Nephrol. 2017;28:2221–32.
32. Whitlam JB, Ling L, Skene A, et al. Diagnostic application of kidney allograft-derived absolute cell-free DNA levels during transplant dysfunction. Am J Transplant. 2019;19:1037–49.
33. Oellerich M, Shipkova M, Asendorf T, et al. Absolute quantification of donor-derived cell-free DNA as a marker of rejection and graft injury in kidney transplantation: Results from a prospective observational study. Am J Transplant 2019;19:3087–99.
34. Gordon PM, Khan A, Sajid U,et al. An Algorithm Measuring Donor Cell-Free DNA in Plasma of Cellular and Solid Organ Transplant Recipients That Does Not Require Donor or Recipient Genotyping. Front Cardiovasc Med. 2016;3:33.
35. Beck J, Bierau S, Balzer S, et al. Digital droplet PCR for rapid quantification of donor DNA in the circulation of transplant recipients as a potential universal biomarker of graft injury. Clin Chem 2013;59:1732–41.
36. Boer K, Baan CC, van Donk, N, et al. Donor-Derived Cell-Free DNA as Minimally Invasive Tool to Diagnose Acute Rejection after Kidney Transplantation. Transplantation 2018;102:S689.
37. Zou J, Duffy B, Steward N, et al. Detection of donor cell-free DNA using digital PCR in lung transplant recipients with graft rejection and infection. Hum Immunol 2015;76:68.
38. Tsuji J, Weng Z. Evaluation of preprocessing, mapping and postprocessing algorithms for analyzing whole genome bisulfite sequencing data. Brief Bioinform 2016;17:938–52.
39. Lehmann-Werman R, Magenheim J, Moss J, et al. Monitoring liver damage using hepatocyte-specific methylation markers in cell-free circulating DNA. JCI insight 2018;21: pii: 120687.

Get free continuing education credit for reading this article. AACC designates 0.5 *ACCENT*® credit hours.

Visit www.aacc.org/publications/cln/accent for more information.

Join Us for an Important COVID-19 Webinar

Managing COVID-19 Respiratory Distress Patients Using an Expanded Test Blood Gas Analyzer

COVID-19 patients with respiratory distress require a comprehensive point-of-care test menu to manage their care. This seminar will examine the essential role of an expanded blood gas/critical care test menu, which includes BUN, creatinine, and ionized magnesium for managing acute respiratory distress COVID-19 and its co-morbidities: sepsis, stress hyperglycemia, acute kidney injury and arrhythmia.

Learning Objectives

- Review COVID-19 facts
- Discuss management of critical COVID-19 cases and its co-morbidities
- Review critical care diagnostic tests in the management of COVID-19 patients

Intended Audience

- Point of Care Coordinators
- Lab Managers
- Critical Care Clinicians
- Respiratory Therapy Managers

Presenter

Bogdan Milojkovic, MD
Global Director, Medical
and Scientific Affairs
Nova Biomedical

Educational Credits

- This program offers 1 hour of P.A.C.E. and CRCE continuing education credits.
- This program has been approved by the American Association of Critical-Care Nurses (AACN), for 1.00 CERPs, Synergy CERP Category A, File Number 23117. Approval refers to recognition of continuing education only and does not imply AACN approval or endorsement of the content of this educational activity, or the products mentioned.

Three Webinar Times are Available:

Tuesday, June 2nd, 1 PM Eastern Daylight Time

Thursday, June 25th, 4 PM Eastern Daylight Time

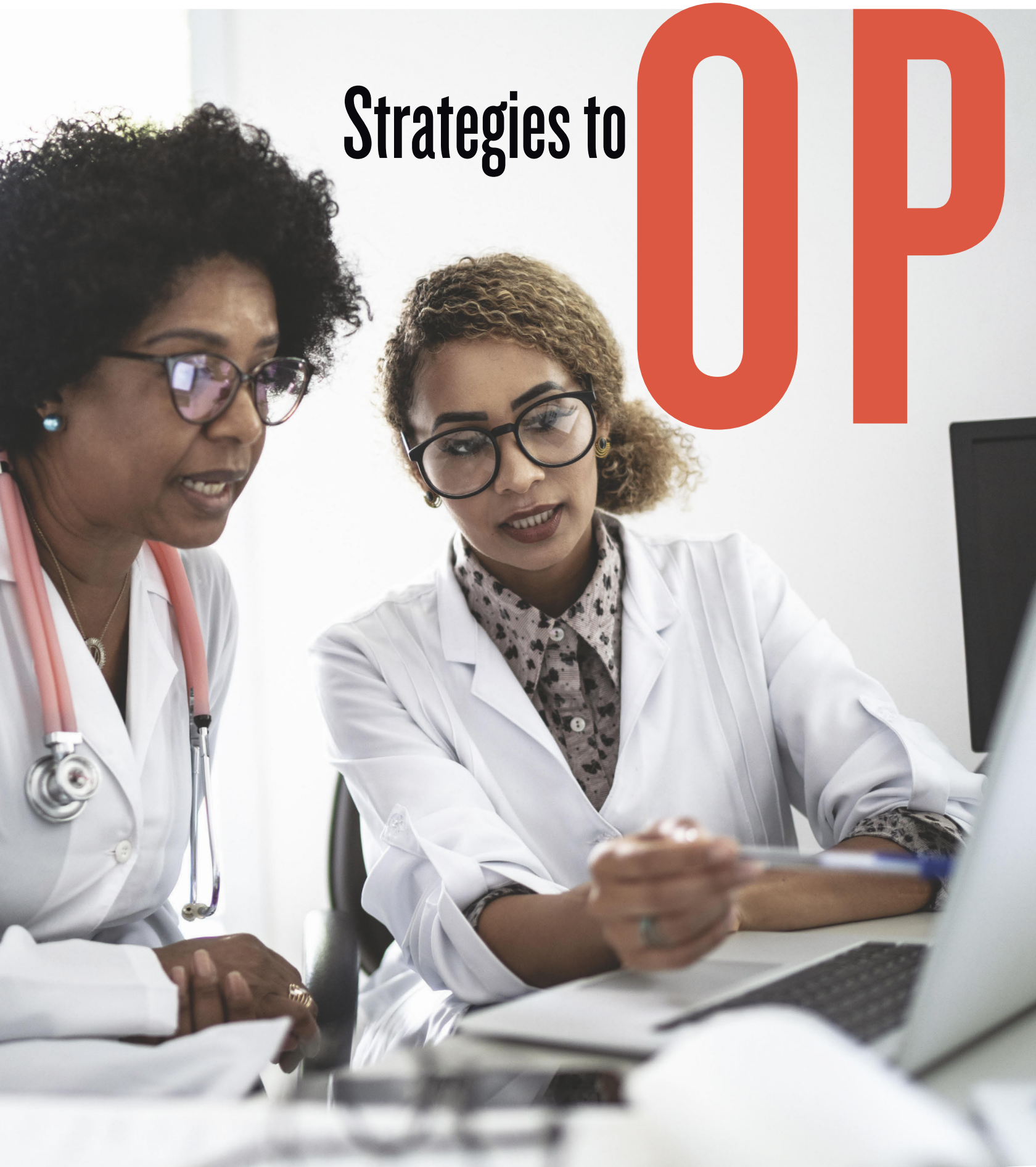
Tuesday, July 14th, 1 PM Eastern Daylight Time

Register Now at:

novabiomedical.com/resp/distress/covid19

nova® biomedical
novabiomedical.com

Strategies to OP



TIMIZE Drug Testing

BY DEBORAH LEVENSON

Data paired with education, communication, and relationship-building drive success

Controlled substance monitoring and other drug testing give clinicians valuable information about how patients adhere to treatment regimens or might be misusing or even abusing drugs. But keeping up with a continually changing drug testing environment challenges most clinicians. New drugs—sold illicitly—keep coming to market. Meanwhile, testing methods have variable performance, and drug testing recommendations evolve. Given all these factors, clinicians need help not only understanding how tests work and how the body metabolizes drugs but also reminders that laboratorians are partners in patient care, according to laboratorians specializing in drug monitoring and toxicology.

"Sometimes physicians can underestimate the complexity of the current drug testing environment," said Jaime Noguez, PhD, director of chemistry and toxicology at University Hospitals Cleveland Medical Center and assistant professor of pathology at Case Western Reserve University. "You can't just rely on a one-size-fits-all approach to drug testing," Noguez added. She urged laboratorians to work with physicians to make sure labs offer useful drug tests, education, and resources.

DEFINING KNOWLEDGE GAPS

Misunderstanding of assays' advantages, disadvantages, and limitations drives inappropriate drug orders, said William Clarke, PhD, DABCC, FAACC, professor of pathology at Johns Hopkins University School of Medicine in Baltimore and co-author of the AACC Academy's practice guideline on monitoring pain management drugs. For example, clinicians who know that an opiate assay will test for presence of various drugs might not realize the assay does not differentiate between morphine and heroin.

Providers also have varying degrees of understanding of drugs' metabolic pathways.

Some clinicians might dismiss results that seemingly make no sense and want to retest patients. Labs should

FG Trade / Getty Images

encourage conversations about potential reasons for odd results. David Colantonio, PhD, DABCC, FAACC, listed a few: genetic polymorphisms, slow-clearing metabolite products, differences in speed of metabolism, or co-administration of drugs that cross-react with an assay. With mass spectrometry (MS) testing especially, labs can measure parent compounds and metabolites and tease out reasons for discrepant results, added Colantonio, clinical biochemist at The Ottawa Hospital, lab director at Pembroke Regional Hospital, and assistant professor of pathology and laboratory medicine at the University of Ottawa in Ontario, Canada.

Kara Lynch, PhD, warned of another potential pitfall for both clinicians and laboratorians: outdated immunoassay panels that test for illicit drugs no longer common in an area. Labs with public health responsibilities should review their panels against current reality, said Lynch, who is an associate clinical professor at University of California San Francisco (UCSF) and co-director of the core laboratory at Zuckerberg San Francisco General Hospital and Trauma Center.

SETTING UP SUCCESS

Labs have many tactics for driving appropriate test orders. At Mayo Clinic in Rochester, Minnesota, clinicians soon will be able to order drug screens via an order entry system driven by algorithms to arrive at the best orders. They will answer a series of questions that lead them to appropriate tests, said Loralie Langman, PhD, DABCC, director of the clinical and forensic toxicology laboratory at Mayo, and Paul Jannetto, PhD, DABCC, MT(ASCP), FAACC, co-director of Mayo's toxicology and drug monitoring lab and metals laboratory. Both are co-authors of the AACC Academy's practice guideline on monitoring pain management drugs.

Mayo's lab report prominently displays interpretive information stating results are consistent with use of particular drugs within the last 3 days. That way, clinicians get the most important information even if they don't read the entire list of analytes and associated results, Langman noted.

At UCSF, Lynch's lab simplifies clinician ordering with a choice of a urine drug screen, a comprehensive MS test with hundreds of compounds, and a list of individual immunoassays. Rules and automatic reflex testing are written into urine test ordering processes and differ by needs of different locations and departments. For example, screening orders from the emergency department (ED) and inpatient units do not get automatic MS confirmatory testing because patients usually are gone before results are ready. Meanwhile, positive urine screen results from clinics automatically reflex to confirmatory testing because clinics might be checking for compliance to prescribed medications. Some immunoassay tests prone to false positives—like a test for amphetamine—are also reflexed to confirmatory testing.

Lynch's lab uses MS for confirmatory testing more sparingly than reference labs because Zuckerberg San Francisco General serves a public health role and operates within a limited budget, she added.

Noguez's lab has a dedicated phone line and email address that pathologists monitor daily to answer questions about test selection and result interpretation in one-on-one conversations with physicians, nurses, and medical assistants. She also gives lectures. Some are recorded and posted online, along with guides to ordering the right test for specific clinical indications and educational and reference documents. They cover topics such as drug detection windows in urine and blood, differences in cutoffs for screening and confirmatory drug tests, and metabolism pathways for common drugs.

Noguez also participates in a health system-wide drug testing oversight committee with laboratory staff, hospital leadership, and practicing clinicians in various specialties. The committee discusses test utilization and new testing needs and works together to design new drug panels. The goal is to arrive at consensus before rolling out new tests and workflows, Noguez explained.

> "Sometimes physicians can underestimate the complexity of the current drug testing environment."
> — Jaime Noguez, PhD

USING DATA

Clinical laboratorians also use data to support testing decisions and communications with clinicians. For example, Noguez regularly uses lab information system (LIS) data on test volume and utilization to guide test menu and workflow changes. Data that show inappropriate ordering by certain physicians or groups can be fodder for educational discussions about proper test utilization, said Jannetto and Langman. Data also inform establishment of hard stops to inappropriate ordering by particular groups, Noguez added.

Colantonio uses various groups' data in discussions with them about how to set up workflows for the new MS lab, which will not be automated.

Noguez also pulls LIS data to learn about local positivity rates for prescription and illicit drugs in various patient populations. Data patterns can reveal new drugs of abuse and trends in older ones and inform care by ED, pain management, and addiction specialists, Colantonio noted.

Lynch, whose hospital offers high-resolution testing for acute drug poisoning, uses LIS data to graph

AACC | *Better health through laboratory medicine.*

AACC Universal Sample Bank

AACC's Universal Sample Bank offers pre-screened and well-characterized sample sets at a competitive price.

The sample set can be used in a variety of clinical studies, including clinical assay development, standardization, and reference range studies.

Features of AACC's Universal Sample Bank include:

- Individual pre-COVID-19 samples available
- Serum/plasma from 700+ healthy individuals
- Ethnically and geographically diverse adult population (18+)
- IRB-approved collection protocol
- Available in serum or lithium heparin plasma
- Comprehensive donor data with health screening information
- Results of HbA1c, Creatinine, and NT-proBNP screens

AACC members who purchase the sample sets for academic research purposes will receive a significant discount.

International shipping now available.

For more information visit www.aacc.org/samplebank.

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.

the prevalence of drugs that UCSF's tests target. She also uses outside data on local drug use and overdoses. The data come from a collaborative group including her local poison control system, public health department, medical examiner's office, city toxicology lab, and needle exchange programs, which monitor local drug use and overdoses. All these partners share information.

BUILDING RELATIONSHIPS

Building relationships and rapport with physicians and other staff is key to educating them and achieving proper test utilization. All the individuals *CLN* interviewed emphasized the importance of accepting opportunities to discuss drug testing and participating in hospital initiatives related to optimizing utilization.

Lab tours "are an amazing way to build professional bridges with various types of staff," including clinical groups, pharmacists, and nurses who are often unaware of lab processes, Colantonio added. Tours include explanations of different aspects of the lab's workflow and of what goes into validating tests and monitoring their quality. Colantonio spends extra time in areas of the lab especially of interest to a group.

The tours also spur trust and understanding when LIS problems delay results, openness to discussing discrepant results, and specific questions about test variability and measurements. Conversations have even led to a few published case studies, including one about a high-dose phenobarbital that can convert to its prodrug primidone (Ther Drug Monit 2013;35:145–9).

Leading physician rounds is an excellent way to find out what clinicians need. When Colantonio reads an article that speaks to questions he commonly encounters in rounds, he will send it to interested parties. Residents especially like his handouts with tables of common cross-reactions, he noted.

Clarke stays plugged into clinical groups that need education. In collaboration with pain management and addiction specialists, he helped develop Johns Hopkins' standards and guidelines for pain management. By request, he speaks about available tests and their limits at the hospital's regularly scheduled pain conference and during grand rounds.

Colantonio and Noguez also suggested involving clinicians from various specialties on lab utilization committees. They can tell labs what tests are not helpful, which new tests might be, and can give valuable insights that lead to effective changes in ordering. In addition, Colantonio recommended offering tailored trainings to emergency, clinical pharmacology, and toxicology residents, both via lectures and one-on-one interactions. Clarke also favors the one-on-one approach, especially when offered proactively. "Be old fashioned. Go to them," he advised.

"You have to understand clinicians' needs. Sometimes you don't know what they don't know," Clarke added. He has worked at his institution for 20 years and is "still meeting groups of clinicians I need to connect with."

Deborah Levenson is a freelance writer in College Park, Maryland.
+EMAIL: dlwrites@verizon.net

FG Trade / Getty Images

WE ARE ALL IN

It has never been more vital for us to come together as one global laboratory medicine community. Be a force for change as we take on the greatest clinical science challenges facing our world today. This is our time to:

DISCOVER critical research advancing the field from 350+ expert speakers and 300 scientific sessions covering infectious disease, emerging diagnostics, genomics and more.

EXPLORE 200+ product and technology innovations at the world's largest exposition for clinical laboratory science.

CONNECT with global leaders working in clinical chemistry, molecular diagnostics, mass spectrometry and other areas of laboratory science.

Join us. Register today at meeting.aacc.org.
Save with the lowest rates available until October 29.

2020 AACC ANNUAL SCIENTIFIC MEETING & CLINICAL LAB EXPO

DECEMBER 13-17 • CHICAGO, IL USA

meeting.aacc.org

AACC

POINT-OF-CARE TESTING Professional Certification

Point-of-Care Testing Professional Certification documents that healthcare professionals working in point-of-care testing have proven expertise in this area and are among the top in their field.

This certification is valuable for those in the clinical setting as well as industry and academia.

The exam tests mastery and knowledge of:

- Test Selection
- Quality Management
- US Regulatory Compliance and Safety

APPLICATIONS ACCEPTED: **JUNE 1 – SEPTEMBER 14, 2020**

LEARN MORE AT **www.aacc.org/CPP**

AACC | *Better health through laboratory medicine.*

Regulatory Roundup

FDA Authorizes SARS-CoV-2 Tests That Use Samples Self-collected by Patients

In an effort to lower the risk of infection for healthcare professionals involved in sample collection for SARS-CoV-2 testing, as well as to save personal protective equipment, the Food and Drug Administration (FDA) has granted emergency use authorizations (EUAs) to two SARS-CoV-2 tests that use self-collected samples. One of these tests is the first that FDA has authorized to offer a home collection option for SARS-CoV-2. Specifically, FDA reissued the EUA for LabCorp's COVID-19 RT-PCR test to permit testing of samples self-collected by patients at home using LabCorp's Pixel by LabCorp COVID-19 test home collection kit. This kit provides patients with a specific Q-tip style cotton nasal swab and saline for sample collection. Once patients self-swab to collect their nasal sample, they mail their sample in an insulated package to LabCorp for testing. LabCorp intends to make the Pixel home collection kits available to consumers in most states with a doctor's order.

Now that this is an option for COVID-19 testing, however, AACC is concerned that consumers will not be able to collect nasopharyngeal samples correctly and that this could cause false negative results. In a letter to FDA, the association has therefore asked the agency to consider issuing a warning about home-collected samples for COVID-19 testing. As AACC states in the letter, "We share FDA's goal of expanding consumer access to COVID-19 testing and are confident in LabCorp's ability to obtain *analytically* correct results from the test. However, serious *preanalytical* concerns associated with home specimen collection kits exist that must be taken into consideration before deploying these kits widely and allowing physicians to make clinical decisions based on results gained from this … approach."

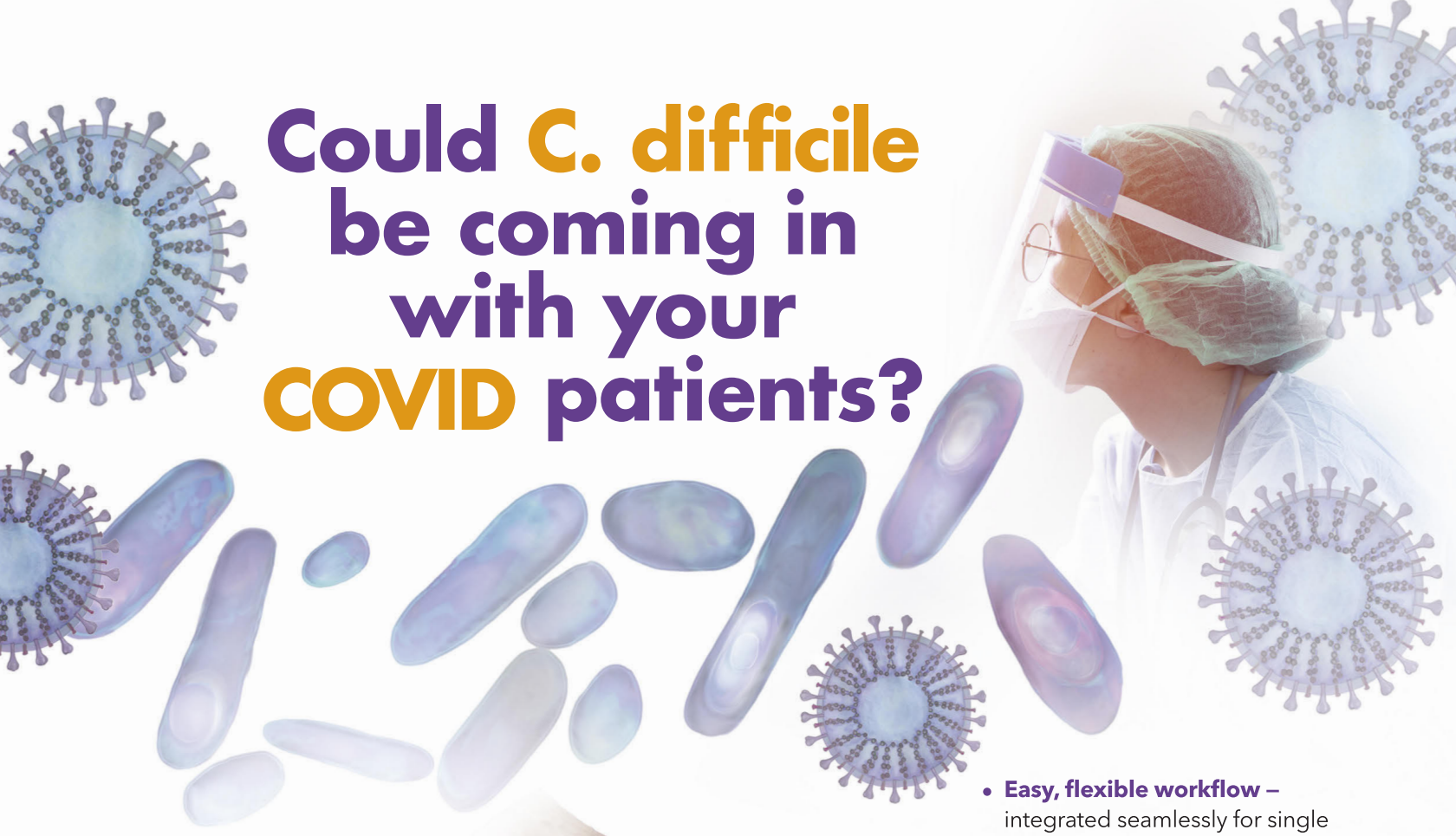
The second self-collection test that FDA has authorized—developed by Rutgers University's cell and DNA biorepository, RUCDR Infinite Biologics, in collaboration with Spectrum Solutions and Accurate Diagnostic Labs—uses saliva samples that patients self-collect at testing sites by spitting into a sealable tube. This saliva-based test is currently available through RWJBarnabas Health network, New Jersey's most comprehensive healthcare system.

WITH NEW FDA APPROVAL, ROCHE'S HPV TEST CAN BE USED ON THE COBAS 6800/8800

The Food and Drug Administration (FDA) has approved Roche's cobas HPV test for use on the company's fully automated, high-throughput cobas 6800/8800 systems. This test identifies women at risk for cervical cancer by detecting the presence of high-risk human papillomavirus (HPV) DNA in cervical samples. Specifically, the test detects HPV genotypes 16 and 18—the two genotypes responsible for about 70% of all cervical cancers—and reports the 12 other high-risk HPV types as a combined result, all in one test and from one patient sample. FDA originally approved this test for the cobas 4800 system in 2011 using data from the ATHENA (Addressing the Need for Advanced HPV Diagnostics) trial. For this most recent approval, the agency considered data from the registrational IMPACT (Improving Primary Screening and Colposcopy Triage) trial, which enrolled almost 35,000 women in the U.S. for the purpose of clinically validating the cobas HPV for use on the cobas 6800/8800 systems.

dragana991 / Getty Images

Could C. difficile be coming in with your COVID patients?



An influx of COVID-19 related hospitalizations brings patients presenting a spectra of symptoms, requiring a spectra of treatments – this convergence could lead to an increased risk of *C. difficile*.

If prioritized COVID-19 testing has you making tough decisions about your C. difficile testing standard and algorithm – it shouldn't!

- **Easy, flexible workflow –** integrated seamlessly for single specimen or **high-throughput** batching up to 12 tests at a time.
- **Minimal training –** get up and **running quickly**
- **The Power of Virena® –** enhanced diagnostics featuring **data analytics** and **surveillance**
- **Compact footprint –** measuring 9.4"x 9.4"x 5.9", **deployable practically anywhere**

Maintain your molecular testing standard for C. difficile with Solana.

QUIDEL | Solana® C. difficile FIA | with the power of Virena

To learn how our Solana C. difficile Assay combined with the data-rich analytical tools of Virena can help you maintain the integrity of your testing algorithm, call **Quidel Inside Sales at 858.431.5814.**

The Accurate. Sustainable. Molecular **C. difficile** Solution.

quidel.com

ADM307200EN00 (05/20)

monkeybusinessimages / Getty Images

FDA APPROVES FOUNDATION MEDICINE'S CO-DIAGNOSTIC FOR BILE DUCT CANCER

Foundation Medicine has received Food and Drug Administration (FDA) approval for FoundationOne CDx, a companion diagnostic for Incyte's Pemazyre (pemigatinib), which is a selective fibroblast growth factor receptor (FGFR) inhibitor approved for adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a *FGFR2* fusion or other related rearrangement. *FGFR2* fusions and related rearrangements occur in 10%–16% of intrahepatic cholangiocarcinoma patients. FoundationOne CDx is a comprehensive genomic profiling assay that identifies patients with these *FGFR2* fusions or related rearrangements who might benefit from treatment with Pemazyre.

Previously, FDA had already approved FoundationOne CDx as a companion diagnostic for 20 unique therapies across multiple other solid tumor types. Using next-generation sequencing, the test analyzes DNA isolated from formalin-fixed paraffin embedded tumor tissue specimens to detect substitutions, insertion and deletion alterations, and copy number alterations in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability and tumor mutational burden.

FDA PROPOSES RECLASSIFICATION OF HCV TESTS FROM CLASS III TO II

The Food and Drug Administration (FDA) has proposed reclassifying two types of hepatitis C virus (HCV) diagnostic tests from class III to II. The two types of HCV devices that FDA is proposing to reclassify are nucleic acid-based HCV RNA devices intended for the qualitative or quantitative detection or genotyping of HCV RNA and certain HCV antibody devices intended for the qualitative detection of antibodies to HCV. If this reclassification is finalized, manufacturers would be able to submit these tests through FDA's 510(k) pathway for clearance instead of through the premarket approval pathway. For both HCV test types, FDA reviewed medical device reporting databases and found that there are a low number of reported events for these devices relative to the number of tests conducted using them. All recalls of these devices have also been resolved without any identified patient harm. When taken all together, FDA believes this indicates a good safety record for these HCV tests and that special controls under the class II device designation will effectively mitigate the risks associated with these devices.

SIEMENS HEALTHINEERS GETS FDA NOD FOR POINT-OF-CARE BLOOD GAS ANALYZER

The Food and Drug Administration has cleared Siemens Healthineers' RAPIDPoint 500e Blood Gas analyzer, a point-of-care instrument that is intended to help diagnose and monitor critically ill patients. The analyzer, is already available in countries requiring the CE mark. Using 100 µL of whole blood or pleural fluid, this instrument generates a full panel of blood gas, electrolyte, metabolite, carbon monoxide (CO)-oximetry, and neonatal bilirubin results in approximately 1 minute. As a fully cartridge-based analyzer it does not have any maintenance requirements; the measurement cartridge includes the planar sensors, sample probe, and CO-oximetry chamber, all of which are replaced with every new cartridge. The RAPIDPoint 500e also includes Integri-sense Technology, which performs frequent quality and blood integrity checks before, during, and after every patient sample and features three levels of independent automatic quality control, multiple calibration routines, and advanced software algorithms.

Industry Playbook

Gilead Science, Second Genome Ink $38 Million Agreement

In a 4-year agreement, Gilead Science and Second Genome have partnered to advance microbiome-based research for inflammatory diseases. Through the partnership, Second Genome will provide its Microbiome Analytics Platform to help Gilead identify biomarkers that track responses to five experimental medicines for inflammation, fibrosis, and other diseases. Additionally, both companies hope to identify new biomarkers for the treatment of inflammatory bowel disease (IBD).

"There is a growing body of evidence that the microbiome plays an important role in disease progression and treatment response in inflammatory diseases," said William Lee, PhD, executive vice president of research at Gilead. "We look forward to working with Second Genome to investigate the microbiome's role in inflammatory disease and particularly IBD, where patients can face significant challenges in achieving long-term remission with conventional therapies."

According to the terms of the agreement, Second Genome will receive $38 million from Gilead, with a promise of an extra $1.5 billion if the five medicines get approved for market sale. The company will also receive up to $300 million for IBD programs. In return, Gilead will claim all rights for each drug produced from the partnership.

ONE DROP BUYS SANO FOR DIGITAL TECHNOLOGY PLATFORM

The digital healthcare solutions company One Drop announced its acquisition of Sano Intelligence, a company structured around health sensing technology. One Drop will acquire all assets and intellectual property of Sano Intelligence to expand its platform in digital health. The companies plan to develop adaptive, personalized integrated health solutions for real-time patient monitoring via their mobile devices.

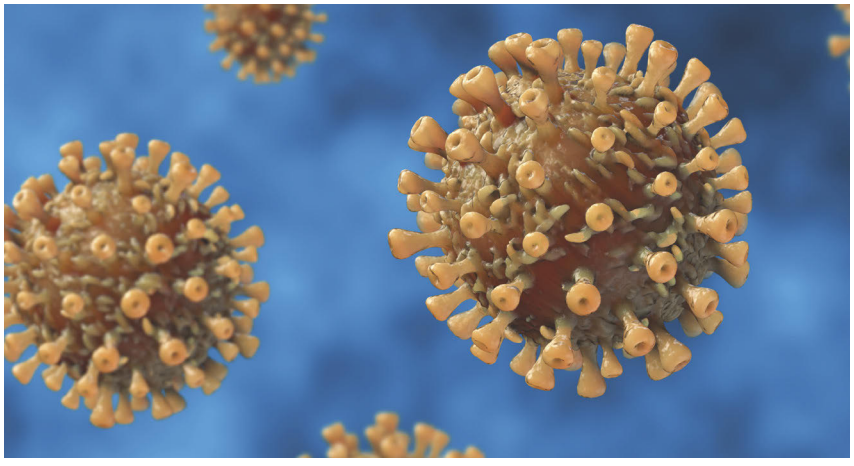
Through the agreement, One Drop will make use of Sano's silicon-sensing production infrastructure to manufacture a painless stick-on device that will assist patients in better understanding and tracking their blood glucose levels. The aim is to enable patients to discover any abnormalities in their health early on to prevent progression to more severe conditions.

One Drop will increase commercialization of the sensing technology by offering end-to-end employer and payor offerings, digital-only offerings, and even retail availability. The company also plans to hire Sano employees as part of the acquisition.

CO-DIAGNOSTICS PARTNERS WITH PROMEGA FOR LOGIX SMART COVID-19 TEST

Co-Diagnostics has partnered with Promega to rapidly advance production and manufacture of its Logix Smart COVID-19 test. Since Co-Diagnostics received Food and Drug Administration emergency use authorization, domestic demand for the test has increased quickly. As part of the agreement, Promega will therefore help Co-Diagnostics expand manufacturing of the test kits across the U.S. and internationally.

"Promega has shown its dedication to customer satisfaction



feellife / Getty Images

time and again, with branches in 16 countries and over 50 global distributors. We are confident they will be instrumental in helping Co-Diagnostics meet the growing demand for our products as we connect with even more laboratories and testing centers in the United States and abroad," said Dwight Egan, CEO of Co-Diagnostics.

The Logix Smart COVID-19 test recently acquired CE Mark approval to be sold as an in vitro diagnostic test to private and public clinical laboratories. The test, which detects RNA from the SARS-CoV-2 virus, has shown 100% sensitivity in patients who show common symptoms, according to the company.

GENETIC TESTING AGREEMENT FOR LYSOSOMAL STORAGE DISORDERS

To improve diagnosis of lysosomal storage disorders (LSD) in children, Axovant Gene Therapies and Invitae are collaborating in the Detect Lysosomal Storage Diseases (Detect) program, which will focus on genetic testing to advance treatment of conditions including GM1 gangliosidosis and GM2 gangliosidosis, more commonly known as Tay-Sachs/Sandhoff disease.

Studies have shown that LSDs are misdiagnosed in a majority of patients, and if not treated early, these inherited metabolic disorders have the ability to cause premature deaths. The Detect program aims to increase genetic testing and turnaround time of results to diagnose patients sooner for earlier treatment and prevention. The program will target 53 LSD-specific genes to ensure accurate diagnosis. Through the agreement, Invitae will offer testing and counseling free of charge for patients affected by LSDs.

Axovant is currently targeting GM1 gangliosidosis through its AXO-AAV-GM1 clinical program at the National Institutes of Health and is seeking clearance through the Food and Drug Administration's investigational new drug pathway for its AXO-AAV-GM2 clinical trial.

FatCamera / Getty Images

ARCHERDX AND ILLUMINA PARTNER FOR WORLDWIDE IN VITRO DIAGNOSTICS

ArcherDX has entered a multiyear agreement with Illumina in a bid to expand its companion diagnostics offerings. Through the partnership, Illumina plans to help ArcherDx commercialize its in vitro diagnostic kits in laboratories and hospitals worldwide.

The collaboration aims to place Archer FusionPlex research products globally while also increasing access to in vitro diagnostic tests performed on Illumina's NextSeq 550Dx and MiSeqDx systems. The deal could also help ArcherDx receive Food and Drug Administration approval for its tumor Stratafide genomic companion diagnostic for monitoring cancer treatments through patient blood or tissue samples, according to the companies.

"Creating broad access to clinically relevant genomic information is core to our company's mission, and we expect this commercial partnership with Illumina will accelerate that process," ArcherDX CEO Jason Myers, PhD, said in a statement. "Illumina's next-generation sequencing instruments are ubiquitous in thousands of clinical and research settings due to their accuracy, speed, and user experience."

Index to Advertisers

Ask The Expert

Using Digital Microscopy in Hematology Labs

EXPERT
Megan O. Nakashima, MD

Which laboratories should consider implementing digital microscopy?

A: There are different digital microscopy systems for a variety of laboratory settings. Most, if not all of these systems have capabilities for remote review, which is almost universally beneficial because it enables technologists to perform complete blood counts with differentials even when they aren't in the hematology area, near the slides, or at a microscope. Some laboratories might use this capability to flex staffing where it is most needed at a given time. Small or remote laboratories that might not have the appropriate laboratory professionals on-site can also use this feature to have their differentials performed remotely or to consult those with more expertise at other sites.

What are the benefits of digital microscopy?

Most digital microscopy systems have onboard libraries of images of different types of cells. Labs can use these during training, and technologists can also refer to them when performing a differential. This and the fact that technologists can easily review a patient's previous cells on a digital system help to increase standardization and quality.

Many technologists also prefer the ergonomic experience with digital microscopy. Because it involves viewing images on a screen rather than at a microscope, they can sit back comfortably in a chair with less neck and wrist strain.

Automated digital microscopy systems add efficiency in larger and specialized laboratories. For example, in our laboratory a slide can be made on a slide-maker/stainer and imaged by the digital microscope without any human intervention. Another potential way to improve efficiency with this technology is to implement slide scans; if a sample is flagged for potential abnormal cells, the technologist can quickly scroll through to verify abnormal cells are absent and release the automated result without having to spend time classifying each cell type.

However, data conflict about whether or not digital microscopy systems actually lessen the time required to perform a differential. These systems provide an obvious benefit for samples with low leukocyte counts since they find and image the cells before a technologist looks at a case, saving the time required to "hunt" for cells. Some instruments even merge images from two slides to get adequate cells for a differential. Interestingly, in our lab the technologists who speed up the most when using digital microscopy are those with fewer years of experience.

What are the barriers to implementing a digital microscopy system?

As with any analyzer, labs must perform a validation study first before putting these systems in place. A more significant challenge is that some staff might resist the change if they are not that comfortable using computers and software. Some technologists also just prefer the experience of looking at a glass slide. While digital microscopy images are generally high quality, you must have adequate computer monitors to approximate the resolution that manual microscopy provides. Different light sources also affect digital image quality. With time, users do become more accustomed to using digital systems and reviewing the images, but some will always prefer the manual option.

What are some limitations of current digital microscopy systems?

One major limitation is that the system may only scan a set area of a slide. In these cases, a technologist has to manually review the slide to look at the feathered edge for suspected platelet clumps (pseudothrombocytopenia). Additionally, larger cells that tend to spread to the edges of the smear may be missed when this happens.

Another potential drawback right now is that a single vendor dominates the market. So many of the things I have mentioned may change as that company's systems evolve or other companies develop new systems. As things currently stand, though, digital microscopy cannot entirely replace its manual counterpart.

Dr. Nakashima will discuss this topic during two roundtable talks (session numbers 43110 and 53210) at the 2020 AACC Annual Scientific Meeting on December 15 at McCormick Place, Chicago.

Megan O. Nakashima, MD, is medical director for automated hematology and urinalysis and a staff hematopathologist at Cleveland Clinic in Ohio.
+EMAIL: nakashm@ccf.org

AMP UP THE SIGNAL.
DIAL DOWN THE NOISE.

Surmodics™ IVD Provides the Gold Standard in Immunoassay Components and Service

For 40 years, Surmodics™ has provided leading in vitro diagnostic companies critical components for developing sensitive, reproducible immunoassays. Whether you are developing an ELISA/EIA, point-of-care device, western blot or microarray, Surmodics products provide the gold standard for increased sensitivity, stability and accuracy. Our high performance, ready to use formulations ensure quality and a quicker path to commercialization.

Our goal is your goal: **ensuring accurate and reliable results every time, for every patient.**

ELISA Stabilizers, Diluents & Blockers

ELISA Substrates

ELISA Stop Solutions & Support Reagents

DIARECT™ Antigens & Antibodies

Microarray Slides/ Surfaces

Your partner in quality
ISO 13485:2016 & ISO 9001:2015 CERTIFIED

For more information or samples, contact orders@surmodics.com.
952-500-7200 | www.surmodics.com/ivd

SURMODICS

K-ASSAY®. . . *High-Quality, Low-Cost Reagents*

Immunoassay Reagents for chemistry analyzers™

Over 38 different assays available

Nutrition
Ferritin
Prealbumin
Retinol Binding Protein
Transferrin
UIBC

Serum Proteins
α-1 Acid Glycoprotein
α-1 Anti-Trypsin
α-1 Microglobulin
β-2 Microglobulin
Haptoglobin
IgA
IgG
IgM

Allergy
Total IgE

Stomach
*H. pylori**

Diabetes
Cystatin C
Hemoglobin A1c
Insulin
Microalbumin
Microtransferrin*

Inflammation / Cardiac
Anti-Streptolysin O
Complement C3
Complement C4
CRP
Rheumatoid Factor

Coagulation
D-Dimer
Fibrinogen
Factor XIII
Plasma FDP*
Serum/Urine FDP*

Lipid Assessment
Apo AI
Apo AII*
Apo B
Apo CII*
Apo CIII*
Apo E*
Lp(a)
Remnant Lipoprotein
Cholesterol*

Lung
KL-6*

* Research Use Only

New Products Now Available!!

- β-2 Microglobulin reagent for chemistry analyzers
- *H. pylori* Test Reagent* for chemistry analyzers
- KL-6 (Krebs von den Lungen-6)* reagent for chemistry analyzers
- Microtransferrin* reagent for chemistry analyzers
- Remnant Lipoprotein Cholesterol* reagent for chemistry analyzers
- Retinol Binding Protein reagent for chemistry analyzers
- UIBC (Unsaturated Iron Binding Capacity) for chemistry analyzers

KAMIYA BIOMEDICAL COMPANY
www.k-assay.com/CLN.php
diagnostics@k-assay.com | 800-KAMIYA-5