June 2019

CLN Clinical Laboratory News

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AI FOR BABIES' RARE GENETIC DISEASES

99%

Precision of AI model vs. expert interpretation

PAGE 8

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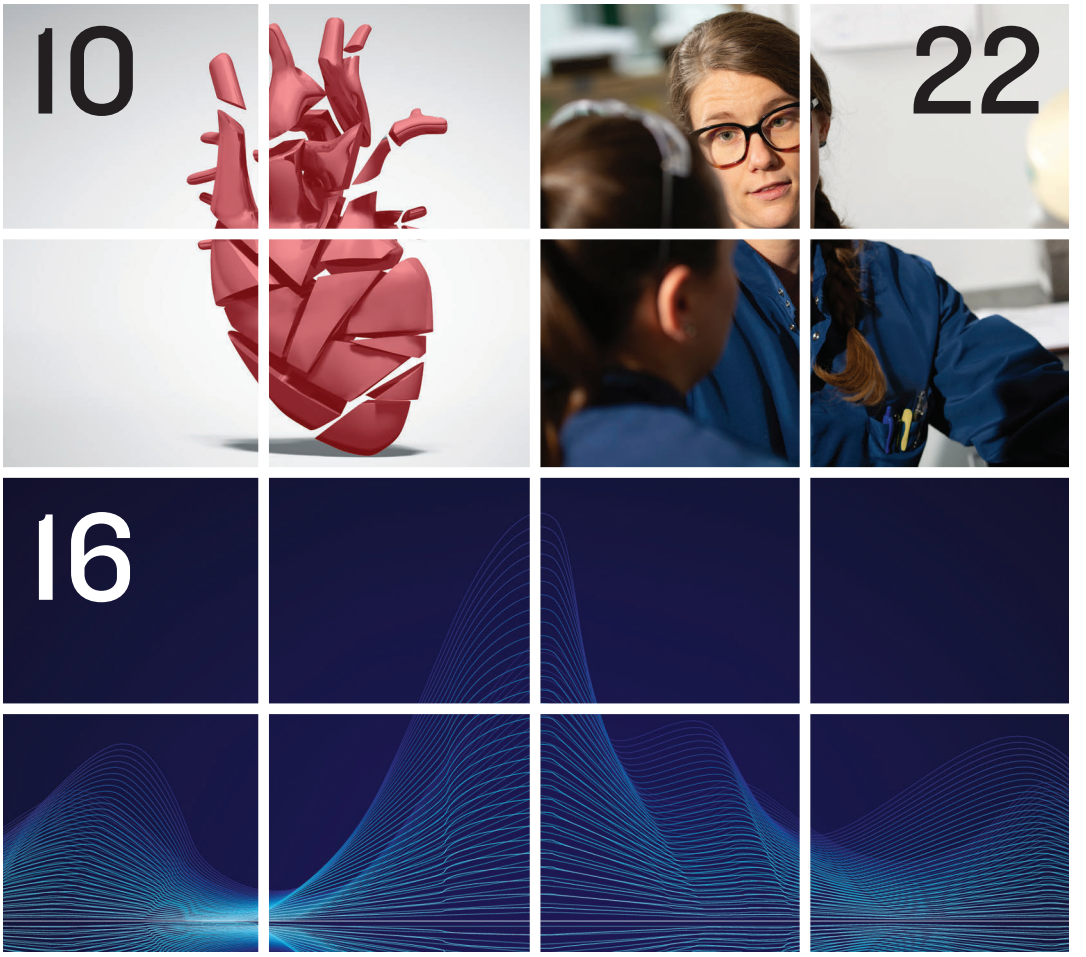

Departments

The correlation between ionized calcium and total calcium can be compromised by alterations in albumin concentration, blood pH, elevated levels of drugs or fatty acids bound to albumin, and unusual serum proteins such as monoclonal immunoglobulins.
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Cover: Brian Fitzgerald

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Federal Insider

AACC Calls for Evaluating Patient Access Under PAMA

AACC is urging the Government Accountability Office (GAO) to examine the effect of the Protecting Access to Medicare Act (PAMA) reimbursement cuts on patient access to testing.

While the GAO issued a report on PAMA in November 2018, it failed to deal with any questions about patient access to care. "Monitoring the effect on patients is part of the mandate Congress gave to the agency," AACC wrote in a letter to GAO. "Legislators specifically asked GAO to study the impact of PAMA implementation on beneficiary access as well as the impact of the new payment system on laboratories that provide a low volume of services and laboratories that specialize in a small number of tests."

AACC believes GAO research on these issues could offer Congress a clearer understanding of the consequences of PAMA reimbursement cuts. The association is recommending that in subsequent reports, GAO cover not only patient access but also how small laboratories are faring, the effect on patients in underserved areas, and whether low-volume laboratories have had to change their test menus.

In its letter, AACC cited data from the National Independent Laboratory Association and COLA, a laboratory accrediting organization. For example, a 2018 COLA survey found that 39% of responding laboratories expected to refer more tests to other laboratories because of PAMA, while 33% planned to alter their test menu. "These data indicate that patient access to testing will diminish under new payment law and that patient care will thereby deteriorate," AACC wrote.

The association also recommended that in assessing the impact on patients and smaller laboratories, GAO employ statistically valid data collection methods to make sure that Congress can use evidence-based data to inform its decisionmaking.

Jose Luis Pelaez / Iconica / Getty Images

AACC SUPPORTS NEWBORN SCREENING LEGISLATION

AACC is urging Congress to pass the Newborn Screening Saves Lives Reauthorization Act of 2019.

This legislation would renew federal newborn screening programs for 5 years and also help these programs contend with new conditions and use new technologies. The bill also would commission a report from the National Academy of Medicine to make recommendations for modernizing newborn screening.

AACC has worked with a coalition of healthcare organizations for many years to ensure that the nation's newborn screening program continues to receive federal funding. AACC contributed to efforts that led to the passage of the Newborn Screening Saves Lives Reauthorization Act of 2014 by holding a congressional briefing, visiting individual congressional offices, and releasing a position statement that affirmed AACC's endorsement of public and private efforts to maintain, improve, and expand newborn screening programs.

NEW PAYMENT MODEL DRIVES VALUE-BASED PAYMENT FOR PRIMARY CARE

A new proposal from the Trump administration reflects the bipartisan consensus in Washington that the federal government must move away from fee-for-service payment models to contain healthcare costs. The Centers for Medicare and Medicaid Services (CMS) has announced a renewed effort to bring value-based reimbursement and capitated payment to primary care after a steady expansion of this approach for inpatient hospital care.

Called the CMS Primary Cares Initiative, the new payment scheme aims to reduce costs, cut the administrative burden on primary care providers, and nudge providers to spend more time caring for patients.

Beginning in January 2020, the initiative will roll out five new payment options that the agency hopes will appeal to a broad swath of providers. The models allow providers to receive a single, capitated monthly payment and earn higher reimbursement for specializing in care of patients with complex, chronic needs and seriously ill populations. Some of the models also reward providers with higher payments based on patient outcomes such as controlling high blood pressure, managing diabetes, and screening for colorectal cancer.

Included in the program is a direct contracting model for organizations such as accountable care organizations and managed care organizations so that various groups of providers can participate. These models are "designed to create a competitive delivery system environment where organizations offering greater efficiencies and better quality of care will be financially rewarded," according to CMS.

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Bench Matters

The Curious Incident of the False Lipemia Index Alert

A popular Sherlock Holmes short story focuses on the disappearance of the racehorse, Silver Blaze, on the eve of an important race. The horse was stolen from the stables during the night in Victorian England.

Gregory (Scotland Yard police detective): "Is there any other point to which you would wish to draw my attention?"
Sherlock Holmes: "To the curious incident of the dog in the night-time."
Gregory: "The dog did nothing in the night-time."
Sherlock Holmes: "That was the curious incident."

The "curious incident of the dog in the night-time" to which Holmes alludes is easily explained: The dog made no noise because the thief was no stranger to the dog.

Amy Guimaraes-Young, MD, PhD

Yashpal Agrawal, MD, PhD

HIL INDEXES: LIPEMIA AND MORE

Laboratorians utilize the HIL index to detect potential analytical interference from hemolysis, icterus, and lipemia (HIL) in serum and plasma samples. Thus, implicit to an HIL index alert is the presence of significant hemolysis, icterus, or lipemia in a sample. Indeed, in our experience, lipemia index alerts are accurate 99.9% of the time. But what does it mean when a lipemia alert flags a specimen with no visible evidence of lipemia or turbidity?

MEASURING WAVELENGTHS

Hemoglobin, unconjugated bilirubin, and lipids are detected photometrically at specific wavelengths. While the absorption spectra of hemoglobin and bilirubin overlap significantly, the photometric light scatter induced by lipids can be quite variable. This is due to the heterogeneity of endogenous lipids.

Our instrument at Rocky Mountain Regional VA Medical Center in Aurora, Colorado—the Siemens Dimension Vista 1500—measures lipid interference at the wavelength of approximately 700 nm (determined using intralipid fat emulsion). When HIL interference is detected, the analyzer records the photometric data as an HIL index value. The HIL index, in turn, corresponds to the approximate concentration of hemoglobin, bilirubin, or lipid present in the sample. On our analyzer, lipemia is reported as an index value between 1 and 8. An HIL index alert notifies our staff when a sample has an HIL index value known to produce a 10% or greater change in analyte quantification.

Not all analytes are affected by HIL and those that are can have differing thresholds for interference. We utilize a lipemia index of 3 as our threshold value for flagging samples with HIL index alerts. This translates to a lipid concentration of approximately 100-200 mg/dL.

False lipemia alerts have been reported with certain chemotherapy drugs, circulating immune complexes, and monoclonal proteins. In the case of monoclonal proteins, the sample itself is not turbid, but becomes turbid when mixed with water in the test cuvette during the HIL measurement process. This explains why some samples that trigger a lipemia index alert lack observable lipemia.

ALERTS WITHOUT VISUALLY OBSERVABLE LIPEMIA

There is a tendency to accept as merely outliers alerts for samples that don't have visible lipemia. However, our lab took the opportunity to investigate these cases further and found our version of "the curious incident of the dog in the night-time."

Of the 80,000 comprehensive metabolic panels run annually at our center, false lipemia alerts occur 1 to 2 times each month. Over a 2-year period, we had 25 samples flagged as having a high lipemic index (≥3 out of 8) but with no evidence of lipemia upon visual inspection or no previously documented monoclonal gammopathy (J Appl Lab Med 2019;3:1062). In these cases, we notified the ordering physician and obtained permission to evaluate the samples further by serum protein electrophoresis. In so doing we found that 12/25 (48%) of samples harbored monoclonal immunoglobulins. When we characterized the immunoglobulin heavy chains using immunofixation electrophoresis we found IgM

If your fentanyl assay is not detecting norfentanyl...

True positive samples could be slipping through your fingers.

The opioid epidemic is a serious global crisis affecting public health as well as social and economic welfare. Fentanyl abuse, misuse and diversion is a major contributor to this crisis.

Fentanyl is a potent synthetic opioid used in pain management, that can produce euphoric effects with rapid onset but short duration. While it is a useful prescription pain medication, it is also made illegally and used recreationally, often with heroin and cocaine.

Fentanyl is metabolized to norfentanyl and other metabolites. About 90% of the dose is excreted in urine as norfentanyl, while parent fentanyl accounts for less than 7%. Detection of both parent and this major metabolite is essential to determine fentanyl use and is an integral part of combating the opioid depidemic.

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monoclonal protein in 11 cases and IgG in one.

Monoclonal gammopathy of unknown significance (MGUS) carries a risk of progressing to multiple myeloma, a plasma cell disorder that often presents with vague, nonspecific symptoms including aches and pain, headaches, fatigue, constipation, and fevers. The paucity of distinct clinical features can delay suspicion for and diagnosis of this and similar disorders. Early diagnosis helps clinicians set up a monitoring program for patients to see if their MGUS is changing and determine when treatment should begin.

We have found that using the lipemia index alert in the absence of visible lipemia is a value-added tool in identifying previously unsuspected, undiagnosed monoclonal gammopathies. We believe the lipemia index alert would work similarly on other analyzers, and we encourage our colleagues to dig a little deeper into any seemingly false alerts. Doing so might set up patients for better health outcomes.

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The Sample

Artificial Intelligence Pipeline Speeds Early Diagnosis of Critically Ill Newborns

Building on their prior work aimed at providing early diagnosis to critically ill newborns, researchers at Rady Children's Institute for Genomic Research in San Diego reported using an artificial intelligence (AI) pipeline to speed up diagnosis of rare genetic diseases, doing so in a record median time of 20.10 hours (Sci Transl Med 2019;11.eaat6177). These efforts in a retrospective analysis of children already diagnosed with genetic diseases matched expert interpretation in 95 children with 97 diseases with 97% sensitivity and 99% precision. Prospectively, the AI pipeline correctly diagnosed 3 of 7 seriously ill infants with 100% sensitivity and precision.

Use of this pipeline, which incorporated a machine learning process and clinical natural language processing (CLNP), could be key in broadly disseminating rapid whole genome sequencing (rWGS) to neonatal intensive care units (NICU), according to the researchers.

Standard rWGS with manual analysis and interpretation of genomic data for diagnosing genetic disorders in newborns typically takes a mean of 16 days, although the researchers in a prior study cut this to 26 hours.

The investigators deployed AI and other new technologies to tighten their rWGS workflow. They used a Nextera DNA Flex Library Prep Kit (Illumina) to manually prepare sequencing libraries directly from blood samples or dried blood spots, which cut out several prep steps. They also performed rWGS with the NovaSeq 6000 sequencer and S1 flow cell (Illumina), which is faster and less labor intensive than their legacy Illumina sequencer. In addition, they used an Illumina hardware and software platform (DRAGEN) "highly optimized for speed, sensitivity, and accuracy" to align and call variants.

To speed up the process of reviewing electronic health records (EHRs) to identify patients' phenotypes, the research team used CLiX CLNP (Clinithink), which they optimized to extract clinical features from unstructured text in EHRs.

The investigators also wrote scripts to automatically transfer patients' nucleotide and structural variants from DRAGEN to MOON, an autonomous interpretation software (Diploid) that automates genome interpretation using AI to automatically filter and rank likely pathogenic variants.

URINE DRUG TEST RESULTS CHART DRAMATIC RISE IN FENTANYL USE

A study of 1 million urine drug test (UDT) results ordered as part of routine care by physicians throughout the U.S. found a 1,850% increase from 2013 to 2018 in the rate of nonprescribed fentanyl positivity in samples that also were cocaine-positive and methamphetamine-negative, and a 798% increase in the rate of nonprescribed fentanyl-positive samples among methamphetamine-positive and cocaine-negative results (JAMA Network Open 2019;2:e192851).

The results underscore that fentanyl, either added surreptitiously to or taken with other drugs, could be a contributing factor in the sharp rise in cocaine- and methamphetamine-related overdose deaths, according to the investigators.

The study involved a random sample of UDT results analyzed for definitive testing by Millennium Health using liquid chromatography-tandem mass spectrometry. Positivity thresholds for fentanyl, norfentanyl, benzoylecgonine, and methamphetamine were ≥2 ng/mL, ≥8 ng/mL, ≥50 ng/mL, and ≥100 ng/mL, respectively.

The median age of the study population was 44, and more than half of patients were women. Test orders came from many different practice settings, with substance abuse disorder treatment centers and pain management practices accounting for 53.5% of specimens. Overall positivity rates for cocaine, methamphetamine, and fentanyl were 4%, 3.1%,

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and 1.4%, respectively. Positivity rates for nonprescribed fentanyl in cocaine-positive, methamphetamine-negative results rose from 0.9% in 2013 to 17.6% in 2018; and in cocaine-negative, methamphetamine-positive results from 0.9% to 7.9%.

CLINICAL ASSESSMENT, PROCALCITONIN-GUIDED ANTIBIOTIC THERAPY YIELD COMPARABLE OUTCOMES

A head-to-head comparison of guideline-based clinical assessment versus procalcitonin (PCT)-guided antibiotic therapy in patients with community acquired pneumonia (CAP) found that the two approaches were about equal in the primary outcome of total antibiotic exposure within 30 days of emergency department (ED) admission (Ann Emerg Med 2019; doi.org/10.1016/j.annemergmed.2019.02.025). "Because [PCT] assessments add time and cost to patient care, these findings support strategies" to help providers better understand and follow clinical guidelines for managing patients with CAP, the authors suggested.

This pragmatic multicenter trial of 370 eligible adult patients in 12 French hospitals randomly assigned 143 patients to clinical assessment and 142 to PCT-guided care. The study enrolled patients given the presumptive diagnosis of CAP while in ED, based on meeting at least two of three respiratory infection criteria. All patients had their PCT levels measured but attending physicians did not see results for patients in the clinical assessment group.

In the runup to the start of the trial, all participating physicians received about 2 hours' training on the background and use of guideline-directed clinical assessment as well as the PCT algorithm. The latter recommended against or strongly recommended against starting antibiotics when PCT levels were ≤0.25 µg/L or <0.1 µg/L, respectively. Conversely, the PCT algorithm recommended or strongly recommended starting antibiotics if PCT levels were ≥0.25 µg/L or ≥0.5 µg/L, respectively. If antibiotics were not started in the ED after the first PCT result, another PCT measurement took place after 6 to 24 hours, with antibiotic therapy considered using the same cutoffs.

The antibiotic duration was not significantly different between the two groups, with medians of 9 days and 10 days respectively and a P value of 0.21, nor was it significantly different in the modified intention to treat populations that excluded patients who had received antibiotics for other indications or who had Legionnaires' disease.

BY KRISTIN HARPER

Drug-Use Associated Infective Endocarditis Presents New Patient Profile, Underscores Necessity of Coordinated Screening, Treatment Efforts

THE LATEST FISS IN THE OPIOID CRISIS

URE

The opioid epidemic is cutting a wide swath through American life and culture as individuals struggle not only with their dependence on and abuse of painkillers but also experience financial, social, and emotional fallout from their conditions. Added to these challenges is a growing health menace: drug use-associated (DUA) infectious diseases, which are on the rise across a range of disorders. For example, acute hepatitis C virus infections in the United States more than doubled between 2004 and 2014, with more than 75% of patients reporting injection drug use in recent years. In addition, 2015 was the first year in more than 2 decades in which the number of HIV diagnoses attributed to injection drug use grew.

DUA hepatitis and HIV infections are not the only ones increasing. A less well-known type of DUA infection also is on the uptick: infective endocarditis (IE). A recent study conducted in North Carolina found that annual hospitalizations for DUA IE in that state rose roughly twelvefold between 2007 and 2017 (Ann Intern Med 2019;170:31-40). Similarly, researchers at the University of Virginia in Charlottesville noted a "dramatic increase" from 2000 to 2016 in DUA-IE-related hospitalizations at that institution (BMC Infect Dis 2018;18:532).

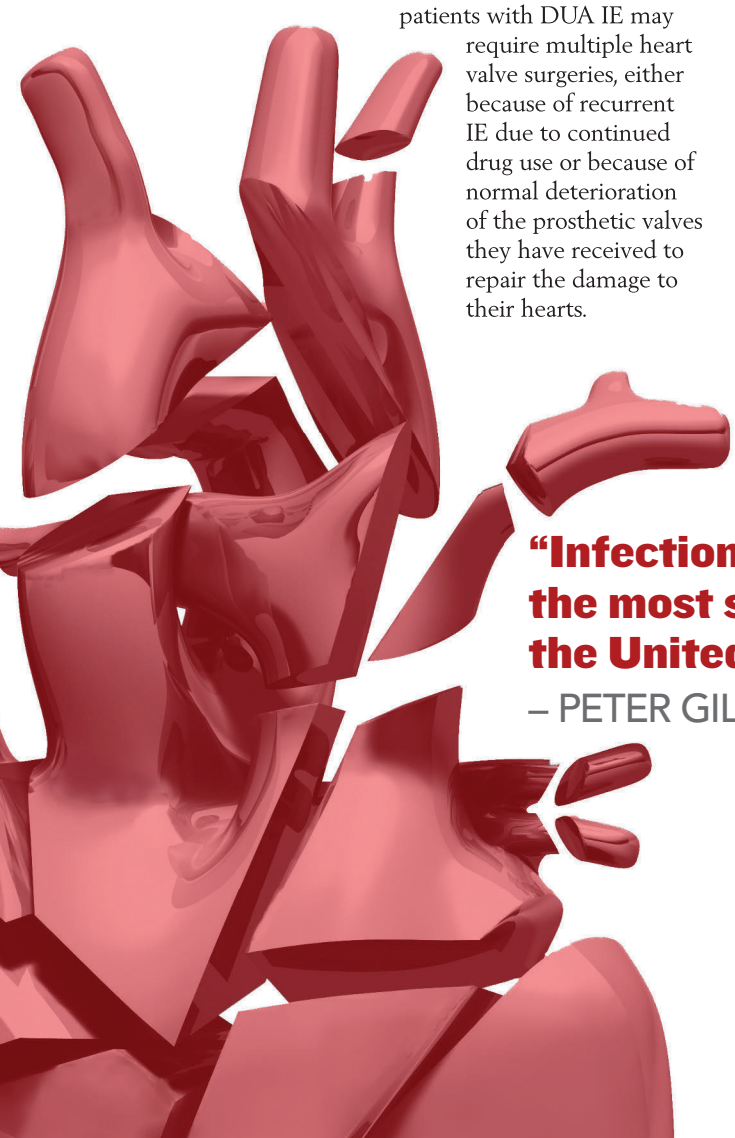
"The rise in endocarditis is making it clear that overdoses are not the only public health concern related to drug use," said Asher Schranz, MD, an infectious disease specialist at

Hiroshi Watanabe / Taxi / Getty Images

the University of North Carolina in Chapel Hill and lead author of the North Carolina study. Based on their findings he and his colleagues averred, "[DUA]-IE is a critical, emerging public health issue that is affecting the lives of young persons, burdening health systems and public insurance payers, and fundamentally reshaping the epidemiology and management of endocarditis."

A New Patient Profile

Patients with DUA IE have a strikingly different profile from patients with IE that is not associated with drug use. First, patients with DUA IE are typically decades younger. In addition, *Staphylococcus aureus* is more often the cause of their IE, and this pathogen results in particularly severe infections and worse post-surgical outcomes. This may help explain the longer, more expensive hospital stays of patients with DUA IE. Finally, patients with DUA IE may require multiple heart valve surgeries, either because of recurrent IE due to continued drug use or because of normal deterioration of the prosthetic valves they have received to repair the damage to their hearts.



Changing Patterns of Drug Use Driving Cases

In Canada, researchers have found that the increase in DUA IE cases has paralleled the use of hydromorphone; these controlled-release pills are more difficult to dissolve and inject than the opioid formulations that came before them (CMAJ 2019;191:E93-9). "Cookers and filters used to prepare the drug are frequently contaminated with *S. aureus*," said Mike Silverman, MD, chief of infectious diseases at St. Joseph's Hospital and London Health Sciences Centre in Ontario, and senior author of the article describing that research. "The contamination seems to be related to the complex method used to prepare the drug, as well as drug excipients that keep *S. aureus* viable longer."

The growth in cases in the United States may result from different patterns of drug use. "There was more injection of prescription narcotics and heroin earlier in the epidemic," said Sandra Springer, MD, associate professor of medicine at Yale School of Medicine in New Haven, Connecticut. "Now, the spike in infectious diseases related to injection drug use is due to a surge in illicit fentanyl analogs, alone and mixed with other drugs—in particular, methamphetamine." Springer served on the planning committee for a 2018 National Academies of Sciences, Engineering, and Medicine workshop on integrating treatment for opioid use disorder and infectious diseases and co-authored a call for action on this issue (Ann Intern Med 2018;169:335-6).

"Infections associated with opioid use are one of the most serious infectious disease problems in the United States since AIDS."

– PETER GILLIGAN

The Diagnostic Workup for DUA IE

Clinical labs may be the first to learn that a patient has IE, and their support is crucial for ensuring that patients receive timely and effective treatment, according to experts. To diagnose IE, labs rely on blood cultures. They may need to help educate clinicians on best practices for gathering samples, said Rachael Liesman, PhD, director of microbiology at Kansas University Medical Center in Kansas City. "Blood should be collected via two venipuncture sites across four to six blood culture bottles—10 mL per bottle. Underfilling bottles results in lower sensitivity."

Identifying the responsible pathogen(s) and performing antimicrobial susceptibility testing "will generally take anywhere from 2 to 5 days, depending on how fast the organisms grow in blood culture," said Peter Gilligan, PhD, director emeritus of the clinical microbiology-pathology laboratories at the University of North Carolina Hospitals in Chapel Hill. As Liesman noted in a minireview she co-authored, documenting two or more blood cultures that are positive for a microorganism capable of causing IE is a major diagnostic criterion for the condition (J Clin Microbiol 2017;55:2599–608).

In 2% to 40% of cases of IE, blood cultures are negative; the most common cause of this is a patient receiving antibiotics prior to the collection of blood cultures. If a patient undergoes valve surgery for her IE, the excised valve can be subjected to 16S ribosomal sequencing to identify the pathogen responsible. However, "in patients for whom surgery is not an option, diagnostic options remain inadequate," said Liesman. "No published molecular or diagnostic assay has demonstrated acceptable clinical sensitivity."

Many patients with DUA IE have other infections that require treatment as well. For that reason, patients with DUA IE should be tested and treated for common blood-borne infections. "Because this patient population is generally [intravenous] drug users, they should be tested for HIV, hepatitis C virus, hepatitis B virus, and hepatitis A virus," said Gilligan.

"They should also be offered immunization for hepatitis B and hepatitis A virus, if they are not already immune," added Schranz.

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"Persons who inject drugs may be candidates for preexposure prophylaxis for HIV as well."

Tracking Opiate Use

Performing tests to help document and monitor a patient's drug use is another way that clinical labs help support the treatment of patients with DUA IE. "If patients' underlying opioid use disorder is not identified, and thus not treated, then they are often unable to get or complete effective treatment for their infections," said Springer. "Surgeons may not operate on a patient who is unable to stop using drugs due to untreated addiction, or patients may be readmitted multiple times for poorly or untreated infections."

Thus, "when persons are hospitalized with DUA IE, or other infections related to injecting drugs, it should be viewed as an opportunity to intervene to help reduce further harms and to offer them substance use disorder treatment services," said Schranz.

Drug screens for opiates are typically performed via immunoassay of urine samples, said Kevin Foley, PhD, director of clinical pathology at Kaiser Permanente Northwest in Portland, Oregon. With their rapid turnaround times, immunoassays allow labs to provide results quickly to clinicians. More resource-intensive liquid chromatography tandem mass spectrometry (LC-MS/MS) assays are typically used to confirm drug use, due to their superior sensitivity and specificity, as well as their ability to produce quantitative information about drug concentrations in a patient's urine. However, Foley noted that LC-MS/MS testing may be difficult to justify for smaller institutions. "To give a sense of scale, we currently have four LC-MS/MS instruments that serve a patient population of about 600,000," he said.

Laboratorians also play an important role in helping clinicians interpret the results of these tests. "Clinicians use concentrations to monitor compliance," Foley explained. "A quantitative result can give useful insights into questions such as 'Is it likely the morphine detected is from poppy seeds?' Or 'Does it appear that this patient stopped using drugs since we last tested him two weeks ago, or is he continuing to use'?"

Labs Support Integrated Care

The growing number of patients with DUA IE is just one highly visible manifestation of the much larger problem of DUA infections. "Infections associated with opioid use are one of the most serious infectious disease problems in the United States since AIDS," said Gilligan. "Since the people who are infected are [intravenous] drug users, often on the fringes of society, this problem has not gotten the attention it deserves."

Because the opioid epidemic shows no sign of abating soon, clinical labs will continue to play a key role in addressing IE and other DUA infections, said experts. By supplying healthcare teams with essential information for diagnosing and managing DUA, labs help ensure that patients are offered prompt and effective treatment for their current health problems and also given the support they need to avoid future problems. To improve the ability of labs to play this role, lab directors and other researchers have been discussing DUA IE data at infectious disease conferences, said Schranz.

"Integrating treatment for opioid use disorder and infectious diseases is critical to ending these coalescing epidemics," said Springer, and clinical labs can provide the testing to help make this type of integration a reality.

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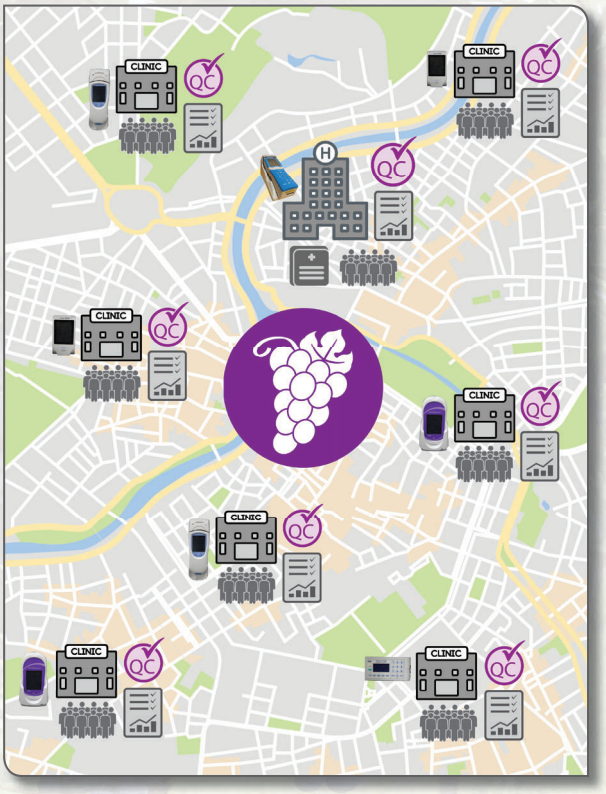

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A Technology Still Awaiting Uptake in Clinical Laboratories

BY MARK KELLOGG, PHD, DABCC, FAACC

Nuclear magnetic resonance (NMR) spectroscopy has a storied history. Edward Purcell and Felix Bloch developed the NMR technology in the late 1940s, for which they earned a Nobel prize in physics. The principle underlying this approach is that radio waves excite intramolecular magnetic fields around atomic nuclei, resulting in chemical shifts and changes in resonance frequency. These changes in resonance are akin to how potassium or sodium give off different wavelengths of light when heated in flame emission photometry.

The earliest applications of NMR were based on the chemical shift that occurs in the process and the ability to use the resulting data to elucidate the structures of complex molecules. Imaging applications followed that exploited the spatial resolution of molecules using magnetic resonance imaging (MRI) platforms.

F2 **Spectra of normal tissue versus that of colorectal cancer sample.**
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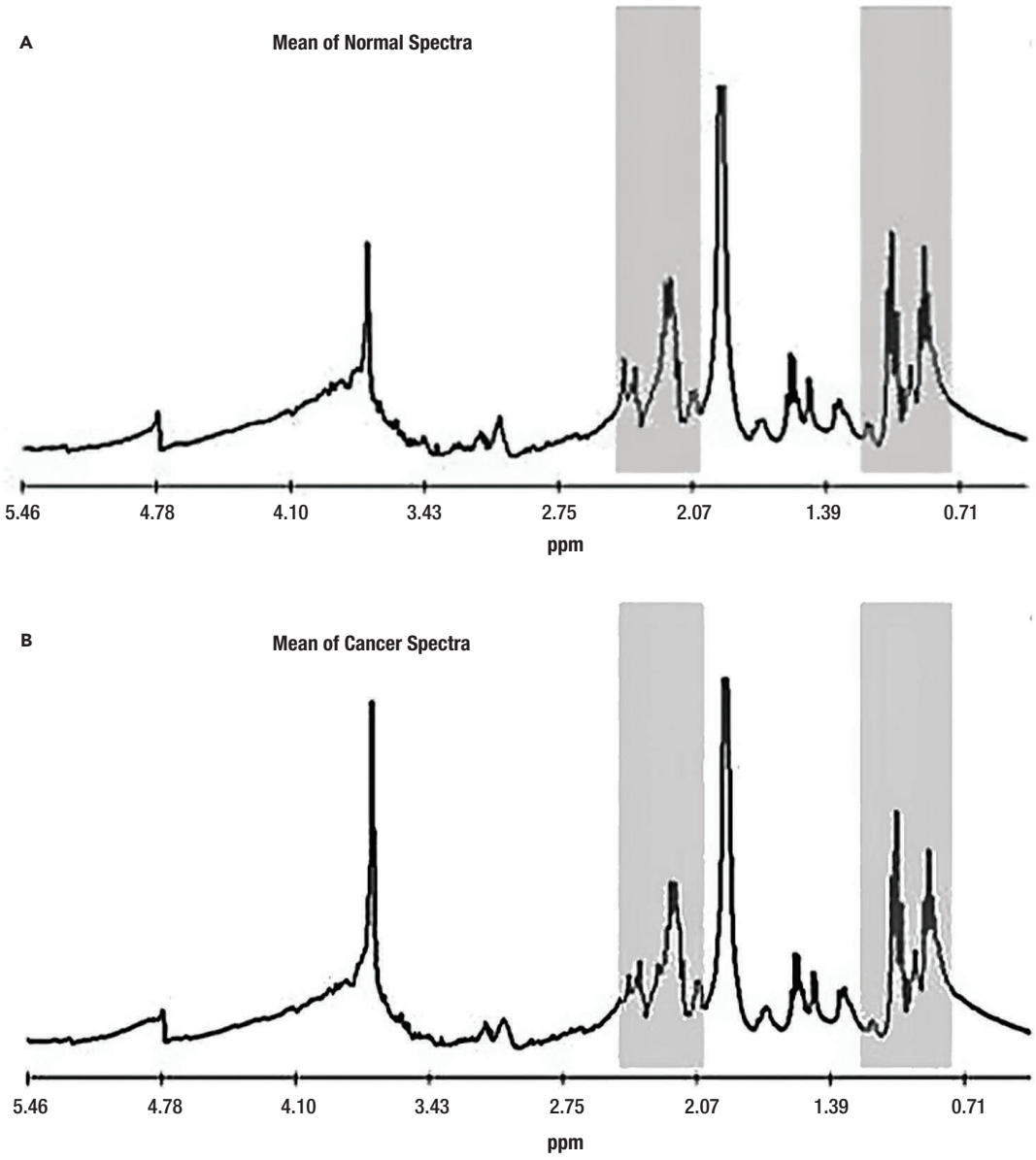


A third area of NMR takes advantage of nuclear spin relaxation rates. In this last category, called NMR relaxometry, the available testing devices have evolved into benchtop devices and even portable configured ones.

Current Uses of NMR

Clinical laboratories make quite limited use of NMR in comparison with methodologies like mass spectrometry and UV-visible light spectroscopy; however, medical imaging departments of major medical centers have adopted NMR widely.

Early versions of MRI were largely designed to provide tissue or organ imaging due to sensitivity limitations associated with other technologies, including spectral analysis. However, later versions of the platform with stronger magnetics allowed MRI to also produce magnetic resonance spectroscopy (MRS) information and provide qualitative and semiquantitative resolution for the various molecules present. These achievements expanded our capacity to evaluate metabolic and physiologic aspects of the body.

One area in which MRS has shown particular promise is in the diagnosis of congenital metabolic disorders. Given the large number of potential metabolites in the body and the high inter-individual variability in analyte concentrations among patient populations, MRS offers useful data. For example, within the brain, MRS recognizes metabolites such as N-acetyl aspartate, creatine, choline, myo-inositol, lactate, glutamate, and glutamine molecules. Figure 1 illustrates the typical spectra seen in a healthy brain.

In addition to its use in discerning congenital metabolic disorders, MRS is very useful in characterizing the metabolism of tumor cells and inflammatory conditions. MRS has been used to detect the presence of brain, breast, and gastrointestinal tumors (Figure 2). Neuropsychiatric applications of MRS in evaluating systemic lupus erythematosus and multiple sclerosis, in targeting brain areas for treating epilepsy, and in predicting risk for Alzheimer's disease and dementia also have been described in the literature.

While these applications are still adjuncts to more traditional diagnostic tools, our colleagues in radiology and medical imaging have taken full advantage of NMR to offer combined imaging and physiologic/pathophysiology assessments using a noninvasive approach.

NMR in Clinical Laboratories

Despite its potential being noted for more than 4 decades in the literature, NMR has not been broadly implemented within clinical laboratories. Today this promising technology is used mainly to quantify and characterize lipoproteins and lipids, along with some qualitative applications in microbiology.

Throughout the literature authors have noted that analytical NMR should be cost competitive with existing automated analyzers, considering there are no reagents and that a single NMR spectrum could replace a dozen or so

chemical analyses. But the clinical utilization reviews for this technology still primarily discuss as its main application: imaging of soft tissues—liver, heart, brain, and kidneys.

While not as commonplace as comprehensive metabolic panel testing, NMR technology helps determine specialized parameters for lipoprotein and lipid testing. Publications describing its use in clinical laboratories began to appear in the literature in the 1980s. NMR spectroscopy can be used to measure the size and density of lipoprotein molecules, and the data it generates improves the risk assessment for atherosclerotic cardiovascular disease compared with low-density lipoprotein cholesterol levels. However, even after a few decades of research and development, use of NMR for lipoprotein profiling still lacks standardization and comparability to other methods. A 2018 article published in *Clinical Chemistry* noted that NMR-based measurements lacked comparability, even within the technology, and that the software used for data analysis was likely part of the problem.

In addition to its role in specialized lipoprotein measurements, NMR has been explored for point-of-care testing. Researchers have proposed using magnetic nanoparticles to enhance or amplify the signal, called microNMR, in order to bring NMR to bedsides or clinics. In fact, in 2014 the Food and Drug Administration approved an NMR-based platform called the T2Dx, from T2Biosystems, with one panel for identifying sepsis-causing bacterial infections and another for fungal pathogens in whole blood. These platforms are capable of detecting the organisms within 3-5 hours of test initiation. Researchers are also working on applications for detecting Lyme disease and carbapenem-resistant organisms.

The same T2Dx NMR benchtop device has been used to demonstrate proof-of-concept testing for several hemostatic parameters. Changes based on the relaxation of molecules offer information on clotting, clot retraction, and fibrinolytic processes. Additional applications that provide hematocrit, platelet activity, and fibrinogen levels have been described. Similar to applications in microbiology, benchtop-based NMR assays provide comparable data to more traditional coagulation assays, but with significantly less sample (<50uL) and with start-to-result times on the order of 15 minutes versus 30-150 minutes for traditional assays.

In addition to its role in specialized lipoprotein measurements, NMR has been explored for point-of-care testing.

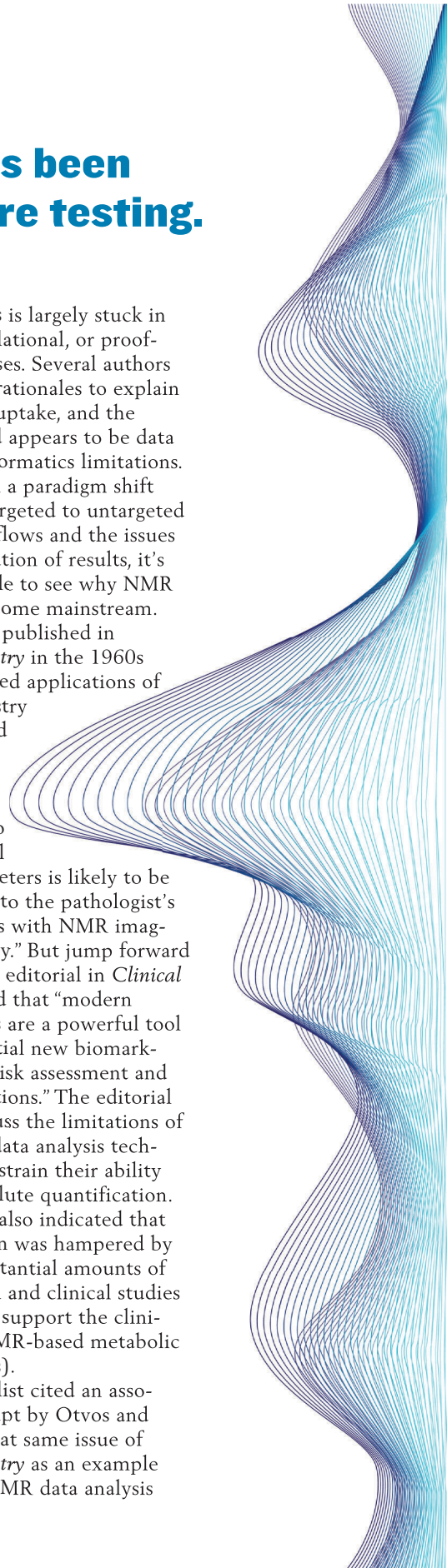
Historically, analysis of inborn errors of metabolism has been based on a targeted approach to diagnostic workflows. Research, though, typically utilizes more untargeted processes in order to take advantage of the deep datasets provided by NMR-based analysis. The evolution or translation of these research findings into clinically actionable data has yet to occur. Tebani and colleagues have used the phrase "the curse of dimensionality" to describe the issue of transforming NMR-based studies' complex, highly dimensional datasets into the more targeted questions typical in the differential diagnosis of a metabolic disease.

Decades of incomplete and poorly designed epidemiologic and biomarker discovery studies have created misconceptions about the power of NMR in metabolomics. As such, the dialogue surrounding the clinical application of NMR spectroscopy for metabolic disease testing still commonly involves the terms "may be useful" or "underappreciated." Yet, the commercially available applications in lipid profiling and microbiology demonstrate the technology not only has potential but also clinical applicability.

To date, other than assessing lipid metabolism, applications of NMR in metabolic disease testing remain in the whole body/tissue imaging arena. NMR-based testing of blood and other fluids is largely stuck in discovery, translational, or proof-of-concept phases. Several authors have put forth rationales to explain NMR's lack of uptake, and the common thread appears to be data analysis and informatics limitations. Combined with a paradigm shift moving from targeted to untargeted screening workflows and the issues with harmonization of results, it's not unreasonable to see why NMR still has not become mainstream.

Manuscripts published in *Clinical Chemistry* in the 1960s and 70s described applications of NMR in chemistry laboratories, and a 1984 review included the comment that "routine in vitro use of analytical NMR spectrometers is likely to be very important to the pathologist's role in diagnosis with NMR imaging/spectroscopy." But jump forward 30 years and an editorial in *Clinical Chemistry* noted that "modern NMR platforms are a powerful tool to reveal potential new biomarkers for disease risk assessment and clinical applications." The editorial goes on to discuss the limitations of NMR spectral data analysis techniques that constrain their ability to provide absolute quantification. But the author also indicated that NMR utilization was hampered by the lack of substantial amounts of epidemiological and clinical studies and the data to support the clinical utility of NMR-based metabolic quantification(s).

The editorialist cited an associated manuscript by Otvos and colleagues in that same issue of *Clinical Chemistry* as an example of a different NMR data analysis



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approach that demonstrated the technology's ability to provide absolute quantification in line with usual clinical laboratory expectations. Fast forward 3 years to 2018 and Ala-Korpela, in a *Clinical Chemistry* perspective, still lacked confidence in getting NMR- based metabolomics to the clinical space, citing as factors no clear criteria for analysis of NMR data and no standards for reporting the data. The author concluded that one of the key issues about disseminating NMR in clinical lab practice was to minimize the hype.

Conclusion

Clearly the potential of NMR-based technology has only improved over the decades but still appears underutilized and under researched. As the metabolome, metabolomics, and personalized medicine become hotter topics in clinical diagnostics, clinical laboratorians need to keep the capabilities of NMR in mind when looking for technology to address the questions being asked and improvements in efficiencies being demanded.

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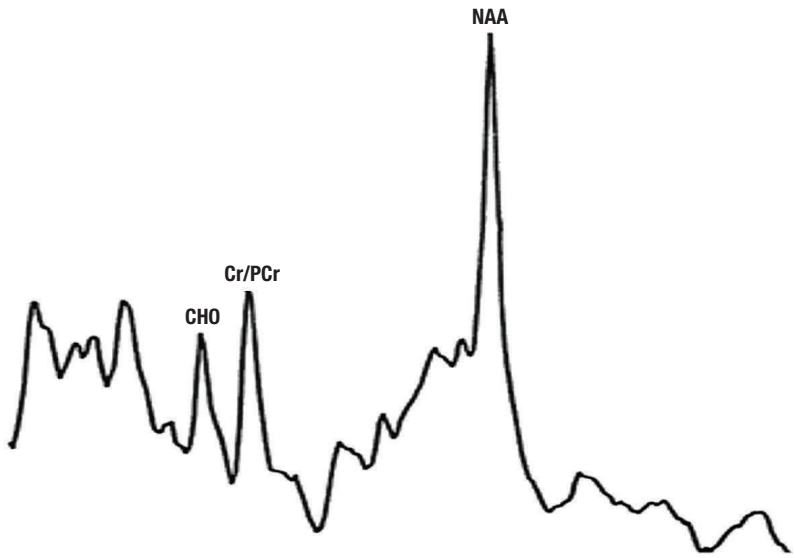
F1 **Typical Brain MR Spectra**
Used with permission from Elsevier J Med Imaging Radiat Sc 2017;48:233–53.



Cho, choline; Cr, creatinine; MR, magnetic resonance; NAA, N-acetyl aspartate; PcR, phosphocreatine.

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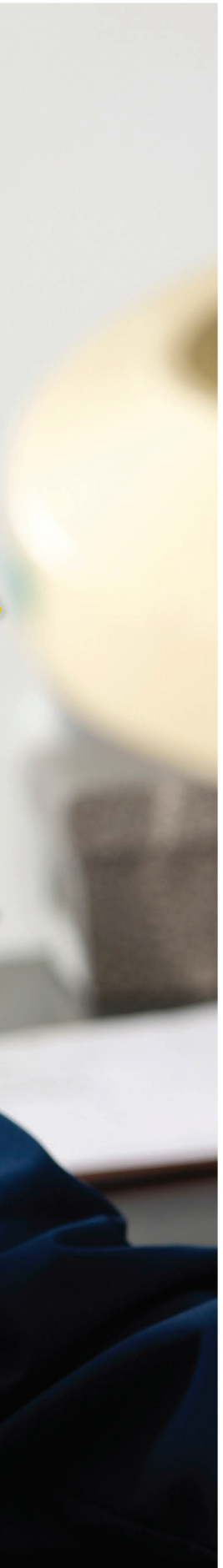


Brian Fitzgerald

A FOCUS ON PATIENT RISK IS DRIVING CHANGES TO OLD PARADIGMS

BY KIMBERLY SCOTT

Despite knowing that errors in testing can lead to serious patient harm, too many clinical laboratories are performing only the minimum amount of quality control (QC) required by regulation and recommended by manufacturers, leading some in the industry to call for labs to adopt more robust statistical quality control (SQC) approaches designed to focus on patient risk.

A recent study of current SQC practices in U.S. laboratories found that 21 leading academic laboratories surveyed typically employ two standard deviation (SD) control limits in spite of their known high false rejection rate. It also found that labs generally use a minimum number of control measurements per run (two) and often perform the minimum frequency of SQC, explained James Westgard, PhD, founder of Westgard QC (Am J Clin Pathol 2018;150:96-104). "Based on this survey, it appears that current QC practices are based on mere compliance to CLIA minimums, rather than the best practices for patient care," Westgard said.

CLIA requires laboratories to have QC procedures in place to monitor the accuracy and precision of the complete testing process. Under CLIA, labs must perform at least two levels of external controls on each test system for each day of testing and follow all specialty/subspecialty requirements in the CLIA regulations for nonwaived tests.

To minimize QC when performing tests for which manufacturers' recommendations are less than those required by CLIA (such as once per month), the Centers for Medicare and Medicaid Services (CMS) has provided guidance to labs on how to develop an individualized quality control plan (IQCP) that involves performing a risk assessment of potential sources of error in all phases of testing and putting in place a QC plan to reduce the likelihood of errors.

However, developing an IQCP is voluntary and many labs choose not to adopt such a plan, instead opting for the CLIA requirement of two QC levels each day. "For comparison of best practices, the [Clinical and Laboratory Standards Institute] CLSI C24-Ed4 guideline for statistical QC recommends that SQC strategies be based on the quality required for intended use," Westgard noted. "Typically that is defined as 'allowable total error,' the observed imprecision and bias of the measurement procedure, the rejection characteristics of the SQC procedure, and the risk of harm from undetected errors, such as those based on Curtis Parvin's patient risk model."

The Patient in Focus

Curtis Parvin, PhD, a longtime leader in clinical laboratory QC, has been instrumental in shifting the focus of QC to place more emphasis on how failures might actually affect patient care. His MaxE(Nuf) patient risk model predicts the maximum expected increase in the number of erroneous patient results reported and acted on when an out-of-control condition occurs in a measurement procedure given a laboratory's QC strategy.

That emphasis on patients helped inform the latest version of CLSI's "Statistical Quality Control for Quantitative Measurement Procedures," C24-Ed4 guideline referenced by Westgard, which was last updated in 2016. The fourth edition is now more closely aligned with the patient-risk-focused approach used in another CLSI guideline, EP23, "Laboratory Quality Control Based on Risk Management," explained Parvin, who chaired the C24 update committee when he worked at BioRad. Parvin is now a consultant.

"EP23 defines patient risk as the combination of the probability of occurrence of patient harm and the severity of that harm," Parvin said. "The higher the expected severity of harm to the patient, the lower the probability of occurrence has to be in order for the risk to be acceptable."

C24-Ed4 uses more patient-risk focused language and updates a number of performance metrics, noted Parvin. "Instead of talking about the probability of a rule rejection for an instrument, you're talking about the expected number of erroneous patient results reported because of an undetected out-of-control condition," he emphasized. "The focus is on the potential for patient harm."

Testing Volume and QC Frequency

As QC in clinical laboratories evolves, a greater emphasis is being placed on QC frequency and QC schedules as a critical part of an overall strategy. The higher the volume of testing, the more labs may need to run QC in order to minimize patient risk.

"Ideally, a technologist would be able to program an instrument to run QC at a certain frequency, such as every 50th sodium test," Parvin said. "A lot of instruments today can't do that, but a tech can schedule QC based on the number of sodium tests typically done each day."

Volume is one part of the equation, but medical risk and cost must also be considered, added Robert Schmidt, MD, PhD, MBA, medical director of quality optimization for ARUP Laboratories in Salt Lake City. "Ultimately, labs should come up with an equation that factors in the cost of running the overall system, the cost of bad results, and the cost of doing QC," he noted. "There's a trade-off among those things."

Westgard suggests labs make an objective assessment using Parvin's risk model that places QC frequency in terms of run size or the number of patient samples between consecutive QC events. Graphic nomograms that relate a method's analytical sigma-metric directly to the control rules, number of control measurements, and run size can be useful tools for laboratories, he said (Figure 1). These nomograms can guide labs in choosing how many patient specimens they reasonably can examine between QC evaluations to be assured that not too many erroneous patient results occur when a test is out of control.

"Rather than tackle the mathematics, labs can now use simple visual tools to determine appropriate QC frequencies for their methods," Westgard said.

Closing the Bracket

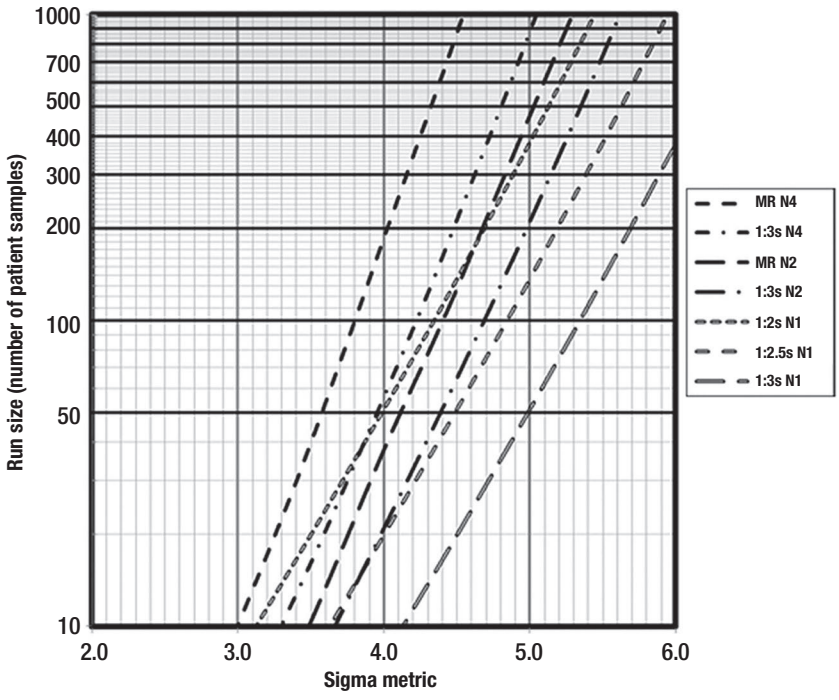
Central Pennsylvania Alliance Laboratory, a specialty lab that performs about 1 million tests per year, has chosen to go beyond the bare minimum in performing QC. Jennifer Thebo, PhD, MT(ASCP), the lab's director of technical operations and scientific affairs, said that technologists perform QC at the start of a shift and again at the end of a shift using three levels of control. This helps minimize delays in catching problems and ensures that the lab deals with an issue immediately.

The downfall of performing QC just once a day or once per shift is that when testing errors do appear, it's impossible to know exactly when they started, Thebo noted. This means a technologist must go back and rerun previous tests to see if they were impacted by the out-of-control condition. For example, imagine one technologist runs two or three levels of control on Monday morning and all are within ranges, Thebo said. Testing continues throughout the next 24 hours. Then a second technologist runs QC on Tuesday morning and finds that results are not within ranges. The second technologist troubleshoots and fixes whatever the problem was, but it is unclear when the problem began, and it's often assumed that the problem was created by performing daily maintenance. Too often, technologists do not perform a lookback to the previous day, which means that some test results that were reported may not be accurate.

"Running QC both at the start of a shift and at the end of a shift closes the bracket and saves everyone a lot of headache," Thebo said. "While this is an example of QC per shift, if the testing volume for a particular test is high, QC may need to be performed at more frequent intervals in order to minimize retesting and corrections."

C24-Ed4 recommends the practice of bracketed QC for continuous measurement processes and goes a step further in recommending that the reporting of patient test results be based on two QC events occurring before and after bracketing a group of patient samples, Westgard noted. The number of patient samples between QC events, or run size, should be optimized on the basis of the risk of harm if erroneous results are reported, he said, adding that this can be done by following the road map for planning SQC strategies outlined in the guideline.

F1 A Sigma-metric SQC run size nomogram



Source: Clin Chem 2018;64; 289-296

Going Beyond Good Enough

Why don't more laboratories go beyond the minimum when it comes to QC? In many cases, it comes down to lack of knowledge or lack of resources, according to Parvin. "I believe that most labs want to do good quality work and believe they are doing good quality work," he said. "They are assuming that the guidance provided by the manufacturer is good enough. But if they're doing the minimum, it's almost guaranteed that for some labs it's not enough. The whole focus of QC design in recent years is that one size fits all just doesn't work."

Thebo, who also performs inspections for the College of American Pathologists (CAP), agrees. "I think most labs are at least minimally performing QC but often they are not doing lookbacks to the previous day when a problem is identified," she said. "A lot of labs are simply understaffed, and they struggle with doing more than the minimum."

Part of the challenge in improving QC is changing perceptions about QC, Schmidt said. "The way QC is viewed in the laboratory is very different than how QC is viewed outside the lab," he explained. "QC in other industries focuses more on using QC data for quality improvement while in labs it's much more about compliance. There's a tendency to think, 'If it's good enough for CAP or CLIA, it's good enough.' We need to go beyond good enough."

Westgard believes better education and training on QC are needed and urges laboratorians to assess their knowledge by asking themselves a few questions: Have I read C24-Ed4? Do I understand what is recommended as best practices? Have I implemented a planning process following the C24-Ed4 road map? Do I have the necessary tools to support applications in my laboratory?

Laboratorians who answered no to any of the questions above lack the knowledge and capabilities to provide appropriate QC and deliver test results that are safe for their patients, Westgard said. He advises taking proactive steps to remedy this deficit. In the end, good QC is all about delivering the best patient care possible.

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Regulatory Roundup

FDA Warns Against Use of Pre-owned or Unauthorized Test Strips for Glucose, Warfarin

The Food and Drug Administration (FDA) has issued a safety communication warning patients and healthcare professionals not to use test strips for glucose or warfarin international normalized ratio (INR) that are either from a previous owner or that FDA has not authorized for sale in the U.S. These test strips could lead to infection or inaccurate test results, causing serious harm or even death. FDA issued this warning because sellers are marketing pre-owned or unauthorized glucose and INR test strips either directly to consumers or through online marketplaces such as Amazon, eBay, and Craigslist. While the agency is not aware of any deaths or serious injuries specifically associated with these pre-owned or unauthorized test strips, these strips still might not be safe to use because they could be expired or stored improperly, which can lead to inaccurate results. It's also possible that the test strips could have small amounts of blood from the previous owner on them, which can put users at risk of infection.

To determine whether or not a test strip is pre-owned or unauthorized, FDA recommends inspecting the package to check whether it has been opened or altered and to check expiration dates. An additional sign that prescription-only test strips may be unauthorized for sale in the U.S. is if they can be purchased without a prescription. Overall, FDA advises patients and healthcare providers to only purchase test strips from a trusted source, such as a local pharmacy or through the test strip manufacturer.

FOLLOWING FDA WARNING LETTER, INOVA GENOMICS PULLS PLUG ON PHARMACOGENETIC TESTS

Inova Genomics Laboratory has stopped offering its MediMap pharmacogenetic tests in response to a warning letter from the Food and Drug Administration (FDA). The letter asserted that, because these tests had not been reviewed by FDA for safety and effectiveness, Inova was illegally marketing them. The MediMap tests claimed to use genetic variants to predict patients' responses to specific medications, including antidepressants, opioids, cancer treatments, anesthesia, and diabetes medications. However, FDA stated that it was unaware of any data establishing that Inova's tests were able to help patients or healthcare providers make appropriate treatment decisions for the listed drugs, and that the agency was concerned these tests could lead to serious health consequences for patients.

FDA requested that Inova respond to the warning letter within 15 working days of its receipt with details of how the company would address this issue. In response, Inova released a statement saying, "After thoroughly reviewing the letter, which clarified FDA's approach to laboratory-developed tests for pharmacogenomics, Inova has decided to end MediMap tests."

FDA CLEARS BECKMAN SEPSIS TEST, FLOW CYTOMETRY SYSTEM FOR LEUKEMIA, LYMPHOMA

Beckman Coulter has received Food and Drug Administration (FDA) clearance for both the Early Sepsis Indicator and the ClearLLab 10C system for clinical flow cytometry labs. The Early Sepsis Indicator tests for a hematology-based cellular biomarker, known as monocyte distribution width and is designed to help emergency department clinicians identify patients with sepsis or increased risk of developing sepsis. Results for the test are automatically reported as part of a routine complete blood count with differential for adult emergency department patients. Compared with reviewing white blood cell count alone, clinical trials show that the Early Sepsis Indicator strengthens clinician confidence in ruling in sepsis by 43% and, together with clinical signs and symptoms, improves clinician confidence in ruling out sepsis by 63%.

The ClearLLab 10C system comprises four 10-color in vitro diagnostic panels of immunophenotyping reagents cleared by FDA for both lymphoid and myeloid lineages. The panels' four dry, premixed antibody tubes use the company's Dry Unitized Reagent Assays Innovations technology, which eliminates the need to pipette antibodies. Alongside the panels, the ClearLLab 10C system includes ClearLLab control cells, a liquid preparation of stabilized human erythrocytes and leukocytes that serve as controls for leukemia and lymphoma immunophenotyping; and new ClearLLab compensation beads for use with the ClearLLab compensation kit.

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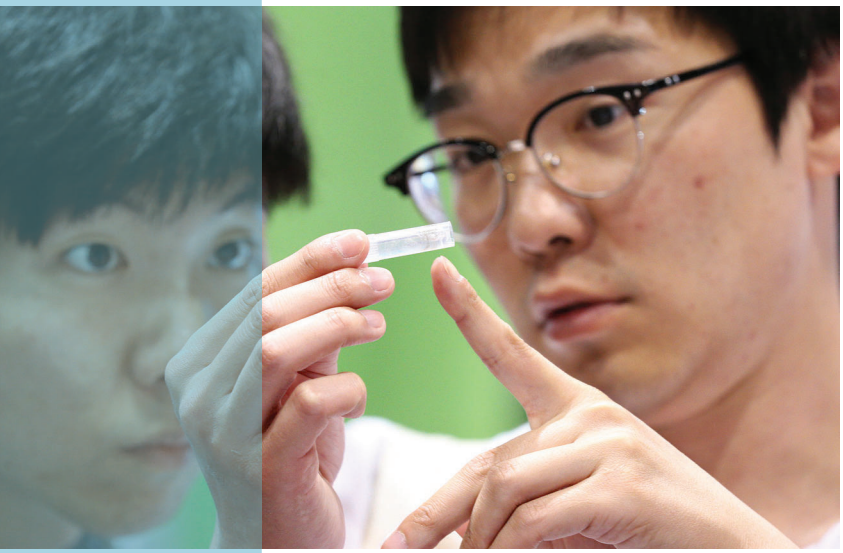
INDEVR GETS FDA OK FOR TEST THAT DIFFERENTIATES SEASONAL, NONSEASONAL FLU VIRUSES

The Food and Drug Administration has granted 510(k) clearance to InDevR for its FluChip-8G Influenza A+B assay. FluChip-8G is a single multiplexed assay that provides same-day results and is the first FDA-cleared influenza diagnostic that qualitatively detects and differentiates between seasonal and nonseasonal influenza A viruses, while also identifying the genetic lineage of influenza B viruses. The influenza A viruses characterized by the test include subtypes with recognized pandemic potential such as H7N9 and H5N1. Overall, this means that the test could be used as part of an early warning system for the emergence of new strains of influenza. The FluChip-8G is an open platform molecular diagnostic system consisting of a low-density microarray and reagent kit, microarray imaging system, and custom software. The assay uses multiplexed reverse transcriptase polymerase chain reaction to amplify whole influenza gene segments, followed by detection on a microarray. The test also uses artificial intelligence-based pattern-recognition to automate result interpretation.

NY STATE AUTHORIZES VERACYTE GENOMIC TEST FOR IDIOPATHIC PULMONARY FIBROSIS

Veracyte has received regulatory authorization from the New York State Department of Health to offer the Envisia genomic classifier to patients in the state. This genomic test is the first commercially available diagnostic that helps distinguish idiopathic pulmonary fibrosis (IPF) from other interstitial lung diseases (ILD). It was developed using RNA whole-transcriptome sequencing and machine learning to identify the usual interstitial pneumonia pattern that is a hallmark of IPF. The test assesses patient samples obtained through bronchoscopy, a nonsurgical procedure commonly used in lung evaluation, and is used as a complement to high-resolution computed tomography (HRCT), the method typically used along with a clinical work-up to help identify IPF. Studies show a high correlation between results obtained with the Envisia classifier and histopathology results read by ILD experts, the latter being the gold standard method for confirming HRCT results. This means that Veracyte's test will enable patients to forgo surgical lung biopsy even if their HRCT results are indeterminate.

GETTING THE MOST OUT OF THE 71st AACC Annual Scientific Meeting & Clinical Lab Expo



The 71st AACC Annual Scientific Meeting & Clinical Lab Expo is on track once again to be a record-breaking event that showcases the best of science and innovation in laboratory medicine. With some 300 educational opportunities in the form of lectures, plenary sessions, scientific sessions, and roundtables—and 800 exhibitors showing the latest technology—there will be a lot to take in. As you look forward to your experience in Anaheim, keep some of these tips in mind.

Brian Fitzgerald

1 Try Something New

Even without attending the meeting every year, you likely have an idea of the session types, events, and activities often seen at conferences. But looking only for the same types of sessions you attended in the past could cause you to miss out.

Think of the meeting more as an exploration than as a to do list and attend a session or event that might not have made your list in the past. For example, while most everyone will attend the plenary sessions, have you come to one of the Meet the Experts sessions? After their presentations, the plenary speakers and other invited experts engage attendees with in-depth conversations in a more intimate setting. Don't forget that seating is limited to 75 people on a first-come, first-served basis.

2 Update Your Social Profile

You may not spend a lot of time on social media and may not even have a social media account. But consider that recruiters may not be the only people checking out your online profile; colleagues and business contacts also might be interested in learning more about you in advance of—or after—the meeting. A solid profile on LinkedIn and Twitter helps, including a decent photo and up-to-date information on your job and education.

If you're an AACC member, you'll also want to make sure your AACC Artery profile is current. On the Artery home page, artery.aacc.org/home, click on the red box "my profile" to get to your profile page. There you can add your picture by clicking on "actions" then "add picture" under the profile image. You also can change contact details by clicking on the edit box next to the text. To complete your profile, share a little about yourself in the bio section and import your education and work history from LinkedIn. Ensure your profile is visible in the AACC member directory by accessing "my account/privacy settings," then selecting "community profile update page."

3 Use the Best Resources

AACC members who have attended the meeting for many years know that the AACC website is the best place to start when planning your experience.

For an overview, start with the meeting site, www.2019aacc.org, where you can search conference sessions by title, speaker name, session type, and session number. As you browse and search sessions, keep in mind that the pricing structure allows conference registrants to access all scientific sessions—except roundtables and AACC University sessions—for a single flat fee. You also have the option of downloading a PDF of the conference program, which is a handy way to explore meeting sessions and events when you're offline.

Keep an eye on your inbox during July for four special issues of *CLN Stat* that focus on the meeting. You'll find smart, relevant reporting on all the science and events that offers a deeper look at what speakers expect to cover as well as insights about their presentations, which in turn might help you better focus your time in Anaheim.

Once you're on-site, look for the official publication of the meeting, *CLN Daily*. AACC publishes this newspaper Monday through Thursday of the conference with articles written by AACC members about the science

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at the meeting, as well as full coverage of the Product Showcase from the Clinical Lab Expo, helpful maps, schedule updates, and other news you'll need during the week.

Finally, download the AACC app on your mobile device. Available in June, this handy interactive reference guide has information on sessions, speakers, posters, exhibitors, and more.

To learn more and register, visit www.2019aacc.org.

CHOOSE YOUR PATH

Need to focus on a specific area of laboratory medicine at the 71st AACC Annual Scientific Meeting? Use these seven pathways to jump-start your planning.

Point-of-Care Testing

Rise and Shine! The Essential Elements of a Point-of-Care Testing Boot Camp Part One

Afternoon Reveille! Continuing the Essential Elements of a Point-of-Care Testing Boot Camp Part Two

Value Added Partnerships Between Clinical Laboratorians and Emergency Medicine Professionals to Improve Patient Care

Racing Against Time: Point-of-Care Testing in Mobile Health Settings

Digital Medicine and the Connected Health Consumer: What You Need to Know

Worldwide Challenges in Point-of-Care Testing - A Focus on Molecular POCT

Managing the Wild Wild West of Point-of-Care Testing

Maternal/Fetal

Predicting and Diagnosing Gestational Diabetes Mellitus: Are We Making Progress?

Highlighting the Emerging Role of Anti-Müllerian Hormone in Ovarian Reserve, Assisted Reproduction, Polycystic Ovary Syndrome, and Other Diseases

Noninvasive Prenatal Testing: Utilization of Cell-free DNA in Fetal Aneuploidy Screening and Beyond

Preeclampsia Screening and Diagnosis: A Novel Approach

Integrating Laboratory Results to Increase Quality Care for Affected Newborns Identified Through Newborn Screening: What Is the Optimal Workflow?

Umbilical Cord Testing - Moving Beyond Blood Gases

Diagnosing Inborn Errors of Metabolism: Challenging Cases in Biochemical Genetics

Infectious Diseases

Maximizing the Impact and Value of Laboratory Automation: Lessons Learned From Clinical Chemistry and Microbiology

Opportunities and New Approaches to Guide Utilization of Urine-based Testing for Diagnosis of Infectious Disease

Sepsis: Novel Biomarkers, New Technology, and Predictive Analytics

The Trials and Triumphs of HIV Testing

HIV Diagnostics: Past, Present, and Future

Journal of Applied Laboratory Medicine: 2019 Hot Topics

Lab Management

Breaking Down Gender From Cis to Trans

Ethical Issues in Laboratory Medicine

Institutional Laboratory Stewardship Programs: Best Practices, Interventions, Informatics

Strategies and Tactics for Practical Test Utilization Management

The Value Proposition: Actionable Strategies for Enhancing the Value of Laboratory Medicine

Healthcare Forum: Laboratory Stewardship in Healthcare Innovation

Toxicology

Opioids and Beyond: The Clinical Laboratory's Role in the Opioid Epidemic

Moving Beyond Immunoassays for the Poisoned Patient: Analytical Approaches and Interactive Case Studies

Impact of Hormones on Drug Testing: From the Bench to the Bedside

Interactive Pain Management Case Studies: Clinician and Laboratory Perspectives

Supporting Opioid Addiction Programs With Unexpected Testing—Ethanol Metabolite Test Development in an Appalachian Laboratory

Artery Hot Topics 2019

Genomics

Clinical Laboratory Genomics: Practical Next-generation Sequencing for Laboratorians

Consumer Genomics, Direct-to-Consumer Genetic Testing, and Patient Empowerment

Chair Invited Session: Race, Genomics, and Medicine

Quality Indicators That Determine the Performance of Next-generation Sequencing Assays in Precision Oncology

Using Biomarkers to Tailor Treatment for Breast Cancer

Clinical Chemistry's Hot Topics of 2019

Pharmacogenomics and Mass Spectrometry in the Clinical Lab: A Fledgling Partnership

Data Analytics

Data Science and Artificial Intelligence in Laboratory Medicine: What You Should Know Now and Will Need to Know in the Future

Learning From Predictions: What We Need to Know About Machine Learning

Storytelling With R: Application Showcase

Pathology and Clinical Laboratory Informatics Boot Camp

Getting Started With R for Laboratory Medicine

Artificial Intelligence and Data Science in Laboratory Medicine: Perspectives and Challenges

Predictive Analytics in the Clinical Laboratory

ADVANCED EXHIBITOR SEARCH

With 800 exhibitors across thousands of square feet of space, it's a good idea to have a plan of action for which booths you'll visit and when. Use AACC's advanced search tool to find exhibitors by name, product, and location in the exhibit hall. You can even save your favorites and print a list or a map.

www.2019aacc.org/clinical-lab-expo

Brian Fitzgerald

71ST AACC ANNUAL

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Conference registration opens April 2019. Check for more details and complete programming at www.2019aacc.org

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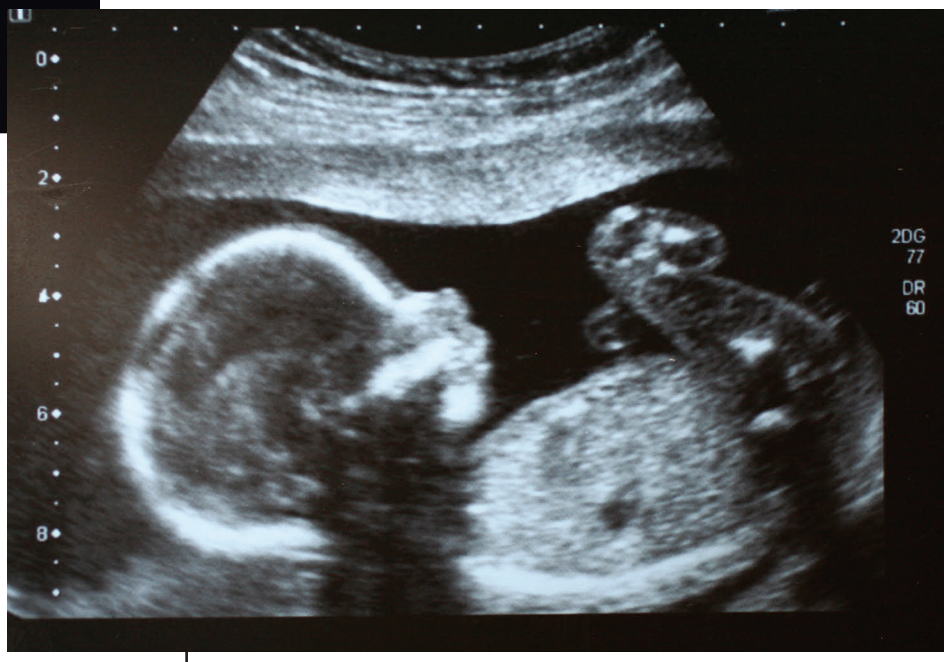
Industry Playbook

Thermo Fisher, NX Prenatal to Develop Tests for Pregnancy-Related Complications

Thermo Fisher Scientific has entered a collaboration with NX Prenatal, a company focused on the detection, monitoring, and management of pregnancy-related complications using novel exosome-based methods. Together, the two partners plan to develop clinical mass spectrometry (MS)-based proteomics assays to monitor fetal health in utero and assess the risk of adverse outcomes, including preterm birth and preeclampsia. The new tests will combine NX Prenatal's NeXosome platform with Thermo Fisher's liquid chromatography (LC)-MS instrumentation to analyze exosome-derived proteomic biomarkers of maternal-fetal health. NX Prenatal's NeXosome platform enriches maternal blood samples for microparticles such as exosomes, which play key roles in maintaining certain physiological balances between the mother and fetus during pregnancy. Aberrations in these balances have been shown to correlate with the likelihood of adverse pregnancy outcomes.



"At NX Prenatal, we are developing novel assays and noninvasive early warning systems to detect subtle molecular changes in the maternal-fetal environment," said Brian D. Brohman, CEO of NX Prenatal. "Our collaboration with Thermo Fisher Scientific brings together our novel NeXosome platform with their leading analytical technology…in an effort to provide the precision necessary for personalized diagnostic solutions to improve health outcomes for both mother and child."

FH FOUNDATION STRIVES TO IMPROVE HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA DIAGNOSIS

The FH Foundation has launched the Flag, Identify, Network, Deliver (FIND) HoFH program to identify individuals at risk for homozygous familial hypercholesterolemia (HoFH), a more severe form of FH. FIND HoFH will build on the FH Foundation's FIND FH initiative, which was established in 2013. Both FIND FH and FIND HoFH use machine learning and big data to analyze national healthcare encounter and laboratory data in order to identify individuals who should be evaluated by clinicians for FH and HoFH. FH Foundation has also entered a multipartner collaboration so that individuals identified by FIND HoFH can receive free genetic counseling through Genome Medical and free confirmatory genetic testing through Invitae. "Genetic testing for HoFH can make a big difference for young people, who may be facing serious cardiovascular risks that might otherwise be missed due to their age," said Robert Nussbaum, MD, chief medical officer of Invitae. "The FIND HoFH program is an excellent example of combining technology and public health techniques to better identify young people who are at risk."

CLEVELAND CLINIC SPIN-OFF, SHIVOM TO HELP PATIENTS MANAGE HEREDITARY CONDITIONS

Family Care Path (FCPI), a spin-off company from Cleveland Clinic, has joined forces with Shivom, a biotechnology data and analysis company that aims to optimize the way genetic data is shared, secured, and analyzed through

blockchain and artificial intelligence technology. Together, the partners will integrate FCPI's MyLegacy and CarePathConnect applications within Shivom's marketplace. MyLegacy is Cleveland Clinic's family history collection and disease risk assessment tool, which uses proprietary algorithms based on practice guidelines developed by the Cleveland Clinic Genomic Medicine Institute and which FCPI has exclusively licensed. CarePathConnect is FCPI's international telehealth counseling network that enables patients to discuss their genetic health risk conditions with genetic counselors and learn about the benefits and limitations of genetic testing via a HIPAA-compliant web-based video platform. Together, these two offerings will give Shivom's customers access to a personalized health risk profile, as well as guidance on how to take proactive steps against hereditary conditions found within their genetic data.

CELLGEN, GENOMIC TESTING COOPERATIVE JOIN FORCES ON IMMUNO-ONCOLOGY CO-DIAGNOSTICS

Cellgen Diagnostics and Genomic Testing Cooperative (GTC) have teamed to help accelerate global development of companion diagnostics for oncology therapeutics. The companies expect their collaboration to focus initially on immuno-oncology drugs. Cellgen will contribute to the partnership a fully automated companion diagnostic platform that can be used across multiple drug pipelines, as well as its Immune Panel assays. According to Cellgen, these assays will enable pharma groups in research and development to use a standard approach to patient stratification and therapeutic response monitoring during clinical trials. Additionally, the collaboration will leverage GTC's capabilities in next-generation sequencing, machine learning, and deep learning to comprehensively profile the tumor microenvironment and create unique patient phenotypic profiles. With the synergies between the two companies, the partners ultimately aim to provide the pharmaceutical industry with an integrated immuno-oncology pipeline that seamlessly moves from discovering and validating biomarkers to developing companion diagnostics.

RXGENOMIX, CORIELL LIFE SCIENCES TEAM TO SUPPORT PHARMACOGENOMICS PROGRAMS

RxGenomix and Coriell Life Sciences are partnering in an effort to advance clinical pharmacogenomics. RxGenomix has created the RxGenomix Training Program in Pharmacogenomics, a pharmacist-led solution to help healthcare providers apply pharmacogenomics to patient care. Coriell Life Sciences, in turn, offers a suite of tools to healthcare providers that provide comprehensive pharmacogenomic risk analysis, accounting for genetic factors alongside risks related to drug interactions, age, cognitive impairment, and numerous other considerations. The companies' new partnership will combine RxGenomix's process for implementing pharmacogenomics with Coriell's risk analyses, reporting solutions, and population-level healthcare analytics. "After surveying the market, we were thrilled to find Coriell Life Sciences as having the perfect complementary bioinformatics services to drive our continued strategy of pharmacist-led [pharmacogenomics] solutions," said Blake Keller, PharmD, RxGenomix chief operating officer.

The two companies hope this collaboration will enable healthcare entities to evaluate the potential effectiveness of pharmacogenomics programs and target their efforts for the greatest patient benefit.

FOUNDATION LABORATORY, YIKON TO OFFER NONINVASIVE PREIMPLANTATION GENETIC TESTING

Yikon Genomics is collaborating with Viazoi, a genetic testing and wellness division of Foundation Laboratory, to launch clinical noninvasive preimplantation genetic testing for aneuploidy (PGT-A) in the U.S. Yikon is a single cell sequencing company focused on reproductive health and cancer diagnostics based in Shanghai, with global operations out of the U.S. The company's noninvasive PGT-A test screens embryos for chromosomal aneuploidy prior to implantation without an invasive embryonic biopsy. Instead, the culture medium used during in vitro embryo culture is collected and then processed for aneuploidy screening through library preparation and next-generation sequencing (NGS). Viazoi has validated Yikon's noninvasive PGT-A test and together with Yikon is selling the service in the U.S. "It was a very obvious decision to partner with Yikon and offer our [NGS] production capacity to support Yikon's noninvasive [preimplantation genetic screening] testing as there is valuable genetic information at the embryonic level that parents can review and make very important decisions with," said Zareh Baghoomian, DDS, vice president of operations at Viazoi.

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Ask The Expert

Ionized Versus Albumin-Adjusted Total Calcium

EXPERT
Tahir S. Pillay, MBChB, PhD, FRCPath, FCPath

Why do labs correct total calcium based on albumin?

A: Ionized calcium is the most accurate test for assessing a patient's calcium status, but its application remains limited. Clinical laboratories were not able to broadly use the first method developed for measuring ionized calcium because it was based on a bioassay requiring frog tissue. Following the introduction of direct potentiometry with ion-selective electrodes (ISE), the availability and precision of ionized calcium measurement has improved, but preanalytical and analytical challenges still hamper its universal application. These include issues related to sample handling, cost, equipment maintenance, analytical performance, and lack of measurement standardization.

In light of this, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) states that total calcium measurement may be used as a surrogate for ionized calcium in patients who do not have protein and pH abnormalities. Labs can measure total calcium using ISE, atomic absorption spectrophotometry, or photometric methods employing metallochromic indicators or dyes such as o-cresolphthalein complexone and arsenazo III. However, the correlation between ionized calcium and total calcium can be compromised by alterations in albumin concentration, blood pH, elevated levels of drugs or fatty acids bound to albumin, and unusual serum proteins such as monoclonal immunoglobulins. This is a major drawback of total calcium measurement, especially in hospitalized patients.

To overcome this, various nomograms and formulae have been developed to estimate ionized calcium by correcting total calcium for total protein, albumin, globulins, and pH. The most widely used of these is the Payne et al. formula: Adjusted calcium (mmol/L) = Total calcium (mmol/L) + 0.02 [40 – serum albumin (g/L)]. This and other correction formulae were derived by determining the linear regression relationship of serum calcium to albumin concentration in healthy patients.

What are the shortcomings of using correction formulae?

The Payne formula and related equations were derived decades ago using the bromocresol green (BCG) method for albumin measurement. Since then, however, analytical techniques for albumin measurement have changed. BCG overestimates serum albumin because of nonspecific dye binding with many proteins, particularly at low serum albumin concentrations, so a large proportion of labs now use the more effective bromocresol purple (BCP) method. If a lab uses the BCP method, this can affect the performance of BCG-based equations. Studies also show that the Payne formula correlates poorly with ionized calcium in specific patient populations such as critically ill surgical patients, renal failure and hemodialysis patients, primary hyperparathyroidism patients, and very elderly hospitalized patients. For these cases, BCP-specific and other alternative formulae have been developed, but experts recommend that labs use ionized calcium for the most accurate results.

How should labs approach calcium measurements?

Taking all of this into account, there are several ways laboratories can handle calcium measurements. Labs may elect to measure ionized calcium in all samples. In some countries this is standard practice, although technical reasons may hinder this approach. If choosing this route, labs can refer to recommendations provided by the IFCC on using ISE to determine ionized calcium in whole blood, plasma, and serum, as well as on sampling, transport, and storage for this test. These recommendations emphasize rapid analysis of an anaerobic sample placed on ice to counteract various causes of pH alteration, which impacts the concentration of ionized calcium. The IFCC also cautions labs to avoid dilution effects from anticoagulant solutions such as heparin.

On the other hand, if testing all samples for ionized calcium proves to be too difficult, labs might elect to measure ionized calcium only in specific patients for whom there is a clear clinical indication. For all other patients, labs can report albumin-adjusted total calcium, with the caveat that—given the differences in the performance of published correction equations—each laboratory should derive its own equation for correcting total calcium based on albumin.

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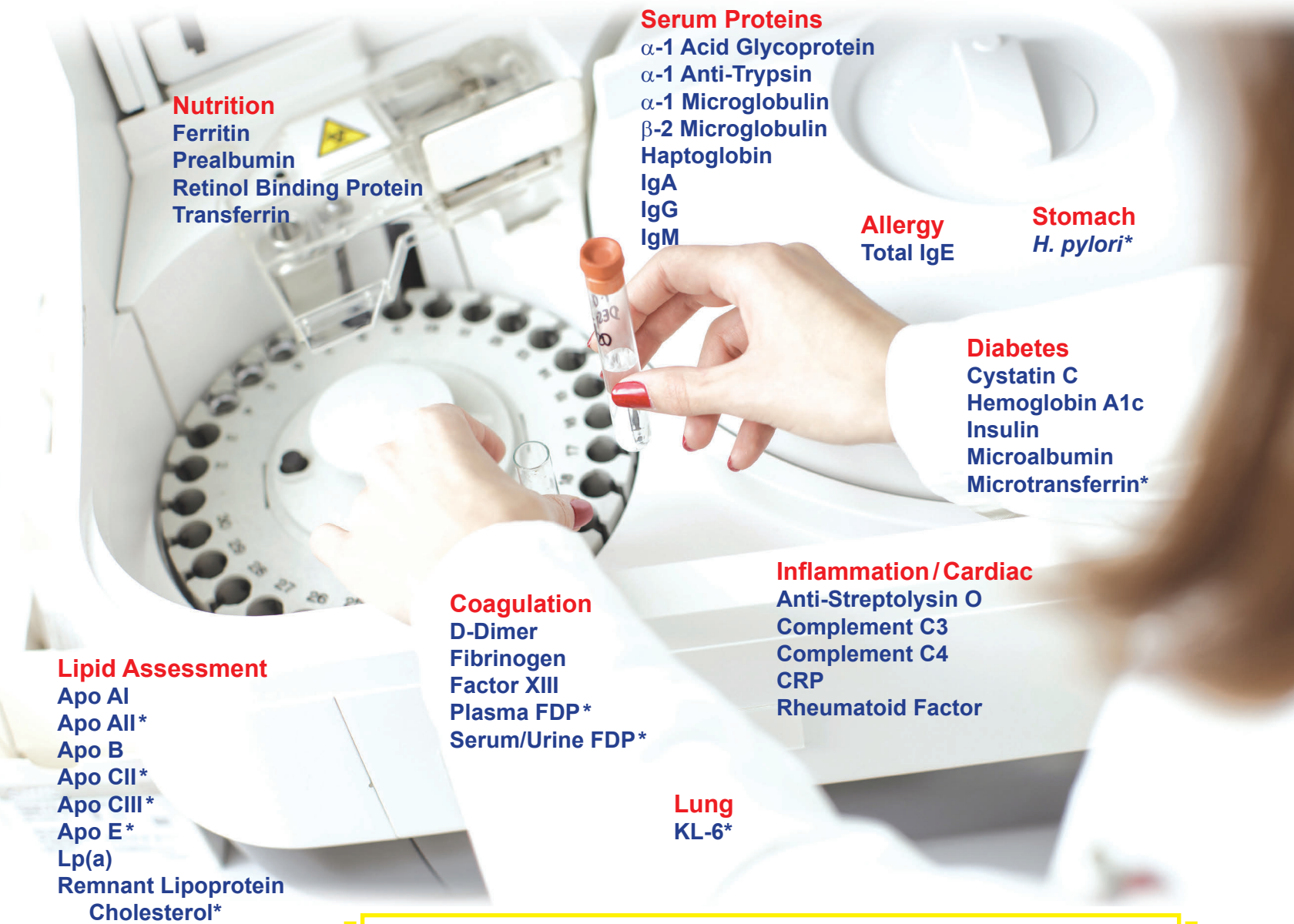

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