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  BeyondCare™ Quality Monitor (BCQM) Quality control — simplified.
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Although oxytocin testing has not yet become a routine clinical assay, in the future it could aid healthcare providers in assessing behavioral, psychiatric, and stress-related conditions. p32
Harnessing the Clinical and Financial Value of the Lab

Insurance company consolidation and changing reimbursement models have health system administrators anxious about the future—working hard to maintain adequate margins and improve patient outcomes while simultaneously evolving to a value-based payment infrastructure. In this Q & A, Jerri Turner-Jacyno, VP of Strategic Relations at ARUP Laboratories, discusses why hospital and regional labs are critical resources for health systems navigating these changes.

“Executives need to shift their perception of the lab from a commodity to a clinical service—from a burden to an opportunity.”

Jerri Turner-Jacyno, VP Strategic Relations, ARUP Laboratories

Q: How can the lab help manage expenses within DRG-based cases?

A: For hospitals to succeed under DRGs, especially as per-case reimbursement rates drop, they need to aggressively standardize patient care processes. Physician- or department-based variation in treatment can quickly shift a case from typical to outlier. If we consider that up to 85 percent of diagnosis and treatment decisions are based on lab results, appropriate test utilization is a critical component of any standardization.

Q: Why is it important to change our view of the lab?

A: It is essential to identify how a system’s lab services can assist in solving problems inherent to healthcare. If an executive team views the lab as a commodity or a purchased service line item, then it misses out on important integration opportunities. What’s worse, executives with this view can be swayed by sales pitches to outsource part or all of a laboratory’s services.

Q: How can labs shift this perception?

A: Laboratory leaders need to establish strong collaborations within the hospital system and demonstrate how their lab impacts quality of care across the entire health system.

Leaders can start by establishing a lab stewardship program to reduce leakage associated with sending tests to commercial labs that compete with the system for payer contracts.

Q: What should every hospital CFO or COO know?

A: The laboratory is an integrated clinical service, not simply a financial bucket. Financial accounting systems alone can’t properly allocate a lab’s contributions to overall financial performance because they do not take clinical interactions and downstream costs into account.

Health system CFOs and COOs need to take a broad view of clinical and financial performance when evaluating the potential of the lab. This will require executives to shift their perception of the lab from a commodity to a clinical service—from a burden to an opportunity.

Through tight integration of lab services and strong laboratory stewardship, health systems can position themselves to reap countless benefits.

Need strategies to communicate the value of your lab? Let us help: go.aruplab.com/labvalue-Jacyno

ARUP is a nonprofit enterprise of the University of Utah and its Department of Pathology.
AACC Calls for CLIA Improvements as Fees Rise

The Centers for Medicare and Medicaid Services (CMS) has increased CLIA fees by 20%, the first increase in 20 years. Federal law requires the CLIA program to be self-sufficient, and costs to run the program have increased beyond the agency’s original projections.

AACC supports the increase but is asking CMS to outline how it plans to allocate the funds, both for current and future programs. AACC recently recommended improvements to CLIA, specifically to restart the agency’s Certificate of Waiver (CoW) project. Until CMS discontinued the program in 2016, the agency inspected 2% of waived laboratories annually and uncovered “serious quality problems” in some of these facilities, AACC notes in a letter to the agency.

AACC believes the data from the inspections could help the Centers for Disease Control and Prevention and CMS develop best practice documents and modules to improve the performance of all CoW laboratories. “As testing performed by waived facilities continues to grow and expand, it becomes more important to ensure these entities provide the highest quality testing possible,” the letter says. “Inspections should include a wide variety of CoW testing sites, such as physician office laboratories, home health agencies, pharmacies, retail stores, and nursing homes.” The number of CoW laboratories grew from 44% of all clinical laboratory testing sites in 1993 to 71% in 2018.

AACC also suggests that with increased income CMS should examine its role in ensuring the quality of laboratory developed tests (LDTs). “AACC believes that the CLIA oversight structure for LDTs is appropriate and would support reasonable evidence-based improvements within the confines of CLIA to address LDT concerns,” AACC emphasizes in the letter. “CMS should play a central role in facilitating this process.”

In October 2018, AACC published a position statement on modernizing CLIA and ensuring quality at CoW laboratories. It called for CMS to resume its CoW inspection program and for Congress to fund a study examining the quality of testing at these facilities.
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 epidemic.

ARK Diagnostics, Inc. now offers an FDA 510(k) cleared, CE-marked immunoassay that detects fentanyl in urine.

- Exceptional analytical sensitivity at a 1ng/mL cutoff level
- Detection of both the parent and major metabolite to identify more true positives
- Crossreactivity to norfentanyl extends the window of detection
- Liquid, ready-to-use convenience improves lab efficiency
- Three suitable kit sizes for low, moderate and high volume laboratories
- Application protocols for most general chemistry analyzers

If your fentanyl assay does not detect the major compounds that are present in urine, your facility may already be losing the fight against fentanyl abuse.
A critical clinical laboratory test result reflects either a life-threatening pathophysiological condition or one that might result in severe harm if not acted on immediately. CLIA regulation requires that laboratories “must immediately alert the individual or entity requesting the test and, if applicable, the individual responsible for using the test results when any test result indicates an imminently life-threatening condition, or panic or alert values.” The Joint Commission included reporting critical results as a national patient safety goal for 2019, with facilities required to “report critical results of tests and diagnostic procedures on a timely basis.” The College of American Pathologists (CAP) also requires laboratories to include critical result reporting as a quality indicator in their quality management plans. However, neither the Joint Commission nor CAP mandate a process for reporting critical results, nor do they provide instructions on establishing critical results or on repeating critical results prior to reporting them to clinicians.

A QUESTION OF QUALITY
Committed to ensuring analytical accuracy, many clinical laboratories in years past implemented the practice of repeating tests that yielded critical results to be doubly sure that these vital measurements were correct before notifying clinicians. This practice probably was due to instruments or testing procedures used in the past that had poor analytical performance. In modern clinical laboratories, however, the performance of our instruments and testing procedures has drastically improved, and we exercise vigorous quality management to ensure accuracy and precision.

Despite these advances, many labs continue to repeat critical results prior to reporting them out. This additional testing not only adds to laboratory costs but also delays reporting of critical results, which could cause patient harm. In contrast, labs expect that noncritical results are accurate and precise, and do not repeat these tests before reporting them out. If the accuracy and precision of our instruments and procedures truly are in doubt, one could argue that these initially noncritical results could become critical when retested.

ANALYZING PRACTICES, CHANGING POLICIES
During my 12 years as section head and medical director of clinical biochemistry at Cleveland Clinic, we debated this issue many times. At the beginning, our policy was to check on the quality of specimens that yielded critical results, including assessing whether they had visible particles and determining the serum index. If we found no quality issues with a specimen, we would repeat testing prior to reporting out critical results.

Proponents of eliminating this repeating step cited the outstanding analytical performance of our modern instruments and our vigorous quality management to ensure accuracy and precision. They also believed it hindered our ability to notify caregivers promptly about critical results, slowing in turn their opportunity to intervene earlier and achieve better patient outcomes. Those who supported the status quo were concerned about potential patient harms due to analytical errors.

Since we laboratorians are data driven, the team considering this issue carried out a retrospective study to help us decide which route we should take. Melissa Zimmer, BS, quality specialist at that time (2016), took on this project. We focused on glucose and potassium measurements in our automated clinical chemistry laboratory, which produced the most critical results.
In our study, we randomly selected critical values and the corresponding repeat results for glucose and potassium tests, all performed on a Roche Diagnostics cobas c 702 analyzer. We found that both the initial and corresponding retest values for glucose (n=100) and potassium (n=100) matched closely with a maximum difference of 2 mg/dL for glucose and 0.2 mmol/L for potassium, well within the CLIA criteria for assay precisions (glucose target: ±6 mg/dL or ±10% and potassium target: ±0.5 mmol/L). In addition, we discovered that the mean elapsed time between initial and retesting results posted in the lab information system was 14 minutes for glucose (n=31; range, 11-49 minutes) and 4 minutes for potassium (n=197; range, 0-37 minutes).

Based on these observations, we concluded that we did not need to repeat testing for critical values prior to releasing the results because of both the high precision of our instruments and the sophisticated quality assurance programs that we employed. Eliminating this unnecessary step allowed our laboratorians to reach out more rapidly to our clinicians, thereby enabling them to respond more promptly to the critical values. In addition, eliminating unnecessary analytical runs enabled us to improve our operational efficiency and overall turnaround time for all patient results in our high-volume laboratory. Of note, as we transitioned to not repeating critical results we allowed our technologists to repeat tests anytime they had concerns over the analytical accuracy or specimen integrity. This gave them peace of mind during the transition.

Sihe Wang, PhD, DABCC, FAACC, is director of clinical laboratories at Akron Children’s Hospital in Akron, Ohio. 

*mean elapsed time between initial and retesting results posted in the lab information system

Tracking Critical Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Time Associated With Retesting*</th>
<th>Number of Retests</th>
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</thead>
<tbody>
<tr>
<td>POTASSIUM</td>
<td>4</td>
<td>197</td>
</tr>
<tr>
<td>GLUCOSE</td>
<td>14</td>
<td>31</td>
</tr>
</tbody>
</table>

How critical is water to your laboratory?

Water impurities can lead to inaccurate test results, or worse, a complete shutdown of clinical analyzers. But water doesn’t have to be a challenge to manage.

With Water One® services from Evoqua, our highly trained service professionals proactively manage your water system. This minimizes down time and ensures you have the quality and quantity of water you need – when you need it.

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Three Lab Tests Predict Risk of Serious Bacterial Infection in Febrile Infants

A new prediction rule using just three lab tests—urinalysis, absolute neutrophil count (ANC), and serum procalcitonin (PCT) levels—accurately identifies febrile infants 60 days old or younger at low risk for serious bacterial infection (SBI) (JAMA Pediatr 2018; doi:10.1001/jamapediatrics.2019.5501). Once further validated, this rule could obviate unnecessary treatments in such young patients, according to the investigators.

SBIs occur in 8%-13% of febrile babies ≤2 months old. Because the consequences of missing an SBI can be so serious, treatment for these young patients often involves lumbar punctures, broad-spectrum antibiotics, and hospitalizations, all of which have associated risks. Algorithms to evaluate this population lack precision and specificity and have demonstrated “less than ideal accuracy,” according to the researchers.

The study involved 1,826 febrile infants seen at 26 emergency departments in the Pediatric Emergency Care Applied Research Network. All babies had blood and urine culture samples taken; attending clinicians decided whether patients underwent lumbar puncture for cerebrospinal fluid (CSF) testing; ultimately 76% had CSF cultures.

The investigators defined urinary tract infections (UTI) as growth of a single urine pathogen with at least 1,000 cfu/mL for culture obtained via suprapubic aspiration, with higher thresholds for catheterized specimens.

For the prediction rule, the researchers considered variables like the patient’s temperature, duration of fever, and clinician suspicion, but after univariable analysis and recursive partitioning analysis the model retained urinalysis, ANC, and PCT to identify babies at low risk of SBI.

In a derivation set of 908 infants, negative urinalysis, ANC ≤4,090/µL, and PCT ≤1.71 ng/mL identified 522 with an SBI risk of 0.4%. In the validation cohort of 913, the prediction rule using these cutoffs had a sensitivity, specificity, and negative predictive value of 97.7%, 60%, and 99.6%, respectively, misclassifying one baby with bacteremia and two with UTIs. It identified all infants who had bacterial meningitis.

CVD Risk Algorithms Perform Similarly After Recalibration

A head-to-head comparison of four commonly used cardiovascular disease (CVD) risk algorithms found that their clinical performance initially “varied substantially” (Eur Heart J 2019;40:621-31). However, after researchers recalibrated the algorithms to account for differences in the risk characteristics of the populations being studied, their clinical performance was “nearly equalized.”

These findings support the notion of using regularly recalibrated risk algorithms in clinical practice, according to the authors. The investigators also suggest that CVD primary prevention guidelines should “shift away from debates about the relative merits of particular risk algorithms and, instead, achieve consensus about the need for more widespread use of any recalibrated algorithm.”

Debate has been ongoing about how well four key CVD risk algorithms—pooled cohort equations (PCE), Systematic Coronary Risk Evaluation (SCORE), Framingham risk score (FRS), and Reynolds risk score (RRS)—capture and predict risk, and guide clinicians in determining the best treatment approaches for their patients.

PCE, recommended by the American College of Cardiology/American Heart Association, and SCORE, recommended by the European Society of Cardiology, as well as FRS and RRS, include common risk inputs but also differ not only in risk factors considered but also their mathematical formulations and the CVD outcomes they employ. A few, relatively small studies have sought to compare the equations. The investigators used individual participant data on 360,737 individuals without CVD in 86 prospective studies from 22 countries to calculate the models’ risk discrimination and calibration, and to
HbA1c: NOT FIRST TEST CHOICE BUT MORE LIKELY TO LEAD TO DIABETES, PREDIABETES DIAGNOSIS

An analysis of screening practices for diabetes and prediabetes since 2010, when the American Diabetes Association (ADA) first recommended HbA1c testing as a screening option, found that while HbA1c testing is used less often for screening than glucose testing (14% versus 86%, respectively) it is more likely to result in a clinical diagnosis (Diabetes Care 2019; doi.org/10.2337/dc17-1726).

The study examined the claims and electronic health records of 12,772 individuals ≥45 years old who had been enrolled in the Blue Care Network of Michigan for 3 consecutive years, who did not have diabetes or take antidiabetic medications, and who received primary care at University of Michigan Health System. The authors conducted a similar study examining screening practices between 1998 and 2000. The investigators found that 78% of individuals had been screened by any method, versus 69% in their earlier study. Almost all glucose tests were performed as part of chemistry panels, with just 18% performed as standalone tests. Abnormal (≥5.7%) HbA1c results were more likely than glucose tests ≥100 mg/dL but no more likely than glucose tests ≥126 mg/dL to be associated with follow-up visits within 6 months. However, an HbA1c result ≥5.7% was more likely than a glucose test result ≥126 mg/dL to lead to a diagnosis of diabetes or prediabetes within 6 months. These findings suggest a need for better defined cutpoints to delineate abnormal random glucose tests, according to the authors. ADA’s recommendation that random glucose levels ≥200 mg/dL could be diagnostic of diabetes when accompanied by signs and symptoms of the disease, might have lulled “practitioners into believing that random glucose levels <200 mg/dL are normal.” The authors stated, however, that random glucose levels ≥126 mg/dL and possibly ≥100 mg/dL, even when performed as part of chemistry panels, “deserve follow-up with a definitive diagnostic test, either an HbA1c or fasting glucose tests.”
Rethinking INNOVATION

BY JULIE KIRKWOOD

New markers, integrated platforms, and informatics shape the future of clinical chemistry

hen it comes to the latest innovations in diagnostic tests, new technologies such as mass spectrometry and next-generation sequencing get a lot of attention. Traditional clinical chemistry assays? Not so much. Many of the assays in core chemistry laboratories are fundamentally the same as they have been for decades.

“To some extent, traditional chemistry has settled in,” said Jonathan Genzen, MD, PhD, section chief of chemistry and medical director of the automated core laboratory at ARUP Laboratories. He is also an associate professor of pathology at the University of Utah School of Medicine in Salt Lake City. Yet experts agree there still is plenty of room for innovation in clinical chemistry. From harnessing the power of data to the discovery of new biomarkers, this field is advancing rapidly, and vendors are still investing heavily in the latest technologies.

“You’re seeing new platforms coming out constantly,” said Susan Evans, PhD, FAACC, principal and founder of BioDecisions Consulting in Los Gatos, California. These systems are becoming more interactive, efficient, and flexible, and they are able to meet the changing needs of core laboratories for smaller sample volumes, more data integration, and quality management. “It’s not like [in vitro diagnostics] companies are sitting around saying, ‘Oh, my mainstream core lab instrument is good enough. It’s going to last for another 10 years because the chemistries are not changing,’” Evans said. “The companies understand that there is a need for continuous change, including the addition of new features and capabilities.”

The worldwide clinical chemistry market (including instruments, service, and reagents) amounts to nearly $8 billion and is one of the largest segments within the $60 billion in vitro diagnostics market, according to Greg Stutman, director of global solutions at IQVIA (BBC IVD Solutions). If heterogeneous immunoassay reagents are included, the total immunochemistry market triples.

“Clinical chemistry is typically the largest volume category of a laboratory and is expected to remain so in the future,” he said. “While novel menu launches in clinical chemistry may not be developing at the same pace as heterogeneous immunoassay, molecular, or next-generation sequencing, companies continue to invest material research and development funds into product line enhancements, such as more scalable and automated solutions, enhanced connectivity with other platforms, and improved [information technology] offerings.”

New Chemistry Assays

When it comes to test menus for clinical chemistry and related areas, several new assays and new biomarkers are in development, noted James Nichols, PhD, DABCC, FAACC, medical director of clinical chemistry and point-of-care testing at Vanderbilt University School of Medicine in Nashville. “Certainly, there are new tests that are always innovating in terms of the core laboratory,” Nichols said.

For example, high-sensitivity troponin assays for diagnosing myocardial infarction are now becoming available to laboratories in the United States, he said. New biomarkers may soon be available for diagnosing and monitoring traumatic brain injury, and encouraging research is emerging for tests for Alzheimer’s disease.

Evans noted developments in multi-analyte markers to screen for cancer and the use of artificial intelligence and machine learning to find combinations of physiological markers that correlate with disease states. For example, multi-analyte markers related to immune response to infection, perhaps in conjunction with molecular techniques, could help diagnose and predict the severity of infectious diseases, such as the outcome of a patient presenting with the early signs of sepsis.
INNOVATION in the Core Lab
Promising research also is underway involving biomarkers for ischemic stroke and for kidney disease, Evans commented. “There’s never a shortage of researchers looking for new markers, especially in the world of immunoassays.”

In addition to new assays, innovations are leading to improved performance of existing assays and in core laboratory instruments, she said. Automated platforms are being designed to handle a wider variety of sample types and smaller sample volumes.

Nichols also noted that radioactive and toxic components of many assays are being replaced with safer materials, and there are innovations in electrical technologies and biosensors.

**Forming New Connections**

Beyond new and improved assays, innovation is underway in how clinical chemistry connects through automation to other areas of clinical laboratories.

This is a continuation of a trend that has been happening over the past few decades, as core laboratories have grown to encompass disciplines spanning chemistry, immunoassay, hematology, and hemostasis, among other categories, Stutman said. “Going forward, more novel technologies once reserved for specialized settings, such as molecular/virology, may increasingly migrate into the core laboratory,” he observed.

Efforts are underway to connect both mass spectrometry and molecular diagnostics instruments to clinical chemistry systems, Nichols said. If mass spectrometry could be connected to chemistry and immunoassay analyzers on the same platform, drugs of abuse testing could be done in real time, with samples moving directly from immunoassay screening to confirmatory testing.

Likewise, if molecular diagnostics instruments were to connect to core laboratories, chemistry and immunoassay testing could be combined for diagnosing and monitoring infectious diseases, with follow-up molecular confirmation using the same sample on the same track, said Nichols. The risk of contamination for molecular diagnostics tests has been a barrier in the past, but companies are coming up with new ways to manage this risk, he added.

**Innovating With Data**

Meanwhile, advances in information technology (IT) and data analysis are impacting every area of clinical laboratories, including clinical chemistry. Diagnostics companies have improved the IT components of their products, Genzen said, incorporating dashboards and access to real-time analytics.

“It’s no longer an afterthought, but an active component of most major diagnostic companies in the clinical laboratory space to offer IT solutions that provide better access to viewing data in a way that’s meaningful,” Genzen said. “… I think it’s clearly going to grow and will hopefully become even more useful.”

With these tools, clinical chemists can use data to improve laboratory performance. For example, they can monitor turnaround time for STAT tests with color codes and alerts. They can review patient medians for drifts or shifts that might indicate a calibration issue. Clinical chemistry labs also are using laboratory-generated data in a research context, looking for patterns that may be predictive of health conditions or that might guide decisions on reflexive testing or add-on tests, Genzen added.

“Because we are used to working with a large number of analytes and substantive data sets, I think chemists in particular are in a good position to play that role and to participate in more [electronic medical record]-based patient care initiatives using all of that laboratory data,” Genzen said.

**Miniaturizing the Core Lab?**

Looking farther into the future, Genzen and Nichols both speculated that the trends that have allowed many clinical chemistry assays to move to the point of care could ultimately influence the size of core laboratories, as well.

“Automation systems and chemistry instrumentation, oddly enough, have gotten a little bit bigger over time,” Genzen said. “With advances in technology and microfluidics, things should at some point start getting smaller.”

Right now, most core laboratories are optimized for economies of scale and high-volume testing based on traditionally sized collection tubes, he said, and cost per test on these platforms is much lower than on small devices at the point of care. Yet if microfluidic technologies were to become less expensive, this calculation could change.

“At some point in the future, the technology will catch up and things in a core clinical laboratory will start getting smaller, because I know a lot of labs are facing space pressures.”

— JONATHAN GENZEN, MD, PHD

Julie Kirkwood is a freelance journalist who lives in Rochester, New York.

+EMAIL: julkirkwood@gmail.com
The mission of the National Lipid Association (NLA) “is to enhance the practice of lipid management in clinical medicine”. NLA advocate advancing the current lipid testing profile. The current lipid panel consists of testing LDL cholesterol, HDL cholesterol and triglycerides, which only detects approximately 20% of atherosclerotic cardiovascular disease (ASCVD) patients. Advanced lipid testing is recommended to optimize patient treatment.

Small-dense LDL cholesterol (sdLDL-C)
A subtype of LDL cholesterol, sdLDL-C is more atherogenic than the large buoyant LDL cholesterol (lbLDL-C) and can more readily permeate the inner arterial wall, increasing the risk of ASCVD 3-fold.

Lipoprotein (a) (Lp(a))
The Randox Lp(a) assay is one of the only methodologies on the market to detect the non-variable part of the Lp(a) molecule and therefore suffers minimal size related bias.

HDL3 cholesterol (HDL3-C)
A subtype of HDL cholesterol, HDL3-C is the most prevalent HDL subclass and is mostly responsible for reverse cholesterol transport. HDL3-C has an inverse relationship with CVD risk.
A BASIC GUIDE TO ANA Testing

Laboratories must consider several key factors before deciding which method is best for their patients and staff.

By Melissa R. Snyder, PhD
Imagine your lab has decided to take the plunge and implement antinuclear antibody (ANA) testing in house, taking it off the send-out menu. You might first ask, What is the best method for ANA testing? Or, what if your lab already performs ANA testing, but the expert technologist who has been reading ANA indirect immunofluorescence (IIF) slides for 30 years has just announced that she is going to retire. This might prompt you to ask, Is it time for us to move from IIF ANA testing to a newer methodology? These are important and relevant questions, but without easy answers. This review aims to provide practical information on ANA testing methodologies, including their diagnostic utility and performance characteristics.

ANA TESTING HISTORY AND CONTEXT

ANAs refer to a collection of auto-antibodies that target a variety of nuclear and cytoplasmic antigens. First described more than 50 years ago, ANAs remain the most sensitive serologic marker for evaluating patients with suspected connective tissue diseases (CTDs), also referred to as ANA-associated rheumatic diseases (AARDs) (1).

The diagnostic potential of ANAs originated with the discovery of LE cells, described as mature polymorphonuclear leukocytes containing phagocytosed nuclear material. LE cells were so-named because they were found only in patients with systemic lupus erythematosus (SLE). LE cells were produced in vitro by taking patient plasma and mixing it with peripheral blood from healthy controls that had been “damaged” by vortexing with glass beads. Ultimately, research demonstrated that immunoglobulin from patient plasma was binding to nuclei from the “damaged” peripheral blood, which neutrophils in turn phagocytosed. IIF was used to further characterize this immunoglobulin, demonstrating its specific binding to cellular nuclear material. This immunoglobulin is what we now know as the ANA.

ANA testing generally involves two parts (2). First, for patients with a suspected AARD, a screening ANA is ordered to detect the ANA regardless of the antigen specificity. Second, for patients with positive screening assay results, additional tests characterize the antigen specificity of their ANA. Identifying the antigen specificity has important diagnostic and prognostic implications for patients. Although dozens of antigens have been associated with ANAs, only a small number are available for routine clinical testing. Depending on a patient’s clinical scenario, a positive ANA may require testing for anti-double standard DNA antibodies, antibodies against one or more of the extractable nuclear antigens (SS-A, SS-B, Sm, Scl-70, Jo-1, and RNP), anti-ribosome P antibodies, or anti-centromere antibodies.
METHODOLOGIES FOR ANA TESTING

Three primary methods are available to clinical laboratories as screening ANA tests: IIF, enzyme immunoassay (EIA), and multiplex immunoassay (MIA) (Table 1) (3). IIF detects antibodies that bind to a tissue substrate which, for ANAs, is usually fixed HEP-2 cells. IIF accomplishes this detection with a fluorescently labeled anti-human immunoglobulin. With EIA, an antigen mixture adhered to a solid surface (usually a 96-well plate) takes the place of the HEP-2 cells, and detection occurs through an enzyme-labeled anti-human immunoglobulin. MIAs are based on polystyrene bead sets distinguished from one another based on their fluorescent signature. Each bead set is conjugated to a known ANA antigen, and the different sets are then combined into a bead cocktail. A patient sample is added to the bead cocktail, and binding of a patient antibody to any of the beads is accomplished with a fluorescently labeled anti-human immunoglobulin.

REPORTING OF ANA TEST RESULTS

From a physician’s perspective, one of the most obvious differences between ANA screening methods is how results are reported. In most cases, MIAs are reported qualitatively as “ANA positive” or “ANA negative,” with screen results being based on the collective assessment of all the individual antigen specificities included in an assay. If all the included antigen specificities are negative, then the ANA screen is interpreted as negative. Conversely, if one or more of the beads show fluorescence exceeding a certain threshold, a sample would be identified as positive. Importantly, for ANA positive samples, the identities of the antigen specificities are not revealed to the laboratory and thus are not reported to patients’ medical records. If a clinician wants to determine the antigen specificity of a patient’s ANA, he or she would need to order the clinically relevant tests.

In contrast, most EIAs are reported as a numeric value with an arbitrary unit of measurement. There is no traceable standard for these assays, so each manufacturer establishes the units and analytical measuring range for its tests. EIAs’ quantitation is based on light absorbance. The enzyme linked to the detection antibody converts a colorless substrate to a colored product, the absorbance of which is compared to a standard curve. Manufacturers will provide a recommended cutoff, which is the unit value above which a sample would be considered “ANA positive”. As with MIAs, a positive EIA result does not reveal the antigen specificity of the ANA, and further testing would be necessary if a clinician wants to know those details.

ANA by IIF is generally reported with both a titer and a pattern. Labs screen all samples initially at a single dilution, usually 1:40 or 1:80. Any sample identified as positive at the screening dilution is titered out either to endpoint or to a pre-defined dilution, depending on the laboratory’s preference. The titer is determined by serial dilution, with the reported titer being the last dilution for which the IIF would be identified as positive. The pattern interpretation is based upon recognition of specific cellular features to which a patient’s antibody has bound (Figure 1).

Because IIF pattern interpretation is based on visual interpretation, standardization in reporting has been a challenge. The International Consensus on ANA Patterns (ICAP), a subcommittee of the Autoantibody Standardization Committee, promotes discussion and generates consensus regarding the morphologic features associated with specific ANA patterns (4). ICAP has also made recommendations regarding how laboratories should report ANA patterns. The group has defined six nuclear patterns as “Competent-Level”: homogeneous; speckled; dense fine speckled (DFS); centromere; discrete nuclear dots; and nucleolar. ICAP recommends that any laboratory performing ANA by IIF should be able to accurately and reproducibly identify these patterns. The remaining nuclear patterns are designated as “Expert-Level” and might be recognizable only by individuals with particular expertise in IIF analysis.

ANA CLINICAL SENSITIVITY AND SPECIFICITY

When considering which ANA test to implement, understanding each method’s clinical sensitivity and specificity is critical. Many studies have compared the clinical sensitivity and specificity of the different methods. Because IIFs, EIAs, and MIAs report results so differently, these studies have focused

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Analytical Characteristics</th>
<th>Clinical Characteristics</th>
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<tbody>
<tr>
<td>Name</td>
<td>Abbreviation</td>
<td>Antigen</td>
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<tr>
<td>Indirect immuno-fluorescence</td>
<td>IIF</td>
<td>HEP-2 cells</td>
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<tr>
<td>Enzyme immunoassay</td>
<td>EIA</td>
<td>HEP-2 cell lysate or other mixture of proteins representing HEP-2 cells</td>
</tr>
<tr>
<td>Multiplex immunoassay</td>
<td>MIA</td>
<td>Individual ANA antigen specificities</td>
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Comparison of various features and characteristics of ANA testing by IIF, EIA, and MIA.
primarily on qualitative agreement. Although seemingly very straightforward, these types of comparisons are more difficult than they appear, largely because estimated sensitivities and specificities and the agreement between methods is heavily dependent on the cutoffs used to differentiate between positive and negative.

Historically, IIF has been considered the most sensitive method for identifying patients with AARDs. In a 2009 position statement on ANA testing methods, the American College of Rheumatology identified IIF as the “gold standard for ANA testing” primarily based on its high sensitivity (>95%) for the diagnosis of SLE (5). However, the statement also acknowledges that the specificity of ANA by IIF is a limitation. In a cohort of patients for whom ANA testing was ordered as part of routine clinical care, we demonstrated that IIF at a titer cutoff of 1:40 had a sensitivity of 94% for the general diagnosis of AARDs (6). This was higher than the sensitivity of either EIA or MIA, at 74% and 67%, respectively. However, the IIF’s higher sensitivity was at the expense of specificity, which, at the 1:40 cutoff, was only 43%. In comparison, the corresponding EIA and MIA specificities were 80% and 87%, respectively. When we increased the cutoff for IIF to 1:80, the specificity improved to 62% but the sensitivity decreased to 84%.

Some data suggest that the titer of the ANA may help in distinguishing between patients with and without AARDs. In a study from 2011, Mariz et al. demonstrated that 45.8% of positive ANAs in healthy controls had a titer of 1:80, while 88.5% of ANA-positive AARD patients had an ANA titer ≥1:320 (7). Many laboratories that perform ANA by IIF are moving away from screening at the 1:40 dilution, opting for improved specificity even with some loss in sensitivity. When labs use higher screening dilutions, the specificities of IFs are on par with those of EIAs and MIAs. Although IFs have the capability of maximizing sensitivity, from a practical perspective, EIAs and MIAs provide a good balance of sensitivity and specificity.

IIF’s sensitivity is attributed to its broad antigen specificity. This method detects antibodies against any of the hundreds of nuclear and cytoplasmic antigens present in a cell. However, not all antigen specificities are relevant for the diagnosis of AARDs. For example, the DFS pattern appears almost exclusively in patients with no evidence of an AARD (7). It has been suggested that the presence of the DFS pattern could be used to rule out an AARD in an individual with a positive ANA. The antigen specificity associated with this pattern has been identified as lens epithelial-derived growth factor, also referred to as DFS70 (8).

Further studies have confirmed that monospecificity for DFS70 in the context of a DFS pattern is not consistent with an AARD. This pattern, and perhaps others like it that have yet to be characterized, may help to address some of the specificity challenges associated with ANA testing by IIF.

### PERFORMANCE CONSIDERATIONS FOR ANA METHODOLOGIES

When labs are considering which ANA method to implement, availability of a qualified technologist to perform the testing is likely a significant concern. Other key considerations include throughput, workflow, and automation of a method.

Although automation of immunological testing has not reached the level of chemistry platforms, significant strides have been made over the last decade, particularly with EIAs and MIAs. EIAs can be performed manually, although more often than not, labs perform this testing on semi-automated or automated platforms. The semi-automated platforms may dilute patient samples and add reagents to the plate, but a technologist’s intervention might be required to wash and move the plate to an absorbance reader. A fully automated system processes an EIA in its entirety, only requiring technologists to load samples and reagents. Most MIA systems are also fully automated.

In addition, MIAs have the advantage of being random access, which facilitates improved workflows. In contrast, EIAs are batched, which, for labs with lower volumes of ANA orders, could have a negative impact on workflow and on turnaround times. Another advantage of MIA systems is they offer labs the opportunity to expand their test menus. Most MIA systems are not limited to ANA testing, and have reagents available for other autoimmune conditions (celiac disease, antiphospholipid syndrome, and vasculitis) and for infectious diseases (Epstein-Barr virus, HIV, and herpes simplex virus). Being able to perform additional testing and maximize an instrument’s utilization could make an MIA system an attractive option.

Historically, IIF has been the ANA method requiring the most clinical technologist resources and expertise.
with automation limited to dilution of patient samples and perhaps addition of sample and reagents to slides. In addition, slide reading was a manual process that relied on experienced technologists to interpret numerous complex patterns. Now, however, systems are available that automate almost the entire process, from slide processing to reading. Processing the slides includes not only sample and reagent pipetting but also slide incubation and washing. After processing, the slides can be moved to an enclosed microscope with a high-resolution digital camera, which obviates the need for a darkroom. This means such systems can be used on a bench in an open laboratory.

Cameras in these newer IIF systems capture several digital images from different areas of slides. The fluorescence intensity of the stain is measured, and values above a certain cutoff are considered positive. For samples identified as positive, the computer algorithm reads the pattern of and interprets the fluorescence intensities in the context of known ANA patterns. Although this step automates the previously manual process of slide reading, final qualitative and pattern interpretation still requires a technologist’s expertise. For each sample, a technologist must confirm the computer-generated result. If he or she disagrees, the result can be changed. Most automated readers recognize the common ANA patterns, and some identify certain mixed patterns.

More complex patterns unidentifiable by the computer still require a technologist’s interpretation. Some automated readers not only automate pattern interpretation at least partially but also estimate titers. These instruments use the fluorescence intensity of an image to estimate a sample’s titer rather than relying on serial dilutions. This can be accomplished either from a single patient dilution or a limited number of dilutions. As with pattern interpretation, an estimated titer can be replaced with a titer from serial dilutions, depending on the pattern and the technologist’s judgment. Overall, although not completely automated by chemistry standards, the availability of automation for IIF, EIA, and MIA gives labs several options for complex ANA testing in a time of shrinking resources.

CONCLUSION
Over the last 10 years, ANA testing has experienced significant advances. Improvements in automation, development of new methods with better workflows, and even a clearer understanding of the diagnostic utility of this testing has widened the options for clinical laboratories. However, choosing among EIA, MIA, and IFA is not easy, even when major guidelines are recommending IIF. No one-size-fits-all method exists, so each laboratory must make its own assessment as to which method is most beneficial for its patients and staff.

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A PLAN FOR
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Clopidogrel is the most commonly prescribed antiplatelet drug for patients following percutaneous coronary intervention (PCI) procedures to treat narrowing of the arteries. However, about 30% of Caucasians and African-Americans, and about 60% of Asians, have genetic variations in the cytochrome p450 2C19 (CYP2C19) gene that affect their metabolism of the drug, leaving them at about a two-fold increased risk of developing a recurring cardiovascular event. In March 2010, the Food and Drug Administration (FDA) added a black box warning to clopidogrel, advising clinicians that poor metabolizers of this drug could experience reduced effectiveness when taking it, that tests for CYP2C19 function are available, and that they might consider prescribing other medications in these high-risk patients.

Even before the FDA box warning, some medical centers had started clinically testing for CYP2C19 genotype in patients undergoing PCI to help guide selection of appropriate antiplatelet therapy, either with clopidogrel or other agents such as prasugrel or ticagrelor. More have followed suit over the past decade, including participants in the Implementing GeNomics In pracTicE (IGNITE) network, a National Institutes of Health-funded research group aimed at implementing genomics in practice. Twelve of these trailblazing institutions recently published their strategies for implementing CYP2C19 genotype-guided therapy (Clin Pharmacol Ther 2018;104:664-74).

“There has been considerable debate and uncertainty surrounding whether using CYP2C19 genetic testing clinically to guide antiplatelet therapy is the right thing to do given the amount of evidence,” said the study’s senior author, Craig Lee, PharmD, PhD, an associate professor in the Division of Pharmacotherapy and Experimental Therapeutics at the University of North Carolina at Chapel Hill (UNC), one of the early adopters of CYP2C19 testing.

Guidelines from groups like the American Heart Association say genotyping high-risk PCI patients might make sense, but they don’t recommend it routinely for all patients. Data from a multicenter randomized clinical trial called TAILOR-PCI, seeking to discover
if genetic testing can determine the best anti-platelet therapy, is expected to be released by September. Meanwhile, evidence accruing through studies from IGNITE and previous pharmacogenomic networks, and a number of small clinical trials in Asia and Europe, are demonstrating improved patient outcomes using a genotype-guided strategy, and an increasing number of institutions have either implemented or sought to implement some CYP2C19 genetic testing, said Lee.

While other antiplatelet agents don’t carry the same interactions with CYP2C19, clopidogrel often is still favored, said the study’s first author, Philip Empey, PharmD, PhD, associate director for pharmacogenomics at the University of Pittsburgh/UPMC Institute of Precision Medicine (UPMC). “The higher potency agents have different side effect profiles and higher rates of bleeding events,” he said. Some older populations can’t take them, and they’re more expensive. “In our cost-focused world, clinicians must consider many factors when making prescribing decisions,” he added.

Which Alleles, Platforms?
Institutions participating in the recent IGNITE study noted several challenges in implementing their pharmacogenomic testing programs, such as selecting a testing platform, determining how to communicate test results, and educating patients and providers. The medical centers used a variety of platforms for genotyping, including Spartan Biosciences’ Spartan RX, GenMark Diagnostics’ eSensor XT-8, and custom TaqMan and QuantStudio assays from ThermoFisher.

UNC uses a TaqMan assay, said Karen Weck, MD, director of the institution’s molecular genetics laboratory. “We looked at a number of genotyping platforms and chose to use this for various reasons,” she said. “It works really well, it’s a fast test, and we have designed a separate assay for the CYP2C19*2 and *3 variants, which are the poor metabolism alleles, and for *17, which is a rapid metabolism allele.” All 12 institutions surveyed in the study said they report at least these three alleles, with some adding results for CYP2C19*4, *10, *12, and *13.

UPMC reports findings for 10 CYP2C19 variants employing the GenMark platform, Empey said. “It has coverage of the variants we think are important, and it made sense in our workflow for what we wanted to return.”

Accuracy and speed are critical factors to look for in platforms, said Empey and Alan Shuldiner, MD, associate dean for personalized and genomic medicine at the University of Maryland School of Medicine (UM) in Baltimore. At UM, results are reported in patients’ electronic medical records within 3-4 hours of tests being ordered. “The key is to make sure the genotype is returned before the patient is discharged,” Shuldiner said, “so that an appropriate therapeutic decision can be made.”

All sites in the IGNITE study report CYP2C19 test results in patients’ electronic health records, often listed as discrete genotype and phenotype results as well as a notation of how patients will metabolize the drug, with a linked text-based full report. Some centers use pharmacists or dedicated teams to provide genotype-informed drug therapy recommendations.

“Discrete results are critical to enabling clinical decision support and alerting appropriately within our health system,” said Empey. “It’s hard to do that solely from a PDF or text-based report.”

Institutional Champions
IGNITE study participants listed several key ingredients for success in implementing pharmacogenomics programs like this. Chief among them are identifying a physician champion and engaging key stakeholders.

UNC was able to encourage CYP2C19 testing more easily because the former head of the cardiac catheterization laboratory helped push for it, said Weck. “The most important issue of clinical success is having a clinical group interested in utilizing the results,” she emphasized.

Also important is to create clinical decision support tools to spur clinicians to order the tests and take appropriate medical action based on the results. After discovering at their own institution that use of the tests fluctuated over time, staff at UNC are in the process of creating automated clinical decision support for CYP2C19 testing, said Lee (Circ Genom Precis Med 2018;11:e002069).

In addition, he said, “Education is really key to assure that those ordering the tests and using the results understand the evidence behind it.” Interdisciplinary collaboration with clinicians and nurses also is crucial. “We really need to make sure everyone who’s involved in the process understands the goals and processes to make it successful,” Empey said.

Laboratorians might want to partner with pharmacists to educate providers, advised Petr Starostik, MD, director of molecular pathology at University of Florida Health (UFH) in Gainesville, “because they will send you samples only if they see there is a need for such testing.”

Future Targets
While CYP2C19-guided therapy for clopidogrel remains the “poster child and most broadly applicable” of the genotyping tests, said Shuldiner, some medical centers—including IGNITE participants—are considering or already running pharmacogenomic tests for additional genes and their drug interactions. “I think a lot’s going to happen over the next few years,” he predicted.

At UFH, for example, the lab also tests for CYP2D6, involved in the metabolism of many drugs, including opioids. Ultra-fast metabolizers of that gene may need higher doses to experience pain relief, Starostik said. In addition, the UFH lab plans to start using an All of Us microarray to study the whole genome. Clinically relevant genes like CYP2D6 and CYP2C19 will be reported per usual in patients’ electronic health records while the remaining data will be held in a biobank for subsequent research.

IGNITE participants emphasize the importance of working with clinicians in determining the need for and implementing any tests. “Pharmacogenomics has not been an example of ‘If you build it, they will come,’” said Weck. “We’ve had several such tests that we have brought online that have not been ordered because of lack of clinical uptake.”

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Improve Patient Care with Advanced CVD Risk Markers from Denka Seiken

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Daniel Anderson, MD, and Michael Astion, MD, PhD, interviewed medical geneticist and thought leader Matthew Fickie, MD, FACMG, of Highmark Health in Pittsburgh, about the challenges of third-party payer management of laboratory testing. Fickie is medical director at Highmark Health Blue-Branded Health Plans, which serves more than 4 million members in Pennsylvania, West Virginia, and Delaware. Fickie is also chair of the Economics of Genetic Services Committee at the American College of Medical Genetics and Genomics.

What are the top challenges third-party payers face in managing genetic testing?

There are six key problems in managing genetic testing: 1) the lack of specific Current Procedural Terminology (CPT) codes; 2) shortage of genetics experts inside insurance companies; 3) the quality of genetic assessments and medical necessity policies; 4) the fact that the focus of medical genetics research has not favored comparative analysis of genetic testing; 5) the lack of innovation and innovative partnerships within the insurance industry; and 6) abusive practices by clinical laboratories.

What kinds of challenges do CPT codes present?

Providers use Tier 1 CPT codes to bill for common genetic tests. Though not perfectly specific, these codes have enough specificity to allow insurance companies to understand what is being purchased. For example, the genetic test for the common cystic fibrosis variants is coded as CPT 81220.

Tier 2 CPT codes, which range from CPT 81400 through 81408, are general genetic testing procedures arranged in order of increasing complexity, with 81400 being the least complex and time-consuming (so-called Level 1) and 81408 being the most complex (Level 9).

Tier 2 codes generally are for rarer diseases and less frequent testing than Tier 1.

Each Tier 2 code has a long list of specific tests that fall under the same code. For example, more than 50 different specific genetic tests belong under CPT code 81401 (Molecular Pathology Procedure, Level 2). This complicates insurers’ ability to deal with these tests because they don’t know the specific Tier 2 tests they are paying for, so can’t easily apply medical necessity criteria. However, Tier 2 codes at least suggest how much work is being done, so reasonable prices can be estimated.

The worst problem from a test management perspective is if a genetic test is not covered by a Tier 1 or Tier 2 code. In this case, clinical laboratories code tests as the dreaded CPT code 81479 “unlisted molecular policy procedure code.” A tremendous amount of spending on expensive cancer genomic profiling and other genetic tests gets buried in this code. Since an insurer can’t be confident about the healthcare service being purchased, it will have difficulty in applying fee sheets or medical necessity policies, both terrible circumstances from a utilization management perspective.

You mentioned a shortage of genetic expertise inside the insurance industry. What expert knowledge is missing and what tasks require it?

The insurance industry lacks medical geneticists and genetic counselors. Currently, most medical directors within insurance companies are generalists, for example family practitioners and general internists, and lack special training in genetic medicine. Yet they are still expected to establish and enforce policies involving genetic testing. Since it takes expertise to understand, create, and enforce fair and effective policies, this lack of expertise is undesirable for patients and for the medical directors who are trying to serve them. When you take this problem and add the aforementioned nonspecific code problem, you can understand how hard this job can be for professionals without genetics expertise.

Can you comment further on the lack of quality in genetic assessments and medical necessity policies?

By genetic assessments, I am referring to analysis of the evidence underlying the use of a genetic test. Does the test measure what it claims to measure, and is it useful in improving patient outcomes?

By genetic assessments, I am referring to analysis of the evidence underlying the use of a genetic test. Does the test measure what it claims to measure, and is it useful in improving patient outcomes?

The types of trials evaluated, and the outcomes prioritized by some health technology groups, are not appropriate for genetic diseases and tests. Medical necessity policies take the results of assessments and translate them into criteria for using a genetic test. For example, which
patients under what clinical circumstances would benefit from the test? Third-party experts or commercial organizations provide many genetic assessments and medical necessity policies, the quality of which varies. Smaller payers in particular are at risk as they likely have fewer resources to hire in-house genetic experts and to pay for high-quality third-party assistance.

What is the challenge with the direction of medical genetics research, and why does it cause problems for third-party payers?
Medical geneticists, most of whom reside in academic settings, do not focus on comparative effectiveness research. Instead, they migrate toward making gene discoveries. My impression is that they would rather discover the tenth genetic finding related to a rare disease than perform comparative studies of various testing strategies on a population for which multiple options are available. This is despite the likelihood that the improved testing strategies would positively impact more people.

What sorts of innovative partnerships should insurance companies pursue, and what strategic advantages do these partnerships provide?
In general, payers have not pursued enough innovative partnerships with the laboratory industry. An example of an innovative partnership is the relationship between Illumina and Harvard Pilgrim Health, a health plan that covers approximately 1.2 million people in New England. This partnership will assess the total costs and clinical outcomes of noninvasive prenatal testing (NIPT) versus traditional screening practices in a risk sharing contract. It will provide open market access of NIPT for average risk pregnancies in a way that limits the extent to which the arrangement increases overall healthcare costs. The risk and information sharing under this agreement is an example of innovative policymaking that would benefit patients, payers, and diagnostic testing companies and could provide clarity on comparative effectiveness as discussed in my prior point. I would like to see more of this type of collaboration and experimentation around covered benefits for genetic testing.

You mentioned as a top challenge abusive practices by some clinical labs. Could you elaborate on this issue?
I recently reviewed a $40,000 cancer genomic profiling test from a commercial lab that raised several red flags with the way it was billed. Unfortunately, this kind of abuse is not rare. Some abnormal billing practices are innocent mistakes caused by a lack of coding expertise. Coding genomic tests can be a complex process, and the rules aren’t as clear as in other fields.

But some of the abusive billing practices are fraud, like purposefully misusing the coding system to maximize the likelihood of a paid claim. A specific example of this type of fraud is switching from a newer, correct CPT code that the insurance company does not cover, to an incorrect, older code that is still covered.

What predictions do you have, and what opportunities do you see, for how third-party payers will handle genetic tests in the future?
I have a few predictions. First, I think the cost of most genetic testing will continue to decline, to the point that eventually it will not be cost-effective for insurance companies to have medical professionals reviewing the claims. Insurers will find a way to automate the process so they are adjudicating the cases with computer algorithms and using human review for only the most difficult, expensive cases, as well as for grievances.

Automation will continue to improve, especially with advances in artificial intelligence (AI). AI can analyze both insurance claims and electronic medical records to filter the laboratory claims most worthwhile for medical professionals to review. The current process is labor intensive and difficult. For example, I think AI might be able to do a better job in natural language processing of notes and separating initial cases of cancer from relapsed cancer. This type of separation is important because relapsed cancer is an indication for a variety of expensive cancer genomic profiling tests and treatments.

Another prediction is that test utilization and policy implementation will improve as a younger generation of medical professionals, who are more educated about genetic testing, rise through the ranks.

I also believe there are opportunities for a variety of technology companies to develop rapid, reliable, web-based tools to better handle the ordering and preauthorization of genetic tests. These tools could also automatically route tests to in-network labs for the insurance companies paying the claims.

Finally, I think there are going to be many more indications for cancer genomic profiling for risk stratification and treatment selection in a variety of neoplasms. This will benefit cases in which there is indeterminate pathology and will be an improvement over current surveillance strategies. Insurance companies will need to have up-to-date medical necessity policies in this arena and adjudicate cases fairly and consistently, as the research on these technologies is moving fast.

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References


Perimortem Genetic Testing in a Children’s Hospital: A Team Approach to Policy Development

Genetic testing in the perimortem period—immediately before or after a patient’s death—involves unique ethical and logistical issues in pediatric hospitals. Genetic testing may be necessary to confirm an underlying diagnosis, yet testing may not be medically necessary because the results will not change medical care for the child. Historically, well-meaning clinical teams at our institution promised unnecessary genetic testing to families. When the Laboratory Test Stewardship Committee would determine that a test was not medically necessary, it led to stress for families, providers, and the laboratory teams, particularly when a family was emotionally invested in the test plan.

In 2017 our Laboratory Test Stewardship Committee created a hospital policy for a consistent and fair perimortem genetic testing process to deal with these dynamics. The committee drafted the policy based on our institution’s existing genetic testing medical necessity criteria and consulted with clinical stakeholders from departments across the hospital, including genetics, biochemical genetics, neurology, cardiology, hematology/oncology, neonatal intensive care unit hospitalists, and pathology. The hospital Medical Executive Stewardship Committee then approved the policy, which has four main elements:

1. Genetic testing is approved when medically necessary for a child’s care;
2. Genetic testing is approved when necessary to guide care of presymptomatic pediatric relatives at high risk for the genetic condition in question;
3. Genetic testing that has prenatal or adult genetic counseling benefits to a family may be performed, but the family assumes financial responsibility for any related charges;
4. DNA banking and autopsy should be offered. DNA banking allows a family to pursue genetic testing in the future. Autopsy can provide additional pivotal information about the differential diagnosis for a deceased patient and may help direct the most appropriate genetic testing.

Communicating the Plan

We communicated the new policy in several ways, including posting it on our institution’s internal website as an appendix to the lab test stewardship policy and via email to leaders of hospital departments (See full policy and example email online). Lab stewardship leaders also offered to present details of the policy to clinical teams.

Importantly, successful implementation required medical teams to be aware of the policy prior to discussions with families about genetic testing options to avoid compliance issues and stress for families, providers, and the laboratory teams. This is particularly important given the unique psychosocial tensions that arise around the time of a patient’s death.

To help guide clinicians, we created an inpatient genetic test coordination flow diagram (Figure 1), as this is the setting in which most perimortem genetic testing requests are made. The diagram begins with guidance to determine if a test meets medical necessity criteria and is needed urgently for inpatient care. It also provides concise recommendations for options to consider when a test is not medically necessary but may have utility for other family members or provide closure regarding the etiology of a patient’s condition. These options include autopsy, postmortem test coordination, out-of-pocket advance payment for medically unnecessary testing, DNA banking, and research.

In this reference tool we also included our laboratory genetic counseling team’s contact information to encourage conversations about laboratory test stewardship so that the optimal options would be offered to families from the outset.
Inpatient Genetic Test Coordination Flow

### Is test medically necessary?

Before discussing a plan to perform a test with patient/family, consider:
- Test should impact patient’s care by providing management guidance or preventing other unnecessary procedures/care.
- Genetic testing is not considered medically necessary for patient when death is imminent or has already occurred. Could autopsy provide information to better guide genetic testing?
- Current SCH policies exclude genetic testing for future reproductive planning and inpatient genetic testing requested with sole purpose to prevent possible loss of follow-up.

#### YES
- Determine if Genetics or Biochemical Genetics team should be involved in test recommendation and coordination. If unclear, contact geneticist or biochemical geneticist on call to discuss. Some genetic testing is coordinated by other specialists.

#### UNSURE
- Consult with Genetics or Biochemical Genetics team. Some genetic testing is coordinated by other specialists.

#### NO
- Stop. If test has utility for family genetic counseling or closure regarding etiology, consider:
  - Autopsy (may be limited in scope)
  - Postmortem test coordination (often out-of-pocket expense for family)
  - Out-of-pocket advance payment for medically unnecessary testing
  - DNA banking
  - Research options may be available.
- Consult with Lab Genetic Counselors for discussion prior to contracting with family.

The written policy and inpatient genetic test coordination flow diagram allow efficient dissemination of information to an inpatient team’s primary contact at the beginning of any triage conversation.

### Building a Shared Understanding

Prior to implementing this new policy, perimortem genetic test requests often created conflict among providers, families, and the laboratory stewardship team: We lacked a shared understanding of which genetic tests were medically necessary. Our policy now provides a common understanding and reference for fair and consistent application of institutional rules that reduces significant disagreements.

Of note, deferring genetic testing to the postmortem period creates billing challenges. It is uncommon for an insurer to approve genetic testing coverage for a deceased person. Pediatric clinical genetic testing can cost thousands of dollars, an out-of-pocket expense many families in our community cannot afford. In fact, approximately half of our institution’s patient population is covered by Medicaid. A charitable fund has been initiated to cover a portion of out-of-pocket charges for families who want rational genetic testing that is currently excluded by our hospital’s medical necessity policy.

Much of the success of this policy can be attributed to the team approach we took during its development. Involving multiple stakeholders from the beginning fostered mutual investment and diverse input. This led to a policy that was compliant, practical, and fair. The policy facilitates consistent decision-making regardless of an individual patient’s psychosocial and economic situation during this most difficult time in a patient’s and family’s care.

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FDA Clears Bio-Rad ddPCR Test for Monitoring Chronic Myeloid Leukemia Response

The Food and Drug Administration (FDA) has cleared Bio-Rad Laboratories’ QXDX BCR-ABL %IS kit and QXDX AutoDG ddPCR system for monitoring chronic myeloid leukemia (CML) patients’ molecular response to treatment. This test uses Bio-Rad’s droplet digital polymerase chain reaction (ddPCR) technology and is the first digital PCR test to receive FDA clearance for determining CML treatment response. CML is managed with tyrosine kinase inhibitor (TKI) therapy, and the current standard method for monitoring patients’ TKI treatment response is reverse transcription quantitative PCR. However, this method can produce variable results, particularly when measuring low levels of the disease. According to Bio-Rad, by using ddPCR, the QXDX BCR-ABL %IS kit enables more accurate monitoring of low levels of residual disease in patients with CML. ddPCR is a method for performing digital PCR that involves fractionating a sample into 20,000 droplets, then performing PCR amplification in each individual droplet. This means that a single sample generates tens of thousands of data points rather than a single result, thereby maintaining the sensitivity and precision of digital PCR while lowering sample and reagent volume requirements and overall cost.

Specifically, labs reported uncertainty about meeting CLIA regulations under an EUA. The task force will work to define, refine, and streamline interagency approaches for the implementation of EUA diagnostic tests. It will also seek to fill other gaps in the federal government’s response to global health threats by providing a forum for each participating agency to coordinate and provide consultation.

FDA, CDC, CMS TO IMPROVE ACCESS TO DIAGNOSTICS DURING PUBLIC HEALTH EMERGENCIES

The Food and Drug Administration (FDA), Centers for Disease Control and Prevention, and the Centers for Medicare and Medicaid Services have launched the Tri-Agency Task Force for Emergency Diagnostics with the aim of accelerating development and deployment of diagnostic tests during public health emergencies. The agencies created this task force after receiving feedback from the clinical laboratory community that labs were uncertain about how to implement diagnostic tests that had received an Emergency Use Authorization (EUA) from FDA.

GRIFOLS SCREENING TEST FOR TICK-BORNE PATHOGENS IN DONATED BLOOD GETS FDA APPROVAL

The Food and Drug Administration (FDA) has approved Grifols’ Procleix Babesia assay for screening blood donations for Babesia, a parasite transmitted to humans either through tick bites or donated blood from Babesia-infected individuals. This qualitative test detects ribosomal RNA from four Babesia species, B. microti, B. duncani, B. divergens, and B. venatorum, in individual samples or up to 16 pooled lysed specimens from human donors, including donors of whole blood and blood components for transfusion. The assay runs on the Procleix Panther system, a fully automated nucleic acid testing platform that also includes blood screening tests for HIV, hepatitis A, B, C, and E viruses, West Nile virus, and Zika virus. To evaluate the performance of this test, FDA reviewed data from a multicenter clinical trial conducted under an FDA Investigational New Drug study at the American Red Cross, Creative Testing Solutions, and the Rhode Island Blood Center (an affiliate of the New York Blood Center) in select areas of the U.S.

CE MARK GRANTED TO HIV TEST FOR EARLY INFANT DIAGNOSIS, DRIED BLOOD SPOT TESTING

Hologic’s Aptima HIV-1 Quant Dx assay has received two new CE marks for early infant diagnosis and for testing an additional sample type, dried blood spots (DBS). This assay is an in vitro nucleic acid amplification test for the detection and quantitation of HIV type 1 (HIV-1) and runs on the fully automated Panther system. It is
intended to aid in the diagnosis of HIV-1 infection, confirm HIV-1 infection, and as an aid in the clinical management of patients infected with this virus. The assay can now be used to qualitatively detect HIV-1 RNA in infants younger than 18 months and to test DBS to monitor viral load and disease progression in HIV-1 infected individuals in European and African countries. The DBS claim is particularly important for HIV testing in African countries because DBS are more stable and easier to transport than liquid blood samples. This CE marking also makes Hologic’s test the first HIV-1 assay with a dual claim for both viral load and early infant diagnosis.

**DE NOVO DESIGNATION GRANTED TO OXFORD GENE TECHNOLOGY’S BLOOD CANCER FISH PROBES**

Oxford Gene Technology has received de novo classification from the Food and Drug Administration for eight Cytocell Aquarius hematology fluorescence in situ hybridization (FISH) probes that detect chromosomal rearrangements in patients with acute myeloid leukemia and acute myelodysplastic syndromes. The probes included in this set are: AML1/ETO (RUNX1/RUNX1T1) translocation, dual fusion; CBFB (CBFB)/MYH11 translocation, dual fusion; Del(5q) deletion; Del(7q) deletion; Del(20q) deletion; EVI1 (MECOM) breakapart; MLL (KMT2A) breakapart; and P53 (TP53) deletion. These probes are designed for use with fixed bone marrow specimens consistent with World Health Organization guidelines for Classification of Tumors of Hematopoietic and Lymphoid Tissues and in conjunction with other clinicopathological criteria. Pre-mixed and ready-to-use, they are supplied as part of a complete kit including the fluorescent stain 4',6-diamidino-2-phenylindole, detailed protocols, and signal pattern analysis guidelines.

**MALAYSIA, THAILAND APPROVE HOSPITALIZED PNEUMONIA TEST FROM CURETIS, ACUMEN**

Curetis and its partner Acumen Research Laboratories have received approval from the respective regulatory authorities in both Malaysia and Thailand to market the Unyvero HPN Hospitalized Pneumonia application cartridge, as well as approval from Thailand’s regulators for the Unyvero BCU Blood Culture application cartridge. Within 4 to 5 hours, the Unyvero HPN and BCU tests detect a broad panel of pathogens and antibiotic resistance markers that are relevant for the diagnosis of hospitalized patients with suspected pneumonia and bloodstream infections, respectively. With these new approvals, Unyvero HPN in particular is now fully registered as an in vitro diagnostic medical device in Singapore, Malaysia, and Thailand, a milestone that Curetis and Acumen hope will enable broader commercial roll out and adoption of this test throughout all member states in the Association of Southeast Asian Nations.

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IBM Watson Health, Broad Institute Partner to Predict Risk of CVD

Over the past 2 years, the healthcare community has strongly criticized IBM Watson Health for not delivering on its promises, especially about Watson for Oncology, which physicians report often gives incorrect treatment recommendations. In spite of Watson for Oncology’s struggles, however, the Watson Health division of IBM is continuing its efforts to harness artificial intelligence (AI) to enable personalized medicine. Most recently, IBM Watson Health expanded its existing partnership with the Broad Institute of the Massachusetts Institute of Technology and Harvard to focus on cardiovascular disease. This 3-year initiative will build algorithms that identify and learn from trends in population-based and hospital-based biobank data, genomic information, and electronic health records. With this AI technology, the partners ultimately aim to produce models that will help clinicians predict with greater accuracy the onset of conditions such as heart attacks, sudden cardiac death, and atrial fibrillation.

Diploid, Genomenon Team to Improve Analysis of NGS Data for Rare Disease Diagnosis

Diagnostic software provider Diploid has partnered with the genomic search company Genomenon to improve genome interpretation for rare disease diagnostics. Using Diploid’s Moon software, labs input next-generation sequencing data along with a patient’s symptoms, sex, and age of disease onset. Moon then employs artificial intelligence algorithms and a disorder model to suggest causal variants in 2 minutes for whole exome sequencing data and in 5 minutes for whole genome sequencing data. “This … saves clinical laboratory scientists a lot of time compared to manually filtering and curating hundreds or even thousands of variants,” said Peter Schols, Diploid’s founder and CEO. Through the collaboration with Genomenon, Diploid aims to make the process of evaluating the variants reported by Moon even more efficient. Genomenon’s Mastermind genomic search engine filters and prioritizes millions of genomic articles to find the most useful and meaningful citations. The integration between this platform and Moon will enable Moon users to see which candidate variants are mentioned in relevant publications.

Epilepsy Society, UCB to Study Genetics of Treatment-Resistant Epilepsy

The U.K.-based Epilepsy Society has joined forces with UCB, a biopharmaceutical company headquartered in Belgium that also has a significant research and development hub in the U.K. The two organizations will use whole genome sequencing to study the genetic components of epilepsy, with the hope that this research will eventually result in better targeted treatments for the disease, as well as improved diagnosis. The 5-year collaboration will focus specifically on people who do not respond to currently available epilepsy treatments.

Lineagen, PWNHealth Collaborate to Offer DTC Tests for Developmental Delay, Autism

Lineagen has teamed with PWNHealth to expand access to its chromosomal microarray FirstStepDx Plus and the whole exome sequencing test NextStep Plus, both of which claim to pinpoint genetic causes of developmental delay and autism spectrum disorder in children. PWNHealth is a telemedicine company that aims to bring oversight to direct-to-consumer genetic testing. The company has established a nationwide physician and genetic counselor network that includes more than 100 labs and technology platforms designed to support a broad range of healthcare consumers. Under the terms of the partnership, consumers will be able to order Lineagen’s tests with the guidance of a licensed healthcare provider through PWNHealth’s digital platform.

“We’re delighted to partner with Lineagen to bring greater access to the clinical benefits of genetic testing to [families dealing with developmental disorders],” said PWNHealth’s medical director of genetic services, Paldeep Atwal, MD. “Our mission is to bridge the gap between consumer demand for genetic testing and the need for medical oversight and sound clinical genetic expertise. Our model integrates physicians and genetic counselors in a way that safeguards the consumer and ensures appropriate follow-up and guidance on results.”
medications. The first phase will generate and analyze individual categories of data that potentially have a role in determining drug response, with an initial focus on the role of genetics. In the latter phases, the project will integrate these different data sets to understand how they act together. “We hope this collaboration could help in the development of tools to better identify difficult-to-treat patients earlier, and ultimately to develop tailored and targeted medicines which could bring significant value to these patients in the future,” said Dhaval Patel, MD, PhD, executive vice president and chief scientific officer at UCB.

**MRM PROTEOMICS, BIODESIX JOIN FORCES ON MULTI-OMICS LUNG CANCER TESTS**

MRM Proteomics and Biodesix are collaborating to develop precision lung cancer assays. Under the terms of the partnership, MRM Proteomics will license to Biodesix its proprietary technology for high-throughput clinical proteomics known as immuno-matrix-assisted laser desorption/ionization (iMALDI). The iMALDI approach involves spiking protein digest from a biological sample with a stable isotope-labeled standard peptide matching the target, after which the endogenous peptides and standard peptides are co-captured on antibodies conjugated to magnetic beads. The peptides eluted from the antibodies are then analyzed with MALDI mass spectrometry. With this technology, Biodesix plans to develop blood-based lung cancer tests that use a multi-omics approach to reveal a more complete molecular profile of a patient’s disease. “Examining a patient’s genomic data has advanced targeted therapies. However, proteins are the targets of most drugs and hold the key to unlocking the promise of precision medicine,” said Christoph Borchers, PhD, chief scientific officer for MRM Proteomics.

**ARCHERDX BUYS GENETIC TESTING LAB BABY GENES**

ArcherDX, a molecular technology company dedicated to advancing personalized genomic medicine, has acquired Baby Genes, a privately held CLIA-certified laboratory that offers newborn and carrier screening genetic testing. Baby Genes’ test menu includes a supplemental newborn screening panel that interrogates more than 100 genes covering more than 72 clinically actionable, inherited conditions, as well as pre-defined carrier screening tests that include full-gene sequencing for cystic fibrosis, spinal muscular atrophy, and fragile X syndrome. In addition, the laboratory also offers customized confirmatory and reflex genetic testing services to physicians. Under the terms of the acquisition, Baby Genes will continue to operate as a wholly owned subsidiary under the name ArcherDX Clinical Services. It will leverage the existing ArcherDX research and development functions, which are based in Boulder, Colorado, while consolidating all commercial profiling services for both companies in Golden, Colorado, where Baby Genes’ laboratory is currently located.
Q

Ask The Expert

The Emergence of Oxytocin Assays

EXPERT
Damien Gruson, PhD

What is oxytocin’s biological function?

A. Oxytocin is a hormone synthesized in brain regions such as the supraoptic nucleus and paraventricular nucleus of the hypothalamus, which are critical for behavioral and physiological homeostasis. In the popular imagination, this hormone is probably best known for its involvement in the control of social, sexual, and romantic attachment and behavior. By studying animal models, neurobiologists have shown the possible involvement of oxytocin in pair-bonding, along with other hormones like arginine-vasopressin and dopamine. Several studies involving the administration of oxytocin in humans have also implicated a role for this hormone in forming and maintaining human romantic relationships.

Oxytocin also functions as a reproductive health regulator, stimulating uterine smooth muscle and serving as one of the most potent uterotonic agents. It also impacts reproduction-related functions for both women and men such as influencing estrous cycle length, promoting follicle luteinization in the ovary and ovarian steroidogenesis, and stimulating erections and ejaculation.

Most recently, emerging evidence shows that oxytocin helps regulate the body’s response to stress, and that it is particularly involved in regulating the hypothalamo-pituitary-adrenal axis and cardiovascular function.

In what clinical scenarios could oxytocin testing be used?

Although oxytocin testing has not yet become a routine clinical assay, in the future it could aid healthcare providers in assessing behavioral, psychiatric, and stress-related conditions. Specifically, this could include the work-up of mood disorders, anxiety disorders, obsessive-compulsive disorder, and the evaluation of burnout.

How is oxytocin measured?

Immunooassays are the most common method for determining oxytocin concentrations. The first oxytocin assays were based on the radio-immunoassay format, but now most are enzyme-linked immunosorbent assays (ELISAs). These ELISA-based tests have acceptable limits of quantification of approximately a few pg/mL and imprecisions usually below 10%. However, they aren’t standardized, and there is clear heterogeneity/lack of commutability between results obtained using different oxytocin immunoassays. This could be related to the specificity of the antibodies used in these assays and also to cross-reacting components, which reinforces the need for a sample’s extraction before testing. Sample extraction has a significant impact on oxytocin results: The concentrations of oxytocin measured by enzyme immunoassay without plasma extraction are more than 100-fold higher than in extracted plasma.

To improve the specificity of oxytocin measurements, assays based on liquid chromatography-tandem mass spectrometry (LC-MS/MS) have now been validated for this hormone. Some of these two-dimensional LC-MS/MS assays are ultra-sensitive, with lower limits of quantification close to 1.00 pg/mL and with imprecisions also lower than 10%.

What sample types are used for oxytocin testing?

Oxytocin can be detected in various physiological fluids such as plasma, serum, saliva, urine, and cerebrospinal fluid. However, as oxytocin assays evolve, saliva could ultimately become the sample of choice because it is less invasive and would also facilitate data comparison due to the fact that a large number of studies are already using this matrix to measure oxytocin.

Although oxytocin testing has not yet become a routine clinical assay, in the future it could aid healthcare providers in assessing behavioral, psychiatric, and stress-related conditions.

Damien Gruson, PhD, is head of the department of clinical chemistry at the Cliniques Universitaires St-Luc and Université Catholique de Louvain in Brussels, Belgium. He also serves in the research unit of endocrinology, diabetes, and nutrition at the university’s Institut de Recherche Expérimentale.

+E-MAIL damien.gruson@uclouvain.be
You are Invited to Attend a Half-day Educational Seminar

Consequences of FDA Changes to Critically Ill Bedside Glucose Testing Regulations

Clinical Consequences
Venous, Arterial, and Now Capillary Specimens Are All FDA Cleared for Critical Care Patient Testing — Are All Specimen Types Analytically and Clinically Equivalent?

The choice of specimen type is an important consideration, particularly for critically ill patients. This presentation will discuss the analytical performance differences between specimen types and their clinical significance. The data is based on the results of an FDA submission comparison study of 16,778 paired patient test results.

Learning objectives:
- Analytical performance differences
- Clinical significance of these differences
- Suggested best practices for testing

Presenter: Evangeline Ntrivalas, M.D., Ph.D.
MASA Director, North America
Nova Biomedical

Clinical Impact of Glucose Meter Accuracy in Critically Ill Patients
Critically ill patients often present with medications and physiological factors that can interfere with glucose meter measurement. Interferences can cause glucose meter errors, insulin misdosing, and adverse events. This presentation will discuss the clinical impact of a glucose meter that measures and corrects for interferences.

Learning objectives:
- Analytical and clinical impact of meter interferences
- Improved outcomes achieved with a glucose meter that measures and corrects for interferences

Presenters: Martha Lyon, PhD*
Clinical Biochemist/Clinical Associate
Saskatoon, Saskatchewan, Canada
or
William A. Clarke, PhD**
Director, Clinical Toxicology, Professor of Pathology
The Johns Hopkins Hospital

Regulatory/Legal Consequences
Regulatory Requirements for Off-Label Testing and Consequences of Non-Compliance
Nova’s StatStrip glucose meter is FDA cleared and CLIA waived for use with all patients including critically ill. Use of all other meters with any critically ill patient population is considered off label by the FDA and CMS. This presentation will discuss the history and rationale for recent FDA changes to critically ill bedside testing and the regulatory and legal consequences of off-label testing for caregivers and hospitals.

Learning objectives:
- FDA changes to bedside glucose testing, 2010-2019
- When bedside glucose testing is off label
- FDA requirements for off-label bedside glucose testing
- Patient risks if performing off-label testing in critically ill patients
- Caregiver and hospital liability when performing off-label glucose testing
- CLIA risks when performing off-label glucose testing

Presenters: Natalia Mazina
Healthcare and pharmacy attorney
specializing in provider FDA medical device and pharmaceutical compliance

Locations, Dates, Times

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- CRP
- Rheumatoid Factor

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