January/February 2019

CLN Clinical Laboratory News

An AACC Publication | Volume 45, Number 1

DETECTING CONGENITAL HYPOTHYROIDISM

48%

Number of babies missed by standard screening

PAGE 6

THE FRAGMENTATION OF MALE FERTILITY

A Hard Look at Waived Testing Labs

Drug Testing Debates

AACC Better health through laboratory medicine.

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 epidemic.

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

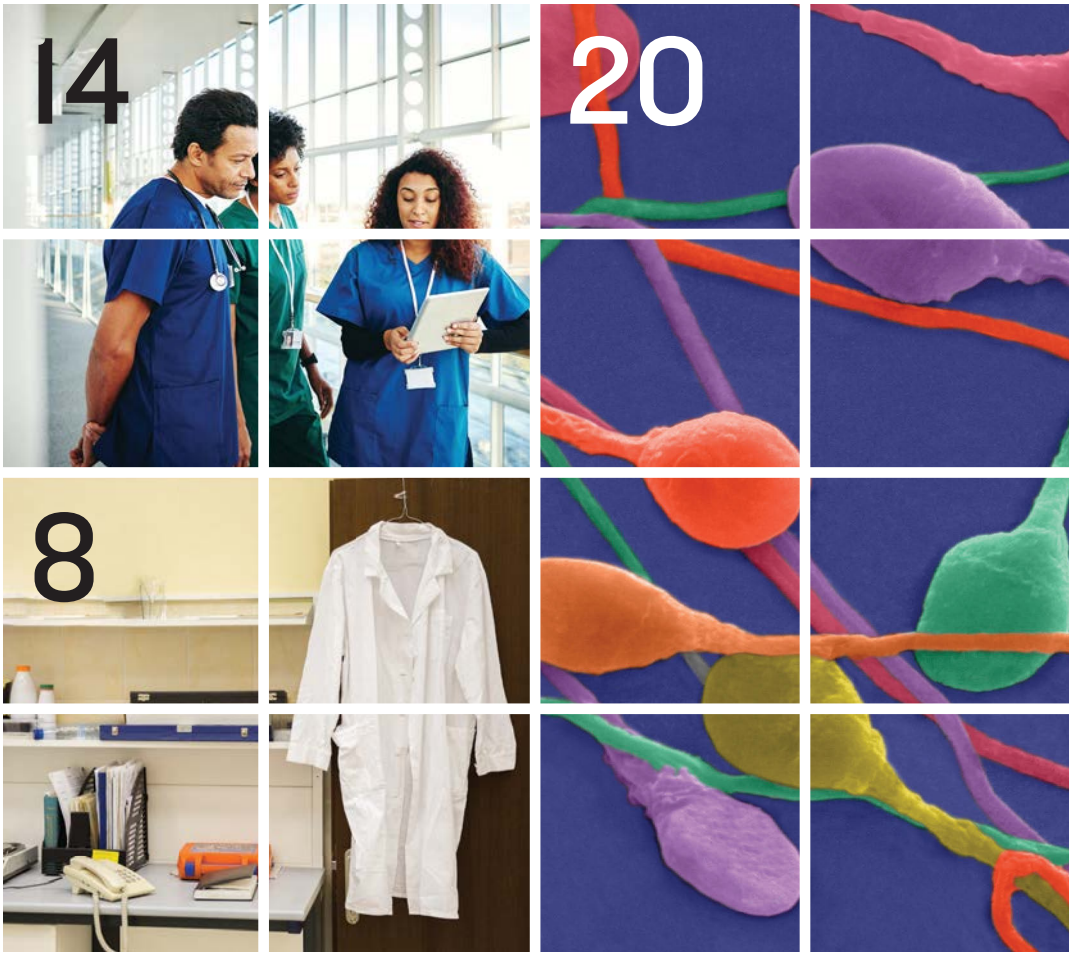
- Exceptional analytical sensitivity at a 1ng/mL cutoff level
- Detection of both the parent and major metabolite to identify more true positives
- Crossreactivity to norfentanyl extends the window of detection
- Liquid, ready-to-use convenience improves lab efficiency
- Three suitable kit sizes for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

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.

ARK Diagnostics, Inc.
NEXT GENERATION ASSAYS

48089 Fremont Blvd, Fremont, CA 94538
877.869.2320
www.ark-tdm.com

CLN Clinical Laboratory News
www.aacc.org



Departments

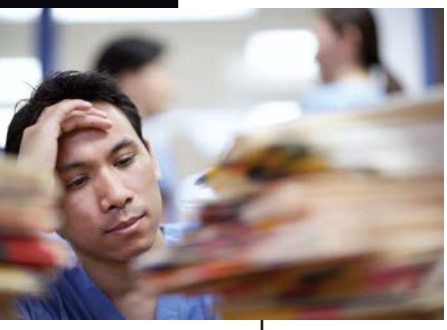
For legal urine drugs of abuse testing, it is important that the donor identify the specimen ... followed by the person who collected the specimen signing the chain of custody forms.
p40

Clinical Laboratory News (ISSN 0161-9640) is published monthly (11 times per year—Jan/Feb., March, April, May, June, July, Aug., Sept., Oct., Nov., and Dec.) by the American Association for Clinical Chemistry. 900 Seventh St., NW, Suite 400, Washington, DC 20001. Phone: +1 202.835.8756 or +1 800.892.1400 Fax: +1 202.833.4568. POSTMASTER: Send address changes to AACC, 900 Seventh St. NW, Suite 400, Washington, DC 20001.

Design and Production Management
imagination.

Cover: Ed White / The Image Bank / Getty Images

Federal Insider



More Questions Than Answers on PAMA Regulation Change

In the final Physician Fee Schedule for 2019, the Centers for Medicare and Medicaid Services (CMS) made changes to regulations related to the Clinical Laboratory Fee Schedule (CLFS) that will require more hospital outreach laboratories to report private payer data. Hospital laboratories with outreach programs will need to closely review their billing and other circumstances to determine whether they will begin sending information to CMS in 2020.

Under the Protecting Access to Medicare Act (PAMA), CMS determines reimbursement for laboratory tests billed on the CLFS based on a weighted median of private payer rates calculated on a 3-year cycle. AACC and other advocacy organizations have objected to the way CMS wrote regulations that exclude most hospital outreach laboratories and physician office laboratories from data collection. Advocates argued that collecting payment data only from low-margin, high-volume independent labs would skew prices and lead to deeper cuts to the CLFS than Congress intended. Reimbursement for many tests was cut up to 30% on January 1, 2018, when the new payment system went into effect.

CMS' update to the PAMA regulations expands the definition of an "applicable laboratory" for private payer data collection to include laboratories that submit claims to Medicare using the 14X type of bill used specifically by hospital outreach laboratories. Ostensibly this would lead to a more diverse survey of how laboratory tests are actually paid for. However, it's difficult to predict whether the changes CMS made will mean a significant bump in rates the next time the agency calculates weighted median rates. According to data compiled by the American Hospital Association, which opposes requiring hospital laboratories to report payment data, only 12% of hospital laboratories use the 14X bill.

A related regulatory change might also mean more laboratories need to report data. Under PAMA, a laboratory only has to report data if more than 50% of its revenue comes through the CLFS or Physician Fee Schedule. In 2019 CMS will no longer count Medicare Advantage Part C payments toward the denominator in this calculation, which CMS expects to expand the number of laboratories submitting payment data.

The next data collection period is January 1, 2019, through June 30, 2019. Those laboratories that determine they will have to report payment data will do so during a 3-month window, January 1–March 31, 2020. Revised rates will go into effect January 1, 2021.

A NEW GOVERNMENT STRATEGY TACKLES HEALTH IT PROBLEMS

After years of complaints and warnings from healthcare professionals, the Department of Health and Human Services (HHS) is taking a new look at some of the unintended consequences of the drive to convert from paper to electronic healthcare records (EHR). HHS issued a draft strategy led by the HHS Office of the National Coordinator for Health Information Technology.

Many of the areas that the strategy identifies as needing improvement relate to clinical laboratory test ordering and result retrieval. These include harmonizing user actions across EHR systems for ordering tests, harmonizing test codes to support mapping across systems, and a uniform presentation of results.

The main goals of the draft strategy are reducing the effort and time required to record health information in EHRs for clinicians; reducing the effort and time required to meet regulatory reporting requirements for clinicians, hospitals, and healthcare organizations; and improving the functionality and intuitiveness of EHRs. Public comment on the draft ends January 28, 2019.

Pros and Cons: Should Hospitals Sell Their Labs?

Hospital executives increasingly face substantial offers to outsource or sell their lab services to commercial vendors. ARUP CEO Sherrie Perkins, MD, PhD, discusses what we're learning from health organizations that have agreed to these acquisitions. "The first few years may be good, but then these hospital labs are at the mercy of the vendor."

"Most people overlook the fact that the laboratory has more touchpoints with patients than any other area. While they may make up only 3 to 4 percent of the hospital's overall costs, lab services contribute to more than 80 percent of the information in a patient's EMR."

Sherrie Perkins, MD, PhD,
CEO, ARUP Laboratories

Q: Financially, what is the value of keeping the lab in-house?

A: While outsourcing may provide an infusion of cash into a health system, it comes with crucial trade-offs. When lab services are kept in-house, the health system retains the ability to contain costs. As we move from a decades-old, fee-for-service model that emphasizes volume to a model that places importance on quality outcomes with value-based reimbursement, it is essential to ensure that patients get the right tests for the best medical outcomes at the lowest cost.

Q: From a patient-care perspective, what is the value of keeping lab services in-house?

A: Selling your lab impacts patient care. The best care keeps testing as close as possible to the patient. Oftentimes when a lab is sold, testing goes to other sites, turnaround times increase, specimens may get lost, and it doesn't allow for a close focus on utilization management or the development of lab practices to improve patient care.

Once your lab operations are off-site, it is very difficult to change ordering patterns and communicate with clinicians about appropriate testing. You lose that close communication that makes a healthcare team, including the lab and pathologists, effective.

Q: What should lab personnel know about the prospect of their labs being sold?

A: The decision to outsource or sell is often made at the executive level. Sometimes laboratory personnel are the last to find out, and often employees are let go. The C-suite may view lab testing as just another commodity without fully understanding what value their lab brings to the overall healthcare organization.

Q: What can lab management do?

A: Be proactive. Articulate the value the lab delivers to the health system beyond test results. Develop a laboratory value proposition and make sure members of the health system executive team hear it. Make sure the lab is represented on patient-care teams. The key is to connect the dots between the laboratory, the providers, and their patients in ways that drive outcomes and cut costs.

Q: How difficult is it for a hospital to buy back its lab?

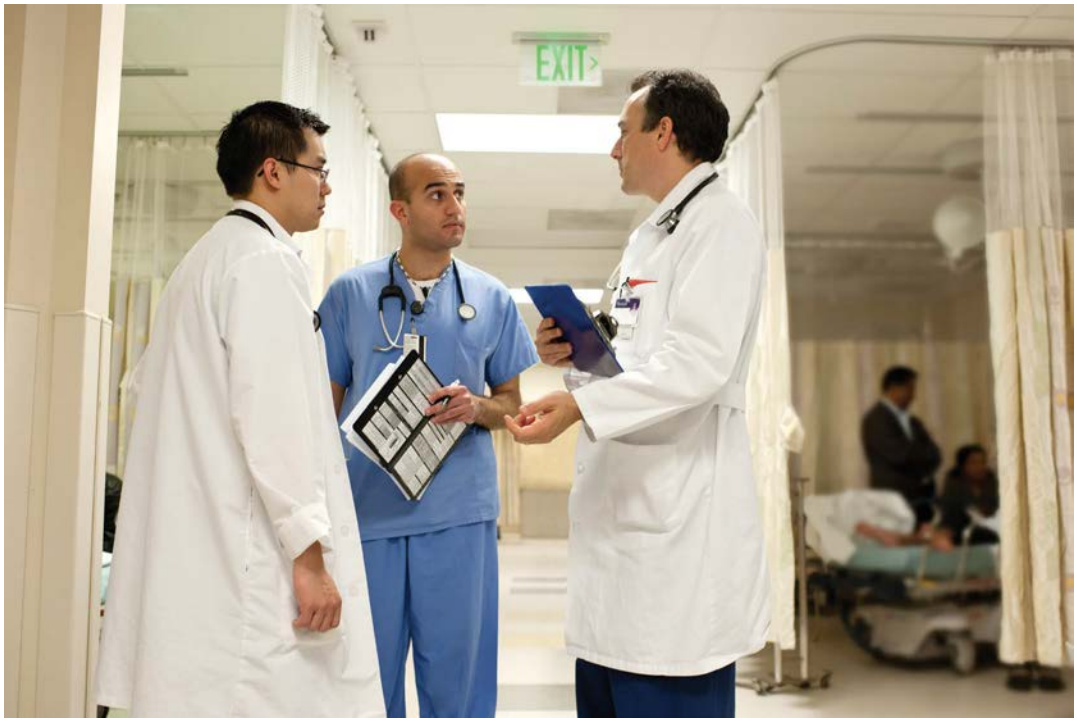
A: Very difficult. Hospitals cannot compete for outreach business for the length of the contract—typically five years. It is costly and complex to bring these services back in-house once they've been sold, both from finding staff and training, as well as repurchasing instruments or reagent contracts. Once the contract is up, the hospital must actively market and sell its services to community-based physicians, a process that typically requires a year to 18 months before a new contract is secured.

Q: How can ARUP help increase the value of hospital labs?

A: Hospital labs are inherently valuable, but this value often goes unrecognized. We help laboratories quantify their short- and long-term value in terms of revenue potential and impact on patient care. We show them how to improve operational efficiencies, grow outreach margins, or engage in laboratory stewardship to address and reduce misutilization.

Bench Matters

Process-focused, Patient-centered: How Data Helps Labs Better Support Emergency Departments



Christine Snozek, PhD, DABCC, FAACC

As clinical laboratorians, we are all familiar with the pressure to provide test results quickly, and in many institutions some of the greatest need for rapid turnaround times comes from the emergency department (ED). Although the competing demands placed on busy labs and equally busy EDs can easily lead to conflict, partnering together on well-structured studies and pilot programs provides objective data to drive best practices that work for both areas.

DISTINCT POINTS OF VIEW; COMMON MISSION

EDs are unique environments: In comparison to other clinical areas they generally have more diverse patient populations presenting with a wider range of conditions, as well as unpredictable demand for their services that can vary in a single day from oversaturation to near emptiness. Throughput is both a quality metric and a constant problem for many EDs, and the focus on optimizing efficiency is so intense that projects decreasing ED length of stay by even less than 10 minutes have been published. EDs also are set up to take care of patients' immediate needs and move them on to their next proper destination, like being hospitalized or discharged home. Given all these pressures, it's quite understandable that EDs emphasize speedy over definitive test results.

This mindset can be difficult for clinical laboratory professionals to understand or accept given their interest in validation, quality control, traceability, standardization/harmonization, and other ingredients for robust and definitive results. Lab-driven initiatives that only measure in-lab waste, or replace faster technologies for slower but more accurate ones, can be met with disinterest or outright rejection if they do not account for the concerns and needs of ED staff.

Despite these differing perspectives, both groups have at heart a single goal: providing excellent patient care. Keeping that common mission at the center of their discussions and recognizing the interests and goals of both sides can lead to extremely successful collaborations that benefit both labs and EDs.

USING DATA TO BRIDGE THE DIVIDE

Laboratorians are no strangers to the idea of using data to guide processes and make decisions. However, the

Reza Estakhrian / Stone / Getty Images

challenge in quality improvement is often less an issue of *Do we have data?* than of *Can we get the right data?* Changes affecting more than one area need input from all parties involved, including their perceptions about the quality gap and which metrics matter the most to them. For a project to succeed, data must reconcile these factors.

Like many institutions, we have experienced a never-ending rise in ED visits for the last several years, which underscores the need for efficient laboratory support. To respond to this need, our lab and ED have collaborated on several projects of various sizes, including evaluating who should collect blood for lab tests (phlebotomy or nursing), how much blood is needed for add-on testing, and whether various point-of-care tests improve time to diagnosis and ED throughput. Each project began with an assessment of the quality gap and a discussion of which endpoint(s) both groups were looking for. These inputs provided the framework for determining what data would be required to address each party's key concerns. For example, a pilot study of point-of-care cardiac troponin testing evaluated not only the length of stay for chest pain patients—the initial impetus for the project—but also which laboratory values were considered when ruling out myocardial infarction. Although the latter endpoint was rather time-consuming to extract, it weighed heavily in our decision-making about whether to implement the new test.

Similarly, looking beyond mere numbers helps in re-examining long-standing practices. When various concerns led to a discussion about the rainbow draw of extra blood in different tube types and colors at our institution, both lab and ED staff were hesitant to curtail this extra blood collection because of the strongly perceived need for add-on tests. To examine this issue further, we surveyed ED staff regarding their opinions about rainbow draws, including how many patients avoided additional collections and how often add-ons were ordered. When we compared the survey responses against add-on test and tube utilization data, we found a striking discrepancy between the subjective perceptions of a highly efficient, patient-centered practice and the objective degree of waste observed. This drove a compromise solution that balanced the concerns of both the laboratory and the ED, to the benefit of patient care.

The pressure to optimize efficiency and improve support for intense clinical practices including the ED is likely to continue growing in the coming years. In my experience, one way to work toward that optimization is by adopting data-driven approaches to process improvement, with an eye toward the needs of both groups, and with the patient always at the center of the discussion.

Christine Snozek, PhD, DABCC, FAACC, is a chemist at Mayo Clinic in Scottsdale, Arizona.
+EMAIL: Snozek.Christine@mayo.edu

The Sample

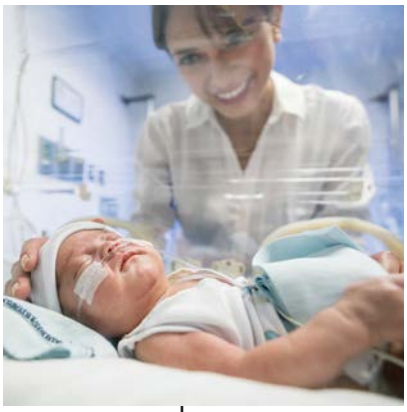
Ideal Screening Strategy for Congenital Hypothyroidism in Preemies: Retest at 1, 2, 4 Weeks

A study to assess the optimal timing of repeat screening for congenital hypothyroidism in preterm babies concluded that the ideal strategy would involve initial screening at 72 to 120 hours followed by retesting at 1, 2, and 4 weeks, and at term-corrected gestational age or upon discharge from the hospital (J Pediatr 2018; doi.org/10.1016/j.jpeds.2018.09.044). The common practice of repeat screening once at 2 weeks "will miss a significant number" of infants with delayed thyroid stimulating hormone (TSH) elevation and decompensated permanent congenital hypothyroidism, according to the authors. Moreover, repeat screening only at 4 weeks will lead to delayed diagnosis in babies with decompensated congenital hypothyroidism.

This study examined 13 years of data involving 898,424 babies who were screened for congenital hypothyroidism in the Republic of Ireland. The same AutoDELFIA immunoassay with a cutoff of 8 mU/L for whole blood TSH levels was used throughout the study. Even if their first TSH result was normal, preterm babies underwent weekly screening until they were term-corrected (37 weeks' gestation) or discharged home.

In all, 586 infants were treated for congenital hypothyroidism, an incidence of 1:1,533 births. Of these babies, 55 were born at <33 weeks' gestation, 50% (27) of whom had delayed TSH elevations and wouldn't have been diagnosed when their first screens took place at 72 to 120 hours. Among the 27 infants with delayed TSH elevation, 12 (40.7%) had decompensated hypothyroidism at diagnosis with free thyroxine (FT4) levels <10 pmol/L, while 4 had severe congenital hypothyroidism with FT4 <5.5 pmol/L at diagnosis. Six of the babies with delayed TSH elevation (22%) have permanent congenital hypothyroidism, and another 12 will be re-evaluated at age 3 years, according to the authors.

If repeat screening had only taken place when these babies were 2 weeks old, 13 (48%) would not have been identified.



iStock.com / andresr

THE LEPTIN SYSTEM IDENTIFIED AS A KEY DRIVER OF TYPE 2 DIABETES DEVELOPMENT

A network analysis comparing levels of 27 biomarkers associated with risk for type 2 diabetes highlighted the central role of the leptin system interacting with other biological pathways in the development of this disease many years in advance of an individual's clinical diagnosis (Diabetes 2018; doi.org/10.2337/db18-0892).

This secondary analysis of a case-control study within the Nurses' Health Study examined participants who developed diabetes versus those who did not, based on baseline blood samples, biennial and supplemental questionnaires, and a formal diagnosis of diabetes over a 23-year period. In all, the secondary analysis included data from 1,303 new cases of diabetes and 1,627 healthy controls.

The investigators analyzed the biomarker network in cases versus controls for cases diagnosed less than 5 years, between 5 and 10 years, and more than 10 years after blood collection. Among participants who developed diabetes, 311, 491, and 501 were diagnosed <5, 5–10, >10 years after blood collection, respectively.

The 27 biomarkers considered in the study involve inflammation, adipokines, insulin-like growth factor (IGF) axis, endothelial dysfunction, glucose regulation, and body iron stores. The investigators created the correlation network based on pairwise Spearman correlations of these analytes that were statistically different between cases and non-cases using permutation tests.

The overarching network the researchers observed featured "leptin as a highly connected node with differential associations to multiple markers spanning different biologic axes," including adipose secretion, inflammation, IGF, and glucose regulation. However, the connectedness of biomarker networks varied over the course of diabetes development, with hemoglobin A1C, leptin, and C-peptide networks more prominent in cases diagnosed

<5 years, 5–10, and >10 years after blood collection, respectively.

WOMEN WITH NEGATIVE HPV TEST RESULTS AT AGE 55 SAFE TO FORGO FURTHER CERVICAL CANCER SCREENING

Women in developed countries with negative human papillomavirus (HPV) test results at age 55 are at low risk for cervical cancer and likely can forgo screening for this disease for the rest of their lives, a modeling study suggests (Lancet Oncol 2018;19:1569–78). Regular cytology screening up to age 75 may still prevent some cancers, though with declining benefits as women age.

The researchers used a Markov model of cervical cancer natural history and screening as a way to resolve the outstanding question of how long women should continue to be screened for this disease. Different clinical guidelines recommend that screening in high-income settings can be safely stopped anywhere from ages 55 to 70, but all note the low quality of evidence underlying their recommendations.

In their model the authors created an age-structured population of women ages 10 to 100, excluded women who had total hysterectomies, used HPV infection and cancer incidence data from Statistics Canada, and employed a three-stage progressive cervical intraepithelial neoplasia model to incorporate different management and treatment decisions depending on disease stage. Their model also considered 14 oncogenic HPV types and a generic group of other potentially oncogenic HPVs. The authors predicted lifetime risk of cervical cancer if a woman was perfectly adherent to screening guidelines, and if she received screening less often, as is typical.

The authors estimated that without screening or vaccination, 1 in 45 women would be diagnosed with cervical cancer. A woman with a typical screening adherence with cytology testing who stops screening at age 55 would have a 1 in 138 lifetime risk of this disease. This woman's lifetime risk would drop further if she stopped screening with cytology testing at age 70. A woman who had perfect adherence to recommended cytology screening from age 29 to age 69 would reduce her lifetime risk to 1 in 532.

In contrast, the investigators estimated that a woman with a negative HPV DNA test for the 14 high-risk types who stops undergoing screening at age 55 would have a lifetime risk of cervical cancer of 1 in 1,940. A woman who had never undergone screening would remain at higher risk of cervical cancer for the rest of her life compared to women with typical screening adherence, but "a single negative HPV test still indicated a relatively low remaining risk of cervical cancer after the age of 55 years," according to the authors.

BY ATHENA K. PETRIDES, PHD, AND STACY E.F. MELANSON, MD, PHD

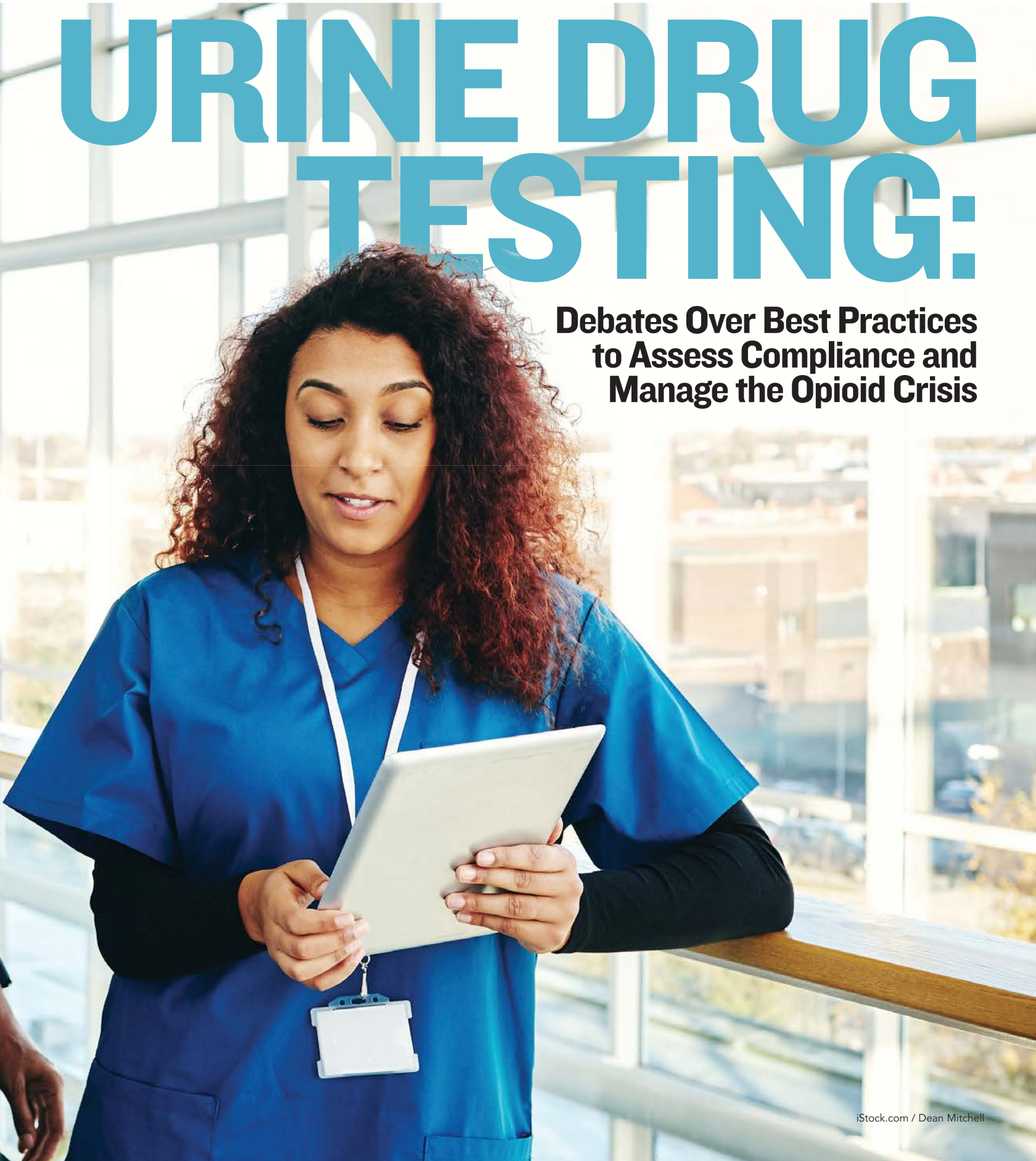
Drug overdose deaths increased dramatically from 1980 to 2016, surpassing deaths from guns, HIV, and car crashes (*1*). At least half of the deaths involved a prescription opioid obtained primarily from a friend or relative (*2*). Furthermore, rates of opioid and drug misuse, including abuse and diversion, continue to rise (*3*). Although opioid prescription rates have dropped in response to the opioid crisis, the average days of prescription supply have increased, and more than 40% of patients report that their pain is not treated adequately (*4,5*). As a result, clinicians face the challenge of providing necessary pain control for patients while maintaining a low risk for substance abuse.

Urine drug testing (UDT) is an effective tool in pain management to monitor compliance with prescribed medications (*6*). National guidelines recommend UDT not only to assess compliance but also to detect undisclosed substances and diversion (*7-9*). Consequently clinical laboratories must be equipped to offer an extensive UDT test menu that includes both commonly prescribed medications as well as commonly abused drugs. According to an audience poll during a scientific session at the 70th AACC Annual Scientific Meeting in 2018, more than 50% of laboratories have adjusted their toxicology testing in response to the opioid crisis (*10*).

Due to its superior sensitivity and specificity, definitive testing—such as liquid chromatography-tandem mass spectrometry (LC-MS/MS)—is recommended by experts, including the American Society of Interventional Pain Physicians and AACC, over immunoassays for UDT for pain management monitoring (*6,8,11*). However, the audience poll at the AACC Annual Scientific Meeting revealed that 66% of laboratories continue to perform a combination of methodologies (e.g. immunoassay and mass spectrometry), with only 9% of laboratories using MS exclusively.

URINE DRUG TESTING:

Debates Over Best Practices to Assess Compliance and Manage the Opioid Crisis



iStock.com / Dean Mitchell

As laboratories adjust their testing methodologies to address clinical needs and improve patient management during the opioid crisis, defining more specific guidelines on the critical components of a definitive testing panel will be helpful. Should laboratories report quantitative and/or qualitative results? Should specimens be hydrolyzed prior to analysis? What cutoffs should be utilized?

In the absence of decisive guidelines to settle these questions, clinical laboratory professionals need to make the best decision possible in their individual institutions. In this article, we discuss the current evidence around these questions and how clinical laboratorians' decisions on each affects how providers interpret test results.

WHAT ARE THE CRITICAL COMPONENTS OF A DEFINITIVE TESTING PANEL?

Debate #1: Quantitative Versus Qualitative Results

Reasons for qualitative reporting

Reporting results quantitatively can mislead providers into utilizing numbers to assess compliance to a prescribed regimen. Many variables—including drug-drug interactions, genetic variation, pharmacokinetics, drug metabolism and clearance, and a patient's clinical condition(s)—may affect drug and metabolite concentrations in urine (Figure 1) (*9*).

Notably, laboratory directors also face challenges in interpreting quantitative results given the lack of correlation studies between drug levels and drug dosage/timing. At the 70th AACC Annual Scientific Meeting scientific session, 24% of the audience responded erroneously that quantitative results for hydromorphone over a 3-month period could be utilized to determine whether a patient was taking medication appropriately.

In short, reporting a binary result (detected/not detected) often offers sufficient information to assess compliance. The technical aspect of reporting qualitative results is also favorable due to using less calibrator and quality control material.

Reasons for quantitative reporting

Quantitative results offer many advantages: Both providers and laboratories can detect simulated compliance (i.e. dropping a drug directly into the urine), normalize results to creatinine, distinguish between metabolism and drug impurities, and determine the parent drug that was ingested.

When attendees at the AACC scientific session saw qualitative results for methadone (detected) and 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) (detected) in a patient prescribed methadone, 90% responded to a poll indicating they believed that the patient was taking methadone as prescribed. However, when the results were updated to methadone (> assay range) and EDDP (5 ng/mL), only 4% of the audience agreed that the patient was compliant, suggesting attendees recognized simulated compliance when presented with the quantitative results.

Drug ratios may also be useful to assess compliance. For example, patients who are prescribed buprenorphine can be monitored for compliance by the metabolite (norbuprenorphine)-parent (buprenorphine) ratio. A ratio less than 0.02 is indicative of simulated compliance in which buprenorphine was spiked directly into the urine sample (*12*). In addition, the relative concentrations of morphine, hydromorphone, and codeine by LC-MS/MS in patients prescribed morphine help determine whether the prescribed medication and/or additional drugs were ingested.

In patients compliant with their morphine prescriptions, hydromorphone (a minor metabolite of morphine) concentrations are typically less than 5% of the total morphine concentration, and codeine (a potential contaminant in the morphine preparation) is typically less than 1% of the total morphine concentration.

Debate #2: Hydrolysis or No Hydrolysis

Reasons to hydrolyze samples before testing

Hydrolysis increases the sensitivity of an assay, as the total concentration of a drug is measured as opposed to the free and glucuronidated forms being measured separately. False negative results can be avoided with higher sensitivity. In addition, fewer standards and controls are required if drugs are hydrolyzed as fewer drugs, namely glucuronidated metabolites, are in a panel.

Finally, results should be less confusing for clinicians to interpret. For the opioids alone, at least six additional glucuronides would need to be evaluated if hydrolysis was not performed. If a laboratory designs a panel with appropriate drugs and metabolites such as oxycodone and the primary metabolite noroxycodone, including a hydrolysis step would not impact the ability to assess compliance (*13*).

Reasons not to hydrolyze before testing

Hydrolysis is time consuming and prolongs turnaround time; dilute-and-shoot allows for decreased sample preparation time. Chemical hydrolysis potentially degrades opioid and benzodiazepine drugs, while enzymatic hydrolysis may be incomplete and have variable efficiency (*14*).

Adding glucuronides might better assess compliance and drug taking patterns (*13*). For example, reporting morphine-6-glucuronide and morphine-3-glucuronide concentrations as opposed to only hydromorphone (a minor morphine metabolite not present in all patients) has allowed our laboratory to rule out simulated compliance (*13*). Lastly, laboratories can develop LC-MS/MS assays with sufficient analytical sensitivity to accurately detect parent compounds and glucuronides when measured separately.

Debate #3: How Low Should You Go?

Reasons to use standard cutoffs

Providers frequently ask questions such as *Was the cocaine strongly or weakly positive?* or *The patient claims she took cocaine two weeks ago—is that consistent with the results?* Using standard cutoffs will help deal with these questions. Results (i.e. detected or not detected) will also be more consistent across laboratories and less confusing for providers to interpret (*15*). Furthermore, scientific data exist defining drug detection windows using standard cutoffs (Table 1) (*16*).

Reasons not to use standard cutoffs

Defining the cutoff according to a method's analytical sensitivity offers several advantages. An increase in positivity rate will be seen for many drugs and/or metabolites using the lower limit of quantitation (LLOQ) or lower limit of detection (LLOD), which is particularly helpful in detecting aberrant drug use. A recent study in our laboratory, where cutoffs are validated at the LLOQ or LLOD depending on the drug, demonstrated an increased rate of detection of all illicit drug combinations (*13*).

Furthermore, using the LLOQ or LLOD will reduce the number of false negative results associated with dilute urines or matrix effects. Pesce et al. reported an approach to define cutoffs and a target for the LLOQ in which they calculated the lower 2.5% of drug concentrations in patients positive for several medications, which may assist other laboratories switching to LC-MS/MS (*17*).

Result Interpretation

Misinterpreting UDT can have important negative consequences, and laboratory directors must partner with providers to avoid adverse outcomes. Patients may be falsely accused of aberrant behavior, potentially resulting in discontinuation of necessary medications. Moreover, illicit drugs, undisclosed prescription use, or simulated compliance—patients diluting their urine or dropping their medication directly into their urine—may go undetected if results are misinterpreted, perpetuating the opioid crisis.

The scientific literature suggests that both attending and resident physicians from a variety of specialties do not understand opioid metabolism or cross-reactivity of immunoassays and are therefore not proficient in interpreting UDT *(18,19)*. As laboratories transition to definitive testing and possibly reporting both free and glucuronidated drugs, we postulate this knowledge gap will widen. Consequently, clinical laboratory professionals need to educate providers so that they interpret results correctly.

At a minimum, laboratories performing this testing should have a director with expertise to assist providers in interpreting results (*9*). Labzories also might offer formal clinical pathology consultations for more complex cases in which medical records need to be reviewed.

In our opinion, laboratories should provide more systematic interpretations of results in conjunction with medications. This will ensure providers can effectively manage patients. Importantly, these interpretations must be documented in patients' medical records.

T1 Detection Windows Using Standard Cutoffs

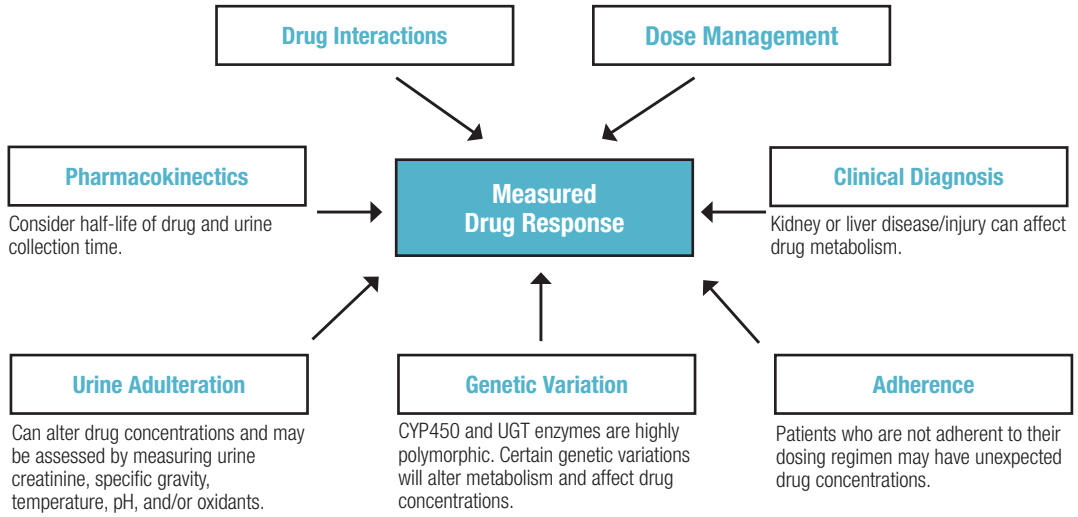
Drugs	Cutoff (ng/mL)	Detection Time (up to)
Amphetamine-Type Stimulants		
Amphetamine	25	3 days
Methamphetamine	25	3 days
MDA	25	2 days
MDMA	25	2 days
Benzodiazepines		
Diazepam	100	10 days
Nordiazepam	100	10 days
Alprazolam	100	5 days
Lorazepam	100	5 days
Oxazepam	100	5 days
Temazepam	100	5 days
Clonazepam (7-amino)	100	5 days
Buprenorphine		
Buprenorphine	0.5	7 days
Norbuprenorphine	0.5	7 days
Cocaine & Metabolite		
Cocaine	50	<1 day
Benzoylecgonine	50	5 days
Fentanyl		
Fentanyl	0.2	3 days
Norfentanyl	1.0	3 days
Methadone		
Methadone	100	7 days
EDDP	100	7 days
Opioids		
6-acetylmorphine (heroin metabolite)	5	<1 day
Codeine	25	3 days
Hydrocodone	25	3 days
Hydromorphone	25	3 days
Oxycodone	25	3 days
Noroxycodone	25	3 days
Oxymorphone	25	3 days
Naloxone	25	3 days
Morphine	25	3 days

MDA: 3,4-methylenedioxyamphetamine; MDMA: 3,4-methylenedioxymethamphetamine; EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine.

Conclusions

Until we have definitive guidelines on how to approach whether quantitative or qualitative results should be reported, whether specimens should be hydrolyzed prior to analysis, and whether standard cutoffs should be utilized, clinical laboratories need

F1 Urine Drug Testing Variables



Many of the variables that affect the concentration of drugs in urine are shown. Additional details are also included below the variable.

to decide what is best for their providers and patient population. In the end, it may be a compromise or require various combinations of results reporting.

In our laboratory, some drugs are reported quantitatively and others qualitatively, specimens are not hydrolyzed, and cutoffs are defined at the LLOQ or LLOD. Our laboratory also is in the process of developing a systematic approach to providing result interpretation as well as an assessment of how it impacts patient care.

References

1. Katz J. Drugs deaths in America are rising faster than ever. https://www.nytimes.com/interactive/2017/06/05/upshot/opioid-epidemic-drug-overdose-deaths-are-rising-faster-than-ever.html (Accessed August 2018).
2. Centers for Disease Control and Prevention. Policy impact: Prescription painkiller overdoses, www.cdc.gov (Accessed August 2018).
3. Groenewald CB, Essner BS, Wright D, et al. The economic costs of chronic pain among a cohort of treatment-seeking adolescents in the United States. J Pain 2014;15:925–33.
4. CDC National Center for Injury Prevention and Control. Annual surveillance report of drug-related risks and outcomes. https://www.cdc.gov/drugoverdose/pdf/pubs/2017-cdc-drug-surveillance-report.pdf (Accessed September 2018).
5. Gilbert JW, Wheeler GR, Mick GE, et al. Importance of urine drug testing in the treatment of chronic noncancer pain: Implications of recent Medicare policy changes in Kentucky. Pain Physician 2010;13:167–86.
6. Christo PJ, Manchikanti L, Ruan X, et al. Urine drug testing in chronic pain. Pain Physician 2011;14:123–43.
7. Trescot AM, Helm S, Hansen H, et al. Opioids in the management of chronic non-cancer pain: An update of American Society of Interventional Pain Physicians' (ASIPP) guidelines. Pain Physician 2008;11:S5–62.
8. Argoff CE, Alford DP, Fudin J, et al. Rational urine drug monitoring in patients receiving opioids for chronic pain: Consensus recommendations. Pain Med 2018;19:97–117.
9. Jannetto PJ, Bratanow NC, Clark WA, et al. Executive summary: AACC laboratory medicine practice guideline—Using clinical laboratory tests to monitor drug therapy in pain management patients. J App Lab Med 2018;2:489–526.
10. Petrides A and Melanson S. Urine drug testing: Debates over best practices to assess compliance and manage the opioid crisis. Scientific session conducted at the 70th AACC Annual Scientific Meeting, Chicago, Illinois. July 31, 2018.
11. Snyder ML, Fantz CR, Melanson S. Immunoassay-based drug tests are inadequately sensitive for medication compliance monitoring in patients treated for chronic pain. Pain Physician 2017;20:1–9.
12. Hull MJ, Bierer MF, Griggs DA, et al. Urinary buprenorphine concentrations in patients treated with suboxone as determined by liquid chromatography-mass spectrometry and CEDIA immunoassay. J Anal Toxicol 2008;32:516–21.
13. Gencheva R, Petrides A, Kantartjis M, et al. Clinical benefits of direct-to-definitive testing for monitoring compliance in pain management. Pain Physician 2018;21;E583–92.
14. Johnson-Davis KL. Opiate & benzodiazepine confirmations: To hydrolyze or not to hydrolyze is the question. J Appl Lab Med 2018;2:546–72.
15. Clarke WA. Are standard cutoff concentrations sufficient for pain management screening? Yes! J Appl Lab Med 2018;2:653–6.
16. Baselt RC. Disposition of toxic drugs and chemicals in man. 8th Ed. Foster City, California: Biomedical Publications 2008.
17. Pesce A, West C, West R, et al. Determination of medication cutoff values in a pain patient population. J Opioid Manage 2011;7:117–22.
18. Starrels JL, Fox AD, Kunins HV, et al. They don't know what they don't know: Internal medicine residents' knowledge and confidence in urine drug test interpretation for patients with chronic pain. J Gen Intern Med 2012;27:1521–7.
19. Reisfield GM, Bertholf R, Barkin RL, et al. Urine drug test interpretation: What do physicians know? J Opioid Manag 2007;3:80–6.

NEARLY 20% OF PROM PATIENTS EXHIBIT VAGINAL BLEEDING[1]

Actim® PROM

The PROM Test Proven Accurate in the Presence of More than Trace Blood and Other Contaminants[2]

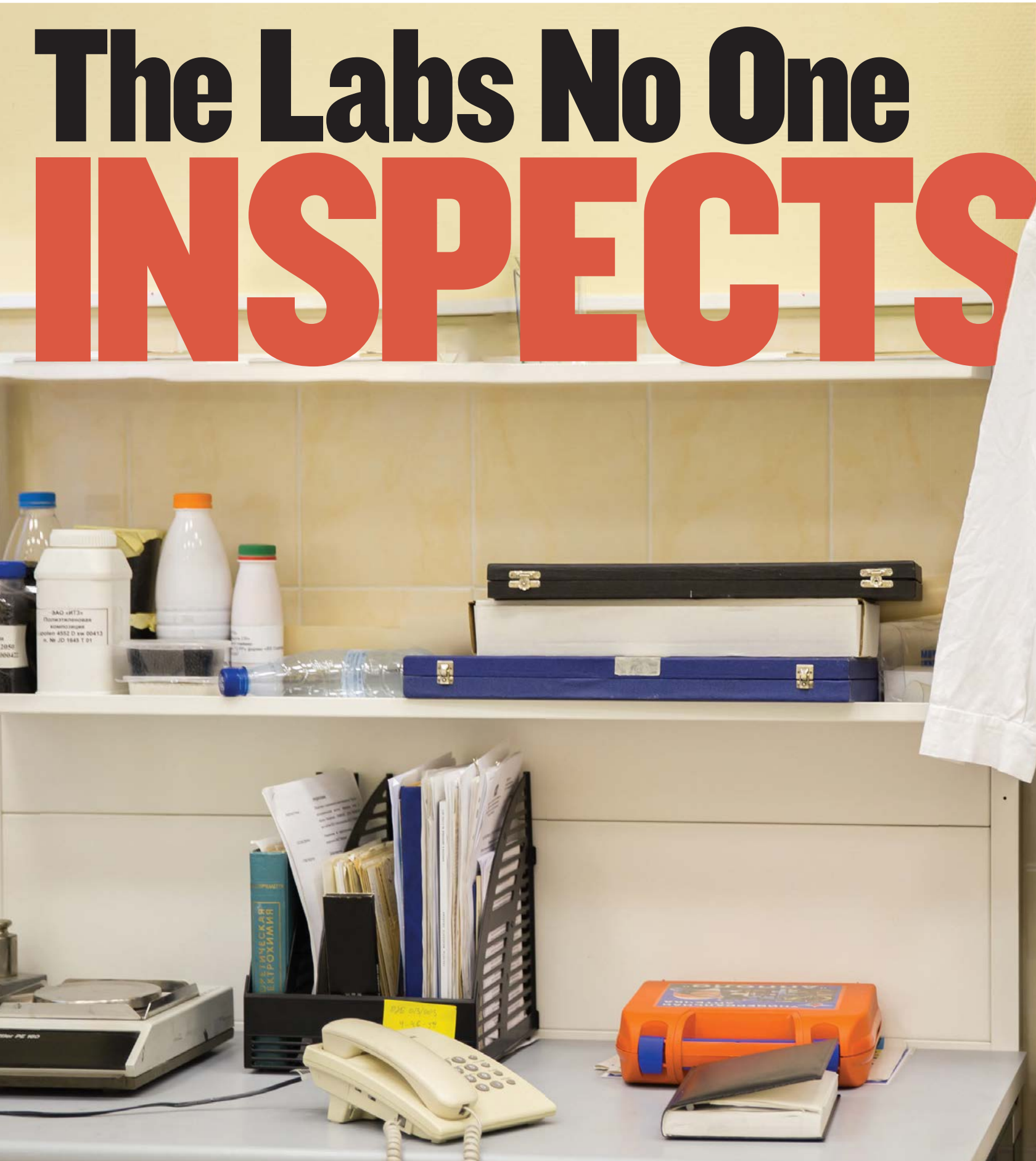
Why risk inaccurate diagnosis when there's a PROM test proven effective for patients with vaginal bleeding? For more than 20 years, Actim PROM has been used to effectively diagnose more than 7 million PROM patients worldwide. Contact us at 800.243.2974 or www.coopersurgical.com.

CooperSurgical

1 Palacio et al.: Meta-analysis of studies on biochemical marker tests for the diagnosis of premature rupture of membranes: comparison of performance indexes. BMC Pregnancy and Childbirth 2014 14:183

2 The test has been designed to minimize interference from bleeding, but in cases of heavy bleeding the blood locally may have a higher concentration of IGFBP-1 protein. In these cases, a positive result should be interpreted with caution. Actim PROM IFU.

The Labs No One INSPECTS



mariakraynova / Shutterstock.com

The number of sites without laboratory experts has skyrocketed with little oversight

BY KIMBERLY SCOTT

Despite tremendous growth over the last 2 decades in the number of sites performing waived testing, federal regulators have maintained a hands-off approach when it comes to ensuring that waived testing is performed properly at these sites, and in 2016 the Centers for Medicare and Medicaid Services (CMS) shut down its small on-site inspection program.

In November, AACC issued a position statement expressing concern about the quality of patient care and calling for greater federal monitoring of waived testing sites, an updated study on the state of waived testing, enhanced training for personnel, and voluntary proficiency testing to tackle the problem.

The number of near-patient laboratory testing sites that perform only Certificate of Waiver (CoW) testing has grown from 44% of all clinical laboratory testing sites in 1993 (67,294) to 71% currently (186,746). The number of waived tests also has grown, from eight when the CLIA were implemented in 1988 to more than 130 today. Much of the increase in waived testing at near-patient sites is due to technological advances in point-of-care (POC) testing devices.

"Waived testing has grown by leaps and bounds, and there has always been a question about quality," said Sharon Ehrmeyer, PhD, a professor in the department of pathology and laboratory medicine at the University of Wisconsin School of Medicine and Public Health in Madison and a member of the AACC Policy and External Affairs Core Committee that drafted the position statement. "Central laboratories in hospitals have good oversight of waived testing. The bigger concern is in places like physician office laboratories where the staff have little knowledge about the tests themselves."

No Instructions—No Problem?

CoW laboratories, which include physician offices, pharmacies, home healthcare agencies, and skilled nursing facilities, operate with little federal oversight. To perform waived testing, these sites are required to complete and submit a form that describes the tests they perform and to pay a biennial fee of $150 to obtain and maintain a CoW.

These laboratories are not subject to CLIA personnel, quality control (QC), or proficiency testing (PT) requirements, nor do they undergo regular inspections. In lieu of these standards, CoW facilities are required to follow manufacturers' instructions for the tests they perform, which prescribe QC and maintenance requirements for the devices, instructions on how to properly store reagents, testing protocols, and other procedures.

In addition, individuals performing testing in near-patient healthcare settings often have little to no formal education or training in laboratory medicine, notes the AACC position statement. Training on protocols and use of the devices is provided by a variety of personnel—the manufacturer's sales representatives or current employees of the facility—or through self-education by reading package inserts.

These multiple training approaches lead to inconsistent quality in POC testing at CoW testing sites. A 2001 report by CMS found that 50% of laboratories performing waived tests do not follow the manufacturers' instructions or don't even have the instructions. In addition, 20% of CoW labs surveyed by CMS were not performing QC as required by the manufacturer, and 12% were not performing the additional QC requirements prescribed by the Centers for Disease Control and Prevention (CDC) as a condition of test waiver.

A separate study conducted by the New York Department of Health found similar problems. And a 2001 report by the Department of Health and Human Services Office of Inspector General (HHS OIG) identified "significant vulnerabilities" in oversight of CoW labs.

Some efforts in the last 15 years have taken on quality problems in waived testing. In 2005, CDC published "Good Laboratory Practices for Waived Testing Sites," and in 2015 released a follow-up document, "To Test or Not to Test? Considerations for Waived Testing." The agency also developed a 1-hour educational training module based on the second booklet.

In 2002, CMS initiated the CoW project, which resulted in the agency visiting 2% of CoW laboratories each year to identify problems and help resolve them. However, CMS discontinued this program in 2016 to focus on physician-performed microscopy laboratories.

Despite these efforts, quality issues with waived testing persist. A 2015 special investigation by the *Milwaukee Journal Sentinel* highlighted the lack of federal oversight of waived testing and the dangers of incorrectly performed tests. According to that report, CMS in 2011 drafted a law that would have allowed routine oversight of waived laboratories, but the proposal never moved beyond that initial phase.

The College of American Pathologists (CAP), the Joint Commission, and COLA, which accredit labs, do have some quality requirements for practitioners who perform waived testing, but those requirements are not as

186,746
Number of laboratories that perform only waived tests

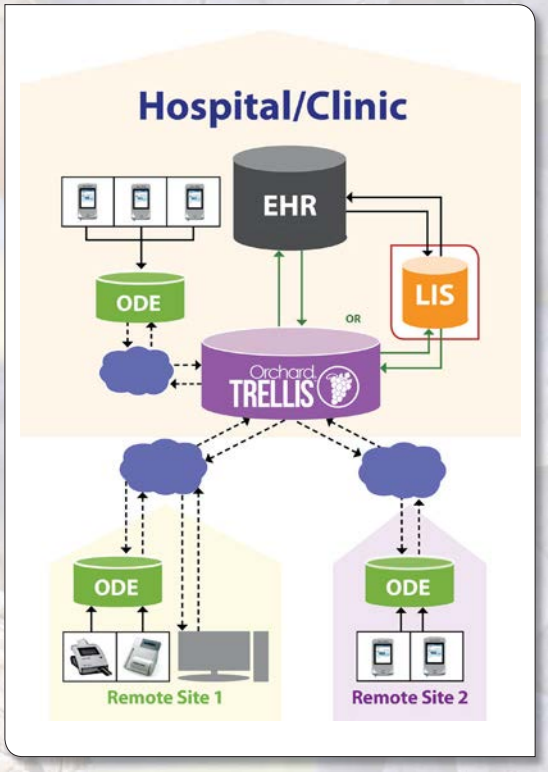
50%
Number of laboratories surveyed by Colorado and Ohio state surveyors in 2001 that had "significant quality and certification problems" (2001 HHS OIG Report)

21%
Number of waived testing labs surveyed in 2002 that reported not routinely checking the product insert or instructions for changes to the information (2005 CDC Report, "Good Laboratory Practices for Waived Testing Sites")

45%
Proportion of Certificate of Waiver sites that reported not documenting the name, lot number, and expiration dates for tests performed; 35% did not maintain logs with records of their quality control testing; 31% did not maintain a log or record of tests performed; and 9% did not require a requisition or test orders documented in a patient chart before performing a test (2005 CDC Report, "Good Laboratory Practices for Waived Testing Sites")

BRIDGE THE POCT GAP

Software to Integrate & Administer POCT



Orchard Software offers a configurable, centralized POCT management and integration software solution—Orchard® Trellis™—that is flexible enough to meet a variety of unique POCT scenarios. This includes working with your existing LIS, managing bedside testing, or managing near-patient testing in a clinic setting. Trellis provides remote handling of POCT training, competency assessments, QC, decision support rules, automated billing, and real-time results delivered to your LIS and EHR to make POCT administration easy to manage from a central location.

- **Convenient dashboard display for remote viewing of all locations**
- **Track patient orders and review POCT results**
- **Sophisticated rules engine for automation**
- **Central repository for QC and reagent lot tracking**
- **Centralized management of all operator certifications**
- **Automated emails to notify operators of upcoming certification dates**
- **Graphs for instrument QC, linearity, and calibration verification values**
- **POCT data mining for analytics**
- **Superior connectivity for diverse POCT devices**
- **Automate POCT billing capture**

If you are looking for a cost-effective way to bridge the POCT gap, call us today for a demonstration of how Orchard Trellis provides the tools to expertly integrate and administer your POCT.

Orchard® TRELLIS | ORCHARD Software

(800) 856-1948

www.orchardsoft.com

stringent as requirements for other types of testing, Ehrmeyer noted. The Joint Commission, for example, first developed standards to address waived testing in 1992 and has a chapter in its standards manual specifically addressing waived testing. The chapter is not restricted to laboratory manuals but is included in the accreditation manuals for hospitals, ambulatory care, critical access hospitals, long-term care facilities, behavioral health, and home care agencies.

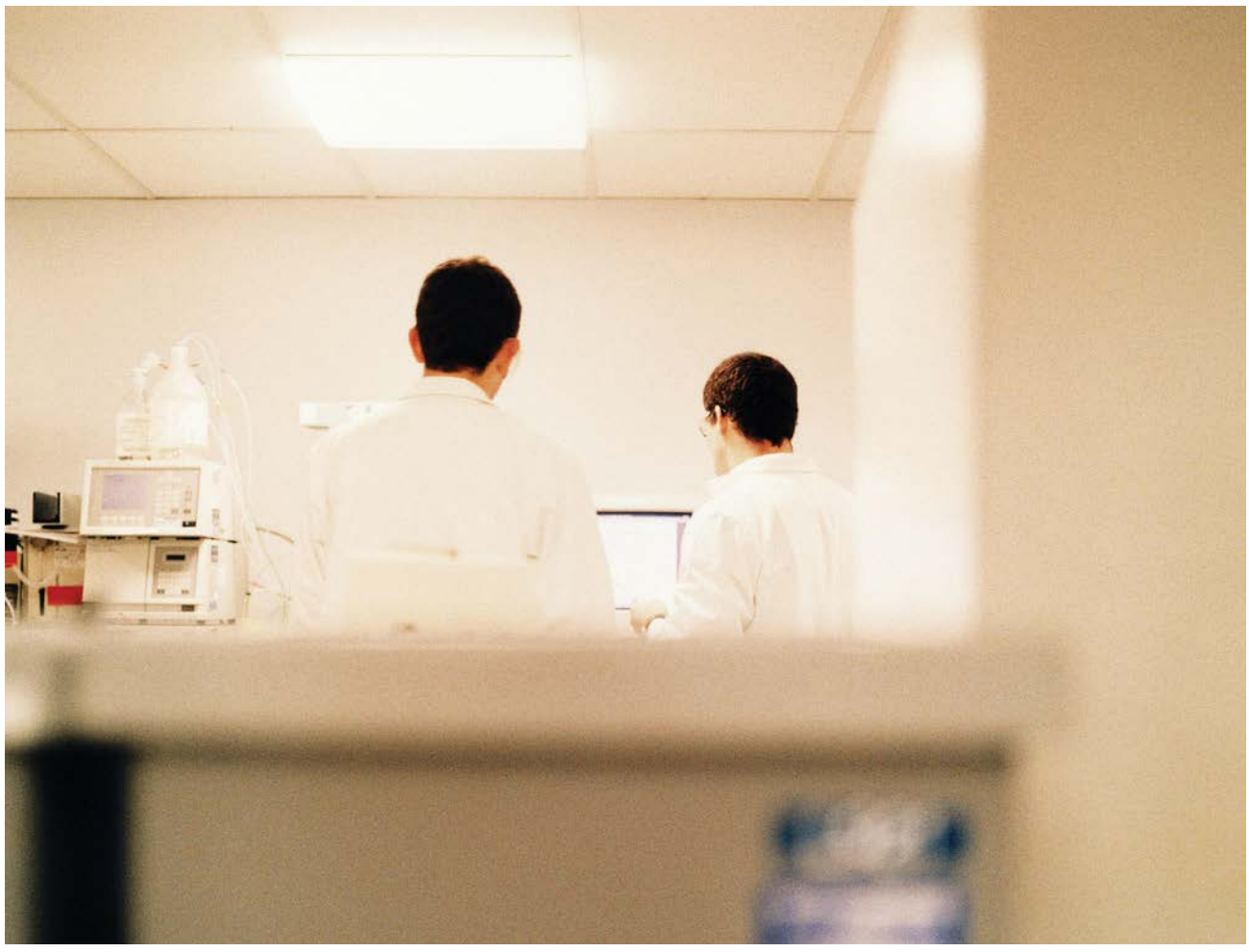
"The standards apply to all staff performing waived testing, including physicians," said Maureen Lyons, a communications specialist with the Joint Commission. "The standards also apply to all locations in the organization where waived testing is conducted. The standards in this chapter address policy and procedures, identifying individuals who supervise and conduct waived testing, competence of individuals performing waived testing, performance of quality control, and recordkeeping."

Even so, the Joint Commission concluded in 2013 that even with well-defined standards, clinical staff struggle with the framework for performing waived tests, especially verifying staff performance.

"Part of the problem has to do with CLIA itself," said James Nichols, PhD, a professor of pathology, microbiology, and immunology at Vanderbilt University and a member of the AACC Policy and External Affairs Core Committee. "The only thing that waived laboratories are required to do are pay their fees, follow manufacturers' instructions, and agree to be inspected if an inspector shows up."

CAP has also encouraged improvements in CoW labs over the years, he added. "The American Academy of Family Physicians has also put some emphasis on quality. Physicians and nurses have the best intent for their patients. They don't intend to go in and cut corners … they just don't realize their actions could have negative consequences."

"Physicians and nurses have the best intent for their patients. They don't intend to go in and cut corners … they just don't realize their actions could have negative consequences."



Nick Daly / The Image Bank / Getty Images

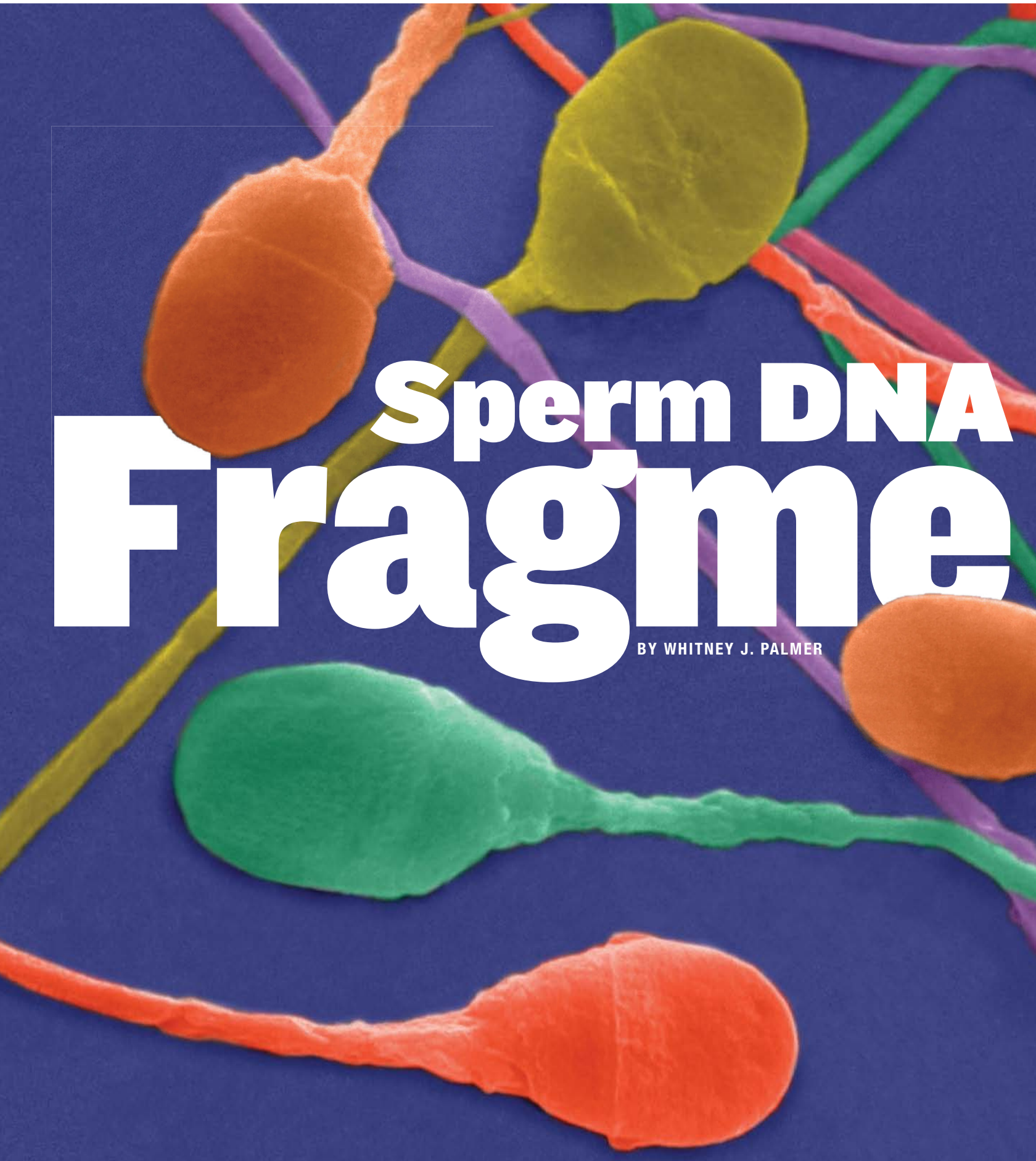
AACC Recommendations

To deal with the lack of oversight and concerns about the quality of waived testing, AACC is urging Congress to direct the HHS OIG to conduct a study on the quality of testing provided by CoW testing sites and make recommendations for improvement. Additional recommendations include:

- CMS should resume its CoW Laboratory Project and annually inspect a minimum of 2% of waived laboratories covering a representative cross section of decentralized testing sites.
- CMS and CDC should provide CoW facilities with the CDC best laboratory practice documents and provide ongoing educational programs designed to improve the quality of testing in these laboratories.
- CoW laboratories should document the quality and reliability of test results (e.g., by participating in proficiency testing).
- CoW laboratories should continually ensure their personnel are properly supervised and trained to consistently and reliably perform clinical laboratory tests necessary for the provision of quality patient care. Manufacturers could provide laboratories with training checklists to document personnel training.
- Professional laboratory organizations should continue to provide training programs and materials that ensure CoW operators gain the knowledge, experience, and skills needed to perform quality laboratory testing.

Just raising awareness about quality issues in waived testing and gathering more information on the current state of waived testing in the U.S. can go a long way in improving testing, Nichols emphasized. "The most recent studies done on this are about 15 years old, and they need to be updated," he said. "It would behoove us to really take note of what's happening out there and try to improve on what we are seeing today."

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



Sperm DNA Fragme

BY WHITNEY J. PALMER

nation:

THE NEW FRONTIER OF FERTILITY TESTING

Ed White / The Image Bank / Getty Images

Worldwide male fertility has followed a disconcerting trend over the last 40 years. Since the 1970s, research shows sperm counts have plummeted by more than 50% in the United States, Europe, Australia, and New Zealand. Because the downward trajectory shows no sign of slowing or rebounding, being able to accurately assess male fertility and its impact on achieving a successful pregnancy has become more critical.

Overall, infertility affects between 10% and 15% of men in prime reproductive age. However, in as many as 15% of cases, conventional semen analysis, based on parameters established by the World Health Organization (WHO), does not identify sperm abnormalities that could cause decreased fertility (Box, below). While the WHO parameters, set in 2010, test volume, sperm count, and motility, they only provide information about sperm presence—not how effectively the sperm will fertilize an oocyte and foster a viable pregnancy.

That means men who fall within normal WHO ranges can still have significant sperm DNA damage. Consequently, there is a need for a technique that provides more detailed information about sperm quality. In the last decade, sperm DNA fragmentation (SDF) has emerged as a possible tool to highlight the level of molecular damage present in a man's sperm. Several SDF tests are currently available, and the results can guide treatment option selections and fertility services. But reservations remain about how widely applicable and accepted SDF should be.

Testing Options

SDF differs from raw semen analysis by examining the number of nicks and breaks present in the sperm's DNA. Four main tests exist to identify a man's DNA Fragmentation Index—the proportion of normal-to-damaged sperm—and each strategy is unique.

Sperm chromatin structure assay uses a chemical dye to stain broken sperm red and normal sperm green. Sperm chromatin dispersion treats sperm with acid denaturation after which normal sperm produce halos. Terminal deoxynucleotidyl transferase 2′-deoxyuridine 5′-triphosphates (dUTP) nick end labeling employs fluorescent dUTP to label single- and double-strand breaks. And, SpermComet uses single-cell gel electrophoresis in which only fragmented sperm travel through the gel.

Although the mechanisms are varied, these tests are valuable to couples who have not been able to identify the root of their infertility, said James Hotaling, MD, assistant professor of surgery and co-director of the Fertility Integrated Practice Unit at the University of Utah School of Medicine in Salt Lake City.

"SDF is the only test that allows us to look at anything other than bulk semen parameters," he explained. "It lets us look at that quality of the DNA packaging critical for early embryo development."

A Promising Approach

Every man has sperm DNA imperfections, said Mary Samplaski, MD, an assistant professor of urology at the University of Southern California Keck School of Medicine in Los Angeles, but levels are higher among sub-fertile and infertile men. High SDF, loosely defined as more than 30%, correlates with all reproductive outcomes, including lower success rates in natural pregnancy, intrauterine insemination, and in vitro fertilization (IVF), as well as higher miscarriage occurrences.

Several factors lead to this damage, said Ashok Agarwal, PhD, director of the Cleveland Clinic Clinical Andrology Lab and Sperm Bank. Oxidative stress, abortive apoptosis, and environmental factors, such as ultraviolet light and cellphone radiation, all can negatively impact DNA. Lifestyle factors, including obesity, diabetes, and sedentary occupations, also pose damage to sperm. Additionally, varicoceles—enlarged testicular veins that cause overheating and injure sperm—are present in approximately 40% of men with infertility.

With SDF test results in hand, reproductive specialists can

2010 WORLD HEALTH ORGANIZATION CRITERIA FOR SEMEN ANALYSIS IN MALE INFERTILITY

Volume (mL)
Sperm count
Total sperm count
Total motility (% motile)
Progressive motility
Vitality (% alive)
Morphology

J Assist Reprod Genet 2016;33:1319–35.

Ed White / The Image Bank / Getty Images

sysmex | Lighting the way with diagnostics

FOR PRECIOUS PATIENT SAMPLES TIME IS PRECIOUS.

GloCyte®
CSF Cell Counter

TIMELY RESULTS YOU CAN COUNT ON

Sysmex America is now the exclusive distributor of GloCyte, an automated cell counter for cerebrospinal fluid (CSF) that provides rapid and accurate red cell and total nucleated cell counts at clinically relevant low levels. With its fluorescence technology, highly specific reagents, and intelligent counting algorithm, GloCyte can handle all of the CSF specimens that enter your laboratory, providing quick and precise results for your most critically ill patients.

www.sysmex.com/glocyte

recommend necessary lifestyle changes and guide patients toward the fertility treatment options that offer the best opportunities for success, he said.

"Rather than having a patient undergo and play Russian roulette with expensive technologies like IVF or [intracytoplasmic sperm injection] that can cost $10,000 to $15,000 per attempt with less than a 30% success rate," he said, "we can avoid pricey and unnecessary treatments for couples with male factor infertility having repeated IVF failure or recurrent pregnancy loss by using SDF outcomes to reduce the DNA damage before undergoing assisted reproduction treatment."

Samplaski agreed, noting that SDF offers vital information, pointing couples struggling with infertility down the right path as early as possible during their best reproductive years. That includes, she added, suggesting men take an antioxidant to counteract any oxidative stress damage.

SDF also supports clinical procedures that reduce DNA damage, according to Sheena Lewis, PhD, FRSB, emeritus professor at Queen's University Belfast School of Medicine, Dentistry, and Biomedical Sciences in Northern Ireland. Removing sperm via testicular biopsy, before it picks up oxidative stress damage traveling along the epididymis (which she called the "war zone"), can yield healthier sperm for fertility procedures. Varicocele repair also offers similar improvement, she said. In fact, research shows men can experience a 3.4% damage reduction within 3 months via SDF retesting (Int Urol Nephrol 2015;47:1471–7).

What Is Holding SDF Back?

Despite providing a greater degree of actionable information, SDF still lags in the quest for widespread implementation. To a large degree, ease of access is a stumbling block, according to Amin S. Herati, MD, assistant professor of urology and director of male infertility at the Brady Urological Institute at the Johns Hopkins School of Medicine in Baltimore. "For these tests, access for patients and providers is a big issue," he said. "Only select labs offer it. Not everyone does it."

Agarwal agreed, but he did not recommend every lab offer these tests as an in-house service. Instead, he said, they should identify a specialty lab, such as his own, already equipped with properly trained personnel, lab space, and equipment to process SDF tests to meet their needs.

Consistency and translatability have also been obstacles. Not only does each SDF test assess DNA fragmentation differently, each also has its own cut point to diagnose sperm quality levels. To make tests more easily accepted, procedures and results reporting must be standardized, Hotaling emphasized.

"There's a lot of variability in how the test is run," he said. "It's not the same from one place to another, so it's hard to compare results between labs." Samplaski concurred, saying the level of existing differentiation makes reproductive specialists reticent to order SDF tests more frequently.

As with all other tests, though, until SDF methods are analyzed in larger clinical trials and submit reliable, reproducible results, providers will remain hesitant about suggesting the test for a wider patient population. Even as an initial SDF advocate, Herati acknowledged that the data to support the methods' robust use has not appeared so far. However, these functional tests provide actionable information for a certain group of men struggling with infertility.

"I still use sperm DNA fragmentation, but its main role in my mind is for someone with normal semen parameters whose partner might have recurrent pregnancy loss," Herati said. "We can decide where the sperm should come from for fertility services and what we can do to optimize that choice. That's really where the utility of DNA fragmentation lies."

Still, Agarwal said, SDF is one of the most important male fertility advancements in the last 60 years. Although it's still in the early adoption phase, it offers hope for a successful pregnancy in cases when male-factor infertility was previously undiagnosed.

"Infertility is complicated, and sperm DNA fragmentation is an important part of testing in male patients, but it isn't a silver bullet," he emphasized. "It's one way to examine, look for, and find hidden problems that aren't told by semen analysis, and that's a big thing. But, it's not for every patient who has a problem with infertility."

"SPERM DNA FRAGMENTATION IS AN IMPORTANT PART OF TESTING IN MALE PATIENTS, BUT IT ISN'T A SILVER BULLET."

Sheena Lewis is the founder of Examen, producer of the SpermCOMET test and managing director of Lewis Fertility Testing, Ltd., a spin-out company of Queen's University Belfast.

Whitney J. Palmer is a freelance journalist in Holly Springs, North Carolina.
+EMAIL: whitneyljhowell@gmail.com

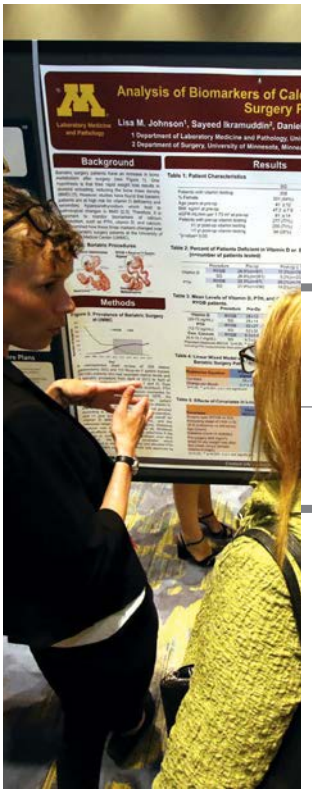
CALL FOR ABSTRACTS

SUBMIT YOUR SCIENCE

71ST AACC ANNUAL

SCIENTIFIC MEETING

& CLINICAL LAB EXPO



AUGUST 4–8, 2019

ANAHEIM, CA USA

Don't miss your opportunity to share your findings, research and discoveries with the world's leading experts in clinical laboratory science at the largest global scientific conference and tradeshow in the field.

SUBMIT YOUR ABSTRACT FOR CONSIDERATION TO BE:

- Presented as a poster at the 71st AACC Annual Scientific Meeting in Anaheim.
- Recognized as a selected abstract for podium presentations.
- A recipient of AACC division and student awards.

AACC | *Better health through laboratory medicine.*

For more information and to submit your abstract, visit www.aacc.org/2019am.

Submission deadline: February 12, 2019, 5:00pm EST.

MASS SPECTROMETRY

FOCUS ON



BY HEIDI SCHIMMELBUSCH, BS, JONATHAN DECENZI, MS, AND JOSEPH HOMAN, MS

Growing Pains in LC-MS/MS Testing

Solving the Challenges of an Expanding LC-MS/MS Test Menu

The versatility of liquid chromatography-tandem mass spectrometry (LC-MS/MS) has made this technique one of the most advantageous in the field. However, the diverse chemical properties of potential analytes pose numerous challenges as clinical laboratory test menus expand.

This article will explore some of these challenges, highlight some best practices for addressing them, and discuss available technology that may represent an opportunity to eliminate some of these challenges today.

How to Optimize Consumables

Many parameters must be optimized when developing LC-MS/MS analytical methods for analysis in biological matrices, including extraction, chromatography, and instrument-specific parameters. Analytical columns are one such area. Columns are an expensive consumable used in routine LC-MS/MS analysis, and laboratories should take care to assure maximum performance of an analytical column throughout an assay.

Laboratories also need to use LC-MS/MS-grade solvents and high-quality deionized water with ultraviolet treatment. Many laboratories are swayed toward lower-priced, lower-quality solvents. However, low-quality solvents come with long-term costs like unanticipated downtime and resource-intensive troubleshooting.

Additionally, inline frits, filters, and any pre-columns used should be changed often between analyses to prevent contaminants from accumulating on the analytical column. Impurities on the analytical column can cause high system backpressure, background noise associated with the flow and gradient, shifting retention times, and abnormal peak shape, adding to the uncertainty of assay results.

Laboratories before analysis also should carefully inspect all vials for particulates and precipitated proteins in extracts. Precipitated proteins can adsorb analyte and contaminate and clog the tubing and injector components of the sample manager.

Paying Attention to the Mobile Phase

Clinical laboratories often use mobile phase additives in LC-MS/MS to optimize the separation and ionization of different compounds of interest. While these additives are frequently necessary, they can contribute to negative outcomes in routine LC-MS/MS analysis if not used properly. Mobile phase should be prepared using only high-quality additives and at the lowest concentration possible in order to achieve the desired result.

When changing over solvents of different composition, lines should be flushed with at least five volumes of high-purity water as an intermediate solvent to prevent salt precipitation. Salt precipitation in the LC-MS/MS system can cause pump failures, high background noise contamination, and reduced sensitivity due to accumulation on source components.

Use of additives and aqueous buffers in LC-MS/MS mobile phase is also conducive to microbial growth that can contribute to many of the same problems encountered with salt precipitation. Laboratories can mitigate microbial growth by sealing mobile phase reservoirs in between assays, discarding mobile phases in use

past a certain timeframe, and rinsing solvent bottles thoroughly between uses or at other defined intervals.

LC-MS/MS Maintenance

One key aspect of monthly maintenance is flushing the LC components. Buildup of contaminants from solvents and extracts often causes common problems such as solvent pump failures, carryover, high system pressure, high background, and interferences. Replacement of expensive parts becomes the solution to most of these issues in the absence of regular flushing.

Laboratories should use a manufacturer-recommended mixture of solvents and aqueous acid and ensure that pumps and needle wash systems are primed and a low flow rate set.

Preventive maintenance along the sample path is crucial.

Injections of solvent at high volume will wash both the sample path and the flow path. To tackle tough system contamination from sample injections of exceedingly high concentrations, laboratories at this step should inject dimethyl sulfoxide at high volume.

During this time, back-flushing using specific solvents and column temperatures based on the column type might revive an analytical column. System flush should always be routed to waste, not into the MS.

Monthly maintenance also includes washing the mobile phase bottles (reservoirs) and testing the solvent pumps for leaks according to the manufacturer's recommendations. For example, using detergents is not recommended for mobile phase reservoirs. Laboratories may also want to test pumps so that they can be rebuilt before they fail while being used.

Due to the volume of samples and the myriad of sample types injected, preventive maintenance along the sample path is crucial. Mitigating contaminant buildup is absolutely essential—beginning with regular front-end column maintenance, through column fittings and PEEK tubing, and ending with front-end maintenance of the mass spectrometer. While proactive maintenance saves time, some reactive maintenance will be inevitable.

The diversity and volume of samples most LC-MS/MS services see also necessitates proper equilibration of both the LC and MS components while switching over a system. While mobile phase lines should be flushed between assays, MS parameters can be set to allow sufficient time for the MS source and desolvation temperatures and gas flows to reach set points. Starting an analysis without properly equilibrating the MS can cause changes in response and inaccurate quantitation. Labs also need to allow the column temperature to reach its set point between assays to maintain consistent backpressure and retention times. Matrix effects can vary depending on where an analyte elutes in the gradient. Once all of these set points are reached, the analytical column should be equilibrated with 10-20 volumes of mobile phase before beginning to run system suitability samples.

For typical mass spectrometry laboratories, maximizing the capacity of LC-MS/MS systems will often mean performing a wide array of methods on the same system. In order to accommodate a growing test menu, a laboratory may very easily generate a wide variety of methods that utilize different extraction techniques, different analytical columns, and different mobile phase compositions. Depending on the daily or weekly test volume, the laboratory may need to change out columns and mobile phases numerous times between different analytical runs.

The amount of equilibration between runs also can vary depending on an analytical method's specific parameters. For instance, an analytical method that utilizes an extraction protocol or specific mobile phase modifiers may be incompatible with another method, requiring more time—and sometimes maintenance—before the subsequent method is ready for use.

System Suitability Testing

Due to the large number of assays running on a given system, system suitability should be performed for each new assay set up on a system. While not specifically outlined in current clinical regulatory guidance, system suitability testing has become a valuable mechanism for ensuring proper system configuration before labs begin analyzing prepared samples. The CLSI C62 guidance document also addresses this issue.

The best approach to assessing system suitability varies greatly. It often entails looking for visual cues that something is not quite right in a system and in the resulting chromatograms. Some cues come before injecting any system suitability samples. Equilibration of a system prior to injections is paramount. Attaching fittings to prevent voids and leaks, checking mobile phase volume and quality, and performing the recommended preventive column maintenance before equilibration are the first steps to proper system setup. If a system is running a single test with no changes across a day, system suitability could be performed daily or as needed. However, system suitability should be assessed anytime a change is made to the setup, including column installation, mobile phase change, or parts replacement.

Before assessing system suitability samples, a user needs to identify key chromatographic criteria: retention time, peak shape, contamination, signal-to-noise (S/N), and peak area/height. Depending on the number of injections, retention time should be monitored within the injections or to compared historical data. Changes in retention time can be related to numerous issues stemming mainly from the LC—such as peak shape, which should be Gaussian—with limited tailing/fronting, co-eluting peaks, and, if utilizing a smoothing algorithm, enough data points to elicit symmetry across the peak width.

With chromatography generated prior to the MS, troubleshooting should be directed to the LC and acquisition methods. By injecting system suitability samples without analyte present (only internal standard), users can assess the presence of interferences, contamination from

analytes of interest, and baseline and background issues. It also helps to observe consistency from injection to injection, ensuring that each injection achieves the same volume.

As a reminder, the intensity of the background present in the source can suppress analytes of interest and cause poor S/N. The quality of solvents used on the LC system usually causes high background. S/N at the lower limit of quantification is commonly monitored as >10, but depending on the intensity of the background present, problems may arise much sooner than S/N 10. Large drops in signal intensity may point to the cleanliness of the source components as well as solvent/mobile phase quality.

Regular front-end maintenance helps reduce large fluctuations in signal, but the number of injections, extraction types, and matrices contribute to the frequency at which the source and probe require maintenance.

In addition, when switching mobile phases, flushing the lines and pumps with water in between prevents salt from depositing on the surface of the source. With the variety of mobile phase concentrations and pH, the water flush is crucial to reduce the frequency of source cleaning.

Caution on Panels

Analysis using panels helps simplify by minimizing the number of different extraction protocols and changing of columns and mobile phases leading to overall more efficient laboratory workflows. However, this causes instrument inefficiency via wasted analytical time, as most samples will likely contain only a small subset of all included panel analytes eluting during the chromatographic window.

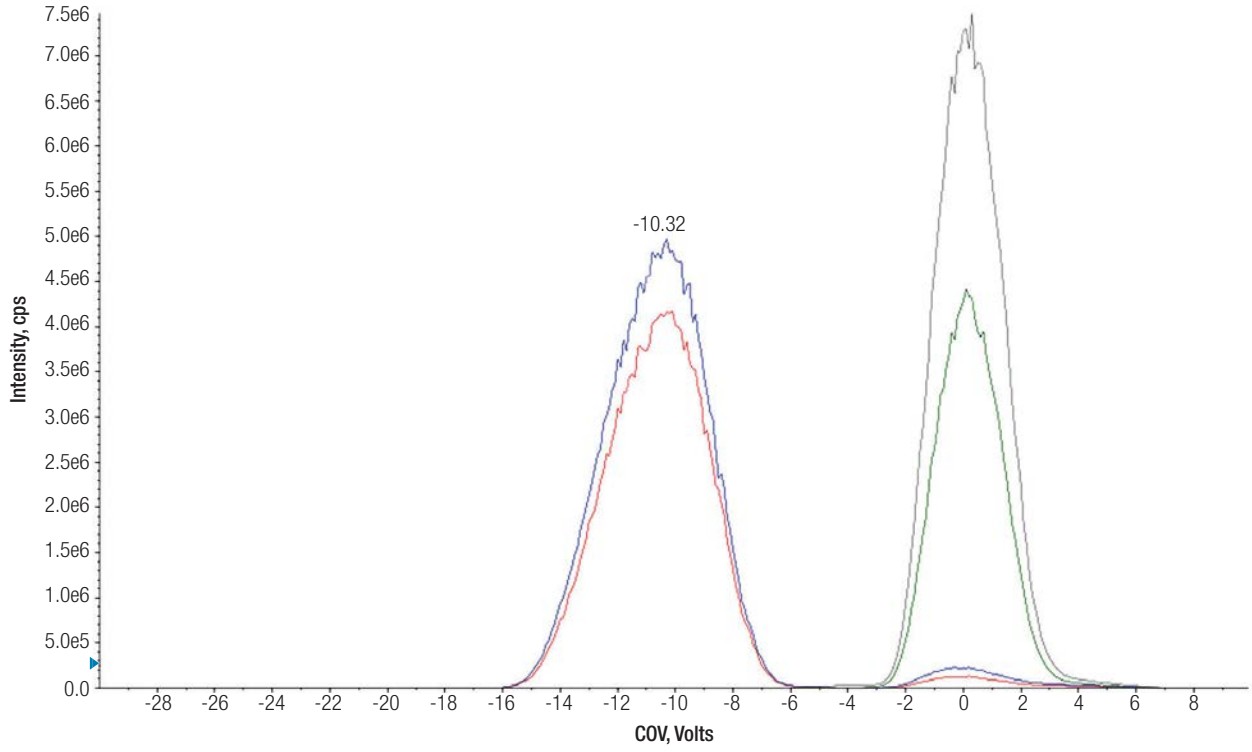
Another negative aspect about using panels is the potential compromise in quality since it's not always feasible to optimize numerous parameters for a diverse group of compounds. Many fast methods reduce the wasted analysis time, but the changeover and maintenance time between diverse analytical setups remain. Many labs deal with these problems by dedicating instruments to specific analytical methods, which in turn increases operational costs and capital equipment expenditures, and potentially poses space limitations.

Using Laser Diode Thermal Desorption

The laser diode thermal desorption (LDTD) ion source, patented by the Canadian company Phytronix Technologies, may be a solution to these operational problems.

LDTD requires spotting up to 10 microliters of sample extract to individual wells on a 96 or 386 LazWell plate. A laser heats the backside of the well using a thermal ramp pattern specified in the instrument analytical method. The analyte is desorbed and carried through the transfer tube by

F1 **Is It Chromatographic Separation?**



Scanning the compensation voltage reveals a visual of separation that can be achieved with differential mobility. The left peaks (blue and red lines) are separate transitions for mycophenolic acid. The right two peaks (gray and green) are separate transitions for mycophenolic acid glucuronide. Note the formation of mycophenolic acid in the source seen as small blue and red peaks—a known phenomenon due to source conditions. Y-axis, peak area; X-axis, compensative voltage (COV). Counts per second (cps).

heated carrier gas. Atmospheric pressure chemical ionization then ionizes the compound which the mass spectrometer subsequently analyses. With no LC component, a lab doesn't need to spend time switching the column and mobile phases between analytical methods. The impact of one analytical method on another is very minimal since there is no mobile phase and no injection.

An additional benefit of not having an injection is the lack of analytical carry over as a source of contamination. Samples are isolated to individual wells, eliminating needle contact with individual samples. The biggest benefit of using the LDTD is increased throughput. The laser pattern typically takes approximately 6 seconds, with about 10 seconds needed to move from one well to another.

One limitation to such a fast injection cycle is that labs need to limit analytical panels to smaller numbers of analytes and their internal standards. However, the LDTD can analyze large analytical panels if a lab spots samples multiple times based on the maximum number of compounds that can be adequately detected in a single injection. With little difference between methods on the LDTD, there is no reason for dedicated instrumentation and all testing can be run on all equivalent instruments.

When labs use LDTD along with ion mobility or differential mobility, they can circumvent anticipated matrix interferences and loss of specificity. For example, with differential mobility, analytes are subjected to a separation voltage that destabilizes the ion flight path. The application of an analyte-specific compensation voltage offsets this destabilization allowing for ion transmission into the mass spectrometer.

As seen in Figure 1, mycophenolic acid and its glucuronide can be resolved easily despite no chromatographic separation prior to entry into the source. To the unfamiliar eye, what appears to be chromatographic separation is actually separation based on gas phase mobility occurring in the order of milliseconds.

LDTD does, however, have its drawbacks that laboratories should consider carefully. These include the potential need for more extensive sample pretreatment, the lack of chromatographic separation of clinically important isomers and isobars, and possible isobaric interference.

Be Ready to Grow

Labs usually justify an LC-MS/MS system financially based on developing one or two relatively high-volume tests. As a typical laboratory grows, its test menu diversifies, physical space limitations become apparent, and it faces pressures to reduce capital expenditures. All of these factors can inhibit laboratories from fully realizing the potential of mass spectrometry.

Rethinking the analytical process and conducting a capacity assessment similar to how system suitability is done (i.e. seeing the parts as well as the whole) provides opportunities for analytical scalability previously not achievable. A healthy and coordinated effort between operational, technical, and research resources, as demonstrated by the authors of this article, provides a strong foundation to allow every laboratory to meet the challenges in the ever-changing landscape of laboratory testing.

Heidi Schimmelbusch, BS, is an Analyst IV at NMS Labs in Horsham, Pennsylvania.
+EMAIL: heidi.schimmelbusch@nmslabs.com

Jonathan DeCenzi, MS, is an Analyst IV at NMS Labs in Willow Grove, Pennsylvania.
+EMAIL: jonathan.decenzi@nmslabs.com

Joseph Homan, MS, is a Senior Scientist III at NMS Labs in Horsham, Pennsylvania.
+EMAIL: joseph.homan@nmslabs.com

BY MICHAEL ASTION, MD, PHD, AND JANE DICKERSON, PHD, DABCC

Laboratory Stewardship Focus: A New Quarterly Section in *Clinical Laboratory News*

LABORATORY STEWARDSHIP FOCUS

Welcome to the inaugural edition of Laboratory Stewardship Focus, a new section of *Clinical Laboratory News* that will appear quarterly. This section follows a successful decade of *CLN* Patient Safety Focus, which ran quarterly from July 2008 to July 2018. Over those years, Patient Safety Focus benefited greatly from contributing authors from institutions across the United States, and covered topics not commonly found in the peer-reviewed or popular laboratory literature. These included neglected areas such as the role of fatigue in errors, the competence-confidence conundrum, apology for errors, response to large-scale lab errors, failure to retrieve results, management approaches to improving a struggling lab, and more. This content remains archived on the AACC website or available by request.

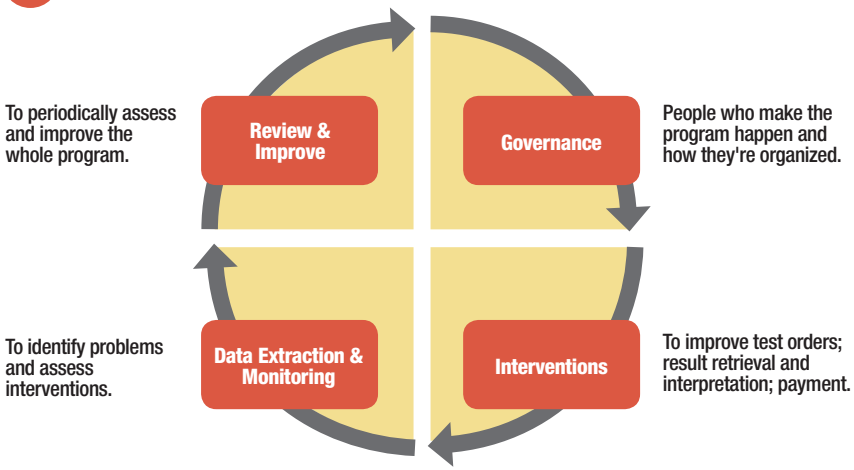
Over the last decade, patient safety has become a mainstream topic. Patient safety programs are embedded in most health systems in the U.S., and most clinical laboratorians have access to copious resources about the nexus between laboratories and patient safety.

At the same time, a new domain in medicine—laboratory stewardship—is growing in importance but still neglected relative to other aspects of laboratory quality. Laboratory stewardship refers to correctly ordering, retrieving, and interpreting laboratory tests. Errors in these three aspects of the total testing process cause most diagnostic errors and the majority of significant patient harm and malpractice litigation in the laboratory industry. In addition, laboratory stewardship encompasses fair payment to labs and reasonable insurance coverage for medically necessary testing for patients. Thus, laboratory stewardship is where patient safety meets financial responsibility. It is where laboratory leaders strive to align with doctors, patients, *and* payers rather than conflict with them.

As shown in Figure 1, the four components of a laboratory stewardship program are: 1) governance, usually through a combination of permanent and ad hoc committees; 2) interventions to improve test ordering, retrieval, interpretation, and payment; 3) data to support all program elements; and 4) methods for periodically assessing and improving the program. In addition, stewardship programs partner with payers to develop evidence-based medical policies and reduce barriers to those policies through reasonable administrative rules that laboratory administrators and the average patient can traverse.

The new *CLN* Laboratory Stewardship Focus is supported by PLUGS (Patient-Centered Utilization Guidance Service), a grassroots organization of 99 member labs—including hospital-based and freestanding, for profit and nonprofit—and

F1 Four elements of laboratory stewardship programs



Dickerson, J et al. Journal of Applied Laboratory Medicine. 2017;2:259-68

multiple sponsors who have created a network to share best practices in laboratory stewardship. PLUGS seeks to improve laboratory stewardship through nurturing this network, and accomplishes this by providing members with tools to stand up stewardship programs, by convening meetings to share best practices, and by forging collaborations directly with payers.

The philosophy of PLUGS is that most healthcare workers come to work to do a great job, whether they labor in a lab, in a clinic, or for a payer. Patients come to care facilities to interact with doctors, nurses, therapists, laboratory workers, and pharmacists. They expect lab services to be evidence-based and a covered benefit by their payer, and they want their laboratory care team to support their health while protecting them financially.

The editors of Laboratory Stewardship Focus welcome you to this experiment in stewardship education. We are a diverse group of editors consisting of a clinical chemist, an informaticist, two pathologists, and a genetic counselor. Our goal is to cover all aspects of laboratory stewardship using a variety of engaging formats including interviews, articles, literature reviews, cases, and more.

Welcome and feel free to submit your ideas for topics to www.seattlechildrenslab.org/plugs or any of the editorial board members.

Michael Astion, MD, PhD, is clinical professor of laboratory medicine at the University of Washington department of laboratory medicine and medical director of the department of laboratories at Seattle Children's Hospital.
+EMAIL: michael.astion@seattlechildrens.org

Jane Dickerson, PhD, DABCC, is clinical assistant professor at the University of Washington and co-director for clinical chemistry at Seattle Children's Hospital in Seattle.
+EMAIL: jane.dickerson@seattlechildrens.org

Why have payers become more interested in laboratory services?

Historically, both commercial and government payers did little to manage laboratory testing because the total cost of testing accounted for so little of their spending—just a few percent. In addition, it was not cost-effective to apply active management practices to lab tests, like requiring preauthorization of services, since most tests have a low cost per unit of service.

Over the last 5–7 years, that has changed significantly. The reasons for active management are shown in the table below. The first trigger for active management of laboratory testing is the growth of high-cost genetic testing, for both inherited disease and for cancer-related genomic profiling. Once tests cost more than $500 per unit of service, the common insurance interventions to prevent misuse—creating and implementing new medical and administrative policies, requiring preauthorizations, and conducting selective post-service reviews—have a solid return on investment for payers, especially if the amount of misuse and abuse is high, which is the case with genetic testing.

A series of studies from multiple healthcare systems has shown that about one-third of genetic testing orders are erroneous, in ways both large and small, and that patients benefit from active management by either payers or labs themselves.

The other roots underlying the growth in active management have a common theme of pushback against overbundling of laboratory tests into panels that are too large, too frequent, or both. This varies from subtle overtesting—for example a five-test celiac panel when two tests suffice more than 90% of the time—to fraud, as has been the case in a variety of urine toxicology schemes currently being litigated.

T1 Factors leading to active management of laboratory tests by payers

• Rapid growth in genetic tests for inherited disease that cost more than $500.
• Rapid growth in genomic profiling of tumors that cost more than $500.
• Fraud and abuse in a variety of areas, most notably urine toxicology testing for managing substance use disorders or chronic pain.
• "Alternative" laboratory testing.
• Overbundling of laboratory tests, for example in the assessment of cardiovascular disease risk or in the assessment of allergy.

References

1. Dickerson JA, Fletcher AH, Procop G, et al. Transforming laboratory utilization review into laboratory stewardship: Guidelines by the PLUGS National Committee for Laboratory Stewardship. J Appl Lab Med 2017;2:259–68.
2. Laposata M. The definition and scope of diagnostic error in the U.S. and how diagnostic error is enabled. J Appl Lab Med 2018;3:128–31.
3. PLUGS. http://www.seattlechildrenslab.org/plugs.aspx. (Accessed November 1, 2018).
4. Dickerson JA, Cole B, Conta JH, et al. Improving the value of costly genetic reference laboratory testing with active utilization management. Arch Pathol Lab Med 2014;138:110–3.
5. Riley JD, Procop GW, Kottke-Marchant K, et al. Improving molecular genetic test utilization through order restriction, test review, and guidance. J Mol Diagn 2015;225–9.
6. Miller CE, Krautscheid P, Baldwin EE, et al. Genetic counselor review of genetic test orders in a reference laboratory reduces unnecessary testing. Am J Med Genet A 2014;164:1094–101.

BY ELISE OCCHIPINTI, MD

Developing Institutional Champions for Laboratory Stewardship

LABORATORY STEWARDSHIP FOCUS

The ever-changing landscape of healthcare delivery has driven laboratorians to bring a value-over-volume mindset to laboratory medicine. Laboratory stewardship refers to systems to ensure the proper ordering, retrieving, and interpreting of laboratory tests. It also encompasses fair payment for labs and fair financial treatment of patients.

Those faced with the daunting mission of overseeing a lab stewardship program look to colleagues in pharmacy, infectious diseases, and radiology for guidance. Successful hospitals have pharmacy formularies, antibiotic stewardship programs, and imaging guidance programs, all of which can lead to the false assumption that laboratory stewardship should easily follow suit.

Our experience has proven otherwise due to pervasive misconceptions about laboratory costs, test indications, and order frequency. We were only able to set the foundation for a successful laboratory stewardship program by engaging administrative, technologic, and physician champions at various points in our program's evolution.

Administrative Champions: The C-Suite

A sure way to the heart of the executive-level C-suite is through improved financials. This can be a challenge for lab leaders since laboratory testing comprises merely 2.5% of direct healthcare costs, and the downstream effect of inappropriate utilization is often difficult to measure.

We garnered support of top leaders by accumulating small wins and objectively showcasing their cumulative effect. One example involves reducing inpatient duplicate testing. This is a direct cost avoidance that we hardwired into computerized provider order entry (CPOE). The savings are concrete, easy to monitor, and grow continuously. In our institution we demonstrated an average test avoidance of 1,400 per month, which translated into $21,000 in monthly institutional cost avoidance. This raised some eyebrows.

Around the same time, our infection control department was struggling with an increase in catheter associated urinary tract infections (CAUTI), a publicly reported parameter that affects Centers for Medicare and Medicaid Services quality ratings and subsequent reimbursement from government payors. We aligned our lab utilization committee with infection control goals for CAUTI by optimizing urine culture orders via a reflex testing algorithm.

These are just two examples of how a laboratory can align with an institutional mission of value-based care and mitigate some of the effects of capitated payments. Collaborations like this helped us gain administrative champions who now regard our lab as a proactive ally in optimizing our health system's financial fitness.

Technologic Champions: IT Resources

Information technology (IT) cooperation is a requirement for stewardship success because 87% of office-based physicians use an electronic health record (EHR) for test ordering and retrieval. Unfortunately, limited IT resources are a common and formidable obstacle in implementing a lab stewardship program.

Our approach was to take advantage of the lab's and IT's shared love of data, which we used to symbiotic advantage. We showcased this in our blood utilization program. The transfusion medicine team paired with a core group of IT analysts to extract complete blood count and coagulation data from the EHR to provide decision support at the point of order.

Not only did we demonstrate cost savings averaging $63,000 per month, but we also established a strong level of trust and shared accomplishment with our IT colleagues as they realized how their services actively improve patient care by reducing unnecessary transfusions. We are now able to extract monthly utilization reports that allow us to target individual providers and services in need of education and other interventions. This has set the stage for strong lab and IT integration on future data capture projects involving population health, order set optimization, and provider efficiency.

Physician Champions: Collaboration and Engagement

When some physicians hear the term laboratory stewardship, they fear loss of autonomy and onerous restrictions that save money at the expense of diagnostic accuracy. We experienced this throughout our campaign to reduce non-diagnostic peripheral blood flow cytometry.

Our pathologists noticed that specimens were saturating the flow cytometry lab, delaying emergent cases, and providing a false sense of "no disease" while also increasing patients' laboratory charges. We discussed this with a core group of oncologists with whom we had already established a foundation of trust via case collaboration. We reinforced our patient-centered focus via a retrospective review of more than 200 cases that highlighted flow cytometry results that were either misleading or not diagnostic.

The data were compelling enough to convince the oncologists to ally with hematopathology in establishing a series of evidence-based criteria for peripheral blood flow cytometry. The first rollout of this initiative involved an educational intervention. Predictably, this had little effect since inappropriate utilization is not solely due to lack of knowledge, but rather is often driven by a need for provider efficiency, patient convenience, or fear of litigation.

We tackled these concerns in two ways. First, at the time of order cancelation we offered alternative diagnostic testing such as peripheral smear review or targeted molecular studies (i.e. when a myeloproliferative disorder was a concern). Second, we hardwired the flow cytometry criteria into CPOE so that it requires acknowledgement at the point of order and prompts clinicians to state a diagnostic concern if criteria are not met. The goal is to encourage physicians to consider the capabilities of the test and discuss this with their patients prior to phlebotomy.

Last year we canceled more than 300 flow cytometry orders with no deleterious effects on patient care. However, our task remains as we hire new physicians and form partnerships with established hospital systems that use our laboratory services. It is impossible to please everyone, so we continue to have uncomfortable conversations explaining how interventions that inconvenience one provider enhance the sustainability of the system in which we all work. Lab leaders could not do this without the oncologists who support our efforts in their system-wide departmental meetings and in our utilization committee.

Most importantly, our oncology champions educated laboratorians to be empathetic toward a physician who cannot always focus on the "good of the system" when faced with a unique patient scenario.

Implementing a laboratory stewardship program is very challenging. Developing champions in administration, IT, and among our physician colleagues is foundational to success and has benefits far beyond the laboratory stewardship program.

Keys to Developing Institutional Champions for Laboratory Stewardship

- Focus on hard dollar savings, such as reduced expenses for supplies and blood products.
- Avoid basing justification on soft savings like saving time.
- Align laboratory stewardship initiatives with major hospital initiatives in high-visibility areas such as infection control and cancer treatment.
- Empathize with physician champions and acknowledge the frustrations they face in practicing medicine in the current burdensome environment.
- Connect IT staff to the patient experience, especially when collaborating on changes that improve safety and reduce suffering.

Elise Occhipinti, MD, is the laboratory medicine director at Ochsner Medical Center in New Orleans.
+EMAIL: eocchipinti@ochsner.org

Regulatory Roundup

FDA Announces Participants in Innovation Challenge to Combat the Opioid Epidemic

As part of the Food and Drug Administration's (FDA) efforts to deal with the opioid crisis, the agency launched an innovation challenge on May 31, 2018, to spur the development of medical devices, including diagnostic tests, that could help prevent and treat opioid use disorder. The innovation challenge's call for applications drew more than 250 submissions from medical device developers. From this pool, FDA has now selected eight challenge participants who will work directly with the agency to accelerate the development and marketing application review of their products. Two of the challenge participants are working on diagnostic tests: The company Milliman is developing a test intended to predict the risk of opioid use disorder called Opioid Prediction Service, while Algomet Rx submitted a test for opioid use monitoring called Rapid Drug Screen. As part of the challenge's next steps, FDA and these companies will collaborate to define the patient and user needs for these devices, as well as the important risks and benefits, and will discuss the potential regulatory pathways going forward.

MERIDIAN BIOSCIENCE RECEIVES FDA AUTHORIZATION FOR NEWBORN CMV TEST

The Food and Drug Administration (FDA) has granted Meridian Bioscience marketing authorization for the Alethia CMV assay test system, making this the first FDA-authorized test designed to aid in diagnosing cytomegalovirus (CMV) infection in newborns less than 21 days of age. The Alethia test detects CMV DNA from a saliva swab. Data from a prospective clinical study involving 1,483 saliva samples collected from newborns showed that the test correctly identified 1,472 out of 1,475 samples as negative for the presence of CMV DNA and correctly identified five specimens as positive. The test incorrectly identified three samples as positive

when they were negative. As part of FDA's evaluation of the test, the agency also reviewed data from a study using 34 samples of archived specimens from babies known to be infected with CMV in which the Alethia correctly identified all specimens as positive. FDA reviewed the test through the de novo premarket review pathway.

PIXCELL MEDICAL GETS FDA OK FOR POINT-OF-CARE HEMATOLOGY ANALYZER

The Food and Drug Administration has cleared PixCell Medical's HemoScreen, a miniature portable hematology analyzer that uses disposable cartridges to perform a complete blood count (CBC). Each cartridge the device uses includes all necessary reagents and is designed to work with a drop of blood collected via fingerstick. According to PixCell, operation of the device requires minimal training and expertise, and also does not necessitate maintenance or calibration. Once a cartridge is inserted into the reader, the blood sample is automatically processed, with the HemoScreen analyzing 20 standard CBC parameters within 5 minutes, including red blood cell (RBC) count, RBC indices, absolute white blood cell (WBC) count, and WBC 5-part differential, as well as hemoglobin and platelet parameters. The device employs patented technology based on microfluidics, machine vision, and artificial intelligence. It also uses imaging flow cytometry, which involves flow focusing cells into a single-layer plane within a microfluidic chamber and then analyzing their images.

FDA GRANTS EMERGENCY USE AUTHORIZATION FOR FINGERSTICK EBOLA TEST

Chembio Diagnostic Systems has received emergency use authorization (EUA) from the Food and Drug Administration for a rapid, single-use test for the Ebola virus that is intended for use in locations where healthcare providers do not have access to standard nucleic acid tests. This is the second Ebola rapid antigen fingerstick test made available under EUA, and the first that uses a portable battery-operated reader, which is designed to help provide clear diagnostic results outside of the lab. The test, called the DPP Ebola Antigen system, is intended for use with blood specimens from individuals with signs and symptoms of Ebola virus disease in addition to other risk factors, such as living in an area with a large number of Ebola cases and/or having contact with other individuals exhibiting signs and symptoms of Ebola virus disease. Specifically, the test is authorized for use with capillary fingerstick whole blood, EDTA venous whole blood, and EDTA plasma.

CERTAIN TEST STRIPS FOR ROCHE'S COAGUCHEK MAY PROVIDE INACCURATE RESULTS, FDA WARNS

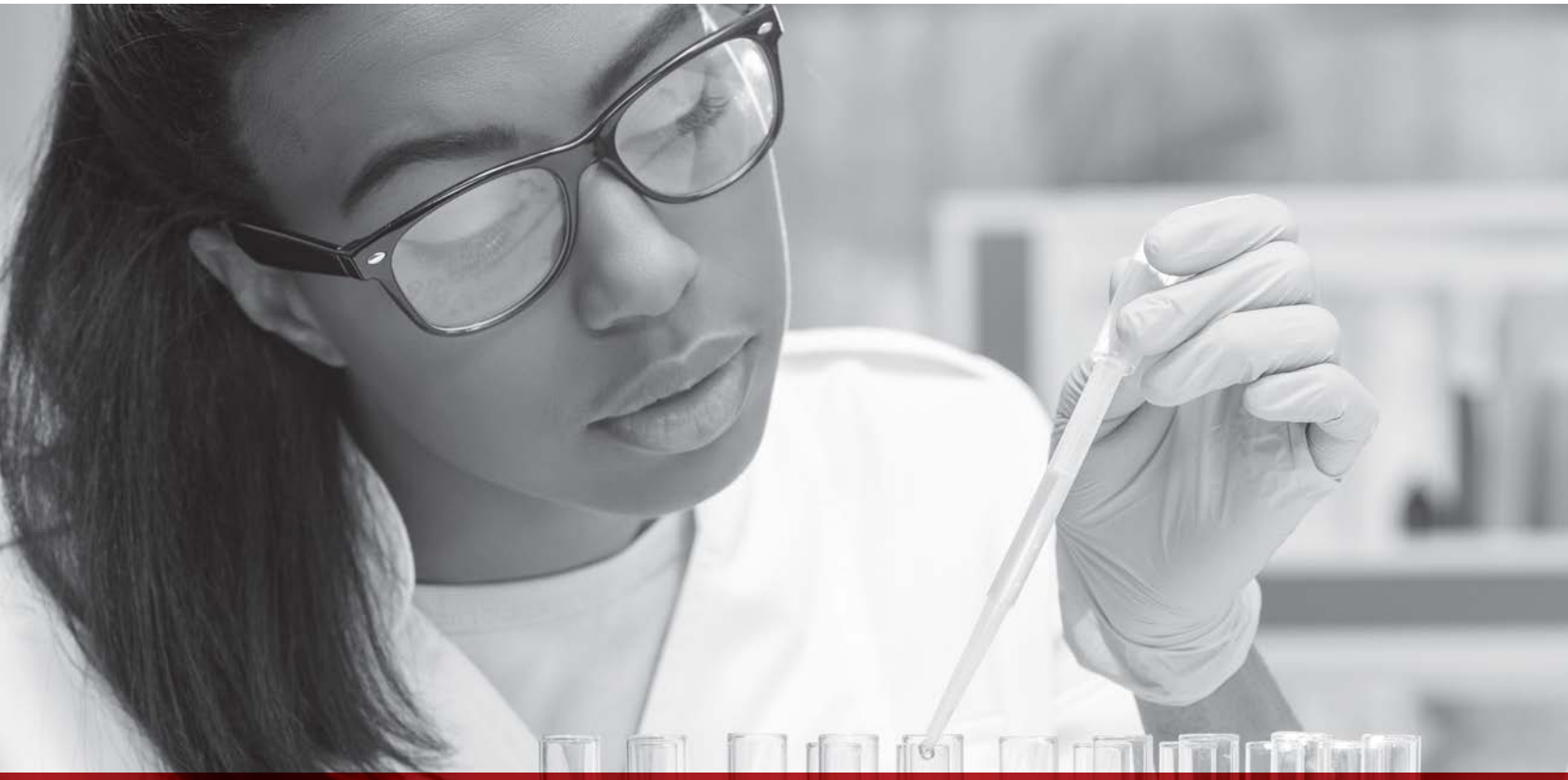
The Food and Drug Administration (FDA) has issued a warning that, when used with certain test strips, Roche Diagnostics' point-of-care CoaguChek test meter devices may provide inaccurate results and should not be relied upon to adjust warfarin dosages. This warning comes in the wake of Roche issuing a voluntary recall of more than 1.1 million packages of CoaguChek XS PT test strips that were distributed nationwide between January 12 and October 29, 2018. Medical device reports submitted by Roche to FDA indicate that the test strips may provide an international normalized ratio result that is higher than the true value. Roche attributed this problem to the fact that the company recalibrated the test strips to a different international standard earlier in 2018. To remedy this issue, Roche recalibrated the test strips again and as of October 29, 2018, began shipping new, FDA-reviewed batches of the strips to healthcare and patient self-testing service providers.

iStock.com / MarkHatfield

FDA DRAFT GUIDANCE UPDATES RECOMMENDATIONS FOR BLOOD GLUCOSE MONITORS

The Food and Drug Administration (FDA) has released two new draft documents intended to guide manufacturers preparing 510(k) submissions for blood glucose monitoring test systems: "Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use" and "Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use." When finalized, these documents will replace the two guidance documents issued under the same titles in 2016. This new draft guidance provides FDA's updated recommendations regarding the studies and information that manufacturers should use when submitting premarket notifications for blood glucose monitors intended for use by healthcare professionals in clinical settings, as well as for monitors intended for use by diabetes patients as an aid in managing their condition. The agency is seeking comments on both draft documents until February 28, 2019. Comments may be submitted at www.regulations.gov.

AACC PROFESSIONAL PRACTICE IN CLINICAL CHEMISTRY



The Clinical Laboratorian: Critical Member of the Healthcare Team

April 25-27, 2019 · Dallas, TX

Register today to gain essential knowledge and practical skills to advance your career in laboratory medicine.

Topics Include:

> Quality Management
> Introduction of Informatics
> Methodology/Techniques Used in Clinical Chemistry
> Pathophysiology of Cardiovascular Disease
> Functions and Diseases of Abdominal Organs
> Clinical Pathology and Laboratory Evaluation of Disease

KEYNOTE SPEAKER
Michael Laposata, MD, PhD
Professor and Chairman, Department of Pathology
University of Texas Medical Branch
Galveston, TX

Preparation materials will be provided online prior to the meeting.

COMMITTEE MEMBERS
Octavia Peck Palmer, PhD (Co-Chair)
Tiffany K. Roberts, PhD (Co-Chair)
Kamisha Johnson-Davis, PhD
Brenda B. Suh-Lailam, PhD

Learn more at **www.aacc.org/PPCC2019**

AACC *Better health through laboratory medicine.*

Industry Playbook

Mount Sinai, AllerGenis Team on Food Allergy Precision Diagnostics

Mount Sinai Health System in New York City is partnering with AllerGenis to develop and commercialize technology for improved food allergy detection. Through this collaboration, Mount Sinai has licensed its proprietary epitope mapping platform to AllerGenis. AllerGenis will initially use this platform to develop a precision diagnostics peanut allergy assay, which it plans to make available in the fall of 2019, followed by a pipeline of assays for other common food allergies including milk, egg, shellfish, and tree nuts.

The epitope mapping platform is based on immunologic research conducted by the Elliot and Roslyn Jaffe Food Allergy Institute at the Icahn School of Medicine at Mount Sinai. The platform subdivides protein allergens into smaller peptides, called epitopes, and measures the reactivity of a patient's antibody levels to these epitopes, generating a unique epitope reactivity signature for each patient. AllerGenis is curating a growing database of human epitope signatures that providers will be able to use in tandem with the tests AllerGenis is developing to assess and manage patients with food allergies.

"AllerGenis' diagnostic technology, using epitope mapping, is expected to expand our ability to accurately diagnose patients with food allergies and, at the same time, should markedly decrease misdiagnosis," said Hugh Sampson, MD, director emeritus of the Elliot and Roslyn Jaffe Food Allergy Institute. "Moreover, it should greatly narrow down the number of people who would have to submit to an oral food challenge, which can potentially be extremely risky for food allergy patients."

ILLUMINA TO BUY PACIFIC BIOSCIENCES

Illumina has entered an agreement to acquire Pacific Biosciences for its long-read sequencing capabilities at a price of $8 per share in an all-cash transaction. While Illumina's short-read sequencing platforms can be used for the majority of sequencing applications, select applications such as de novo sequencing and sequencing of highly homologous regions of genomes are better addressed with accurate long-reads. With its acquisition of Pacific Biosciences, Illumina expects to provide integrated workflows that bring together the best of both technologies. "Combining the two technologies positions us to … accelerate the pace of genomic discovery and bolster our innovation engine which has been a hallmark of Illumina since our inception," said Francis deSouza, president and CEO of Illumina. "[Pacific Bioscience's] relentless pursuit to improve sequencing accuracy, while driving down the cost, underscores the potential of long-reads to expand sequencing to new customers and applications."

UF, KING'S COLLEGE JOIN FORCES ON TYPE 1 DIABETES BIOMARKER DISCOVERY

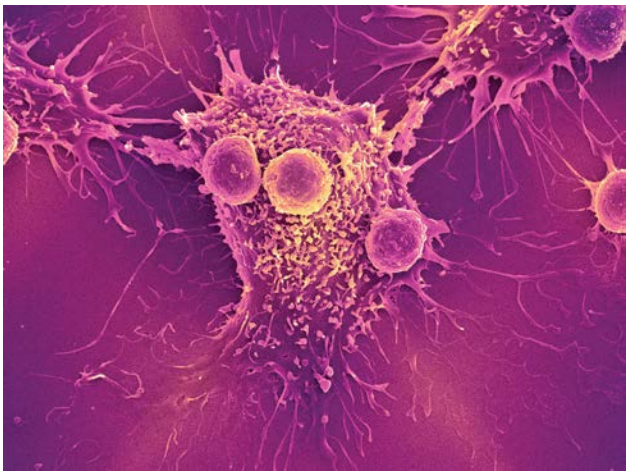
A collaboration between the University of Florida and King's College London in the U.K. has received $3.7 million in support from Adaptive Biotechnologies and the Leona M. and Harry B. Helmsley Charitable Trust to discover molecular biomarkers of type 1 diabetes. The partners will use Adaptive Biotechnologies' genetic sequencing platform to determine the molecular signatures of T-cell receptors, with the aim of identifying the rogue T-cells that destroy insulin-producing beta cells in the pancreas. The University of Oslo in Norway will also contribute its computer algorithms and machine learning approaches for data analysis. The collaboration anticipates that this research will enable the development of a test that predicts who will develop type 1 diabetes and that tracks the disease's progression even before symptoms emerge. This work could

also lead to a test that assesses whether type 1 diabetes treatments targeting the immune system are effective.

JANSSEN TO USE PROTEOMICS INTERNATIONAL TEST TO ASSESS PATIENT RESPONSE TO DIABETES DRUG

Janssen Research and Development and Proteomics International Laboratories have joined forces to advance diabetic kidney disease drug discovery. Under the terms of their agreement, the two companies will conduct a study using Proteomics International's PromarkerD test as an early predictor of kidney function in patients who took part in Janssen's clinical trials for a drug of the gliflozin class that helps lower blood glucose in adults with diabetes. The study will assess how the PromarkerD score correlates with drug response in patients with diabetic kidney disease. "Gliflozin drugs could be hugely beneficial in improving patient outcomes from diabetes complications, and we look forward to determining whether PromarkerD can help in assessing responses to this treatment," said Richard Lipscombe, PhD, managing director of Proteomics International.

The collaboration will also evaluate how PromarkerD performs in predicting heart disease, another major diabetes complication. Diagnosis of cardiovascular disease would be a new application for PromarkerD.



Steve Gschmeissner / Science Photo Library

1CELLBIO, OMI TO HARNESS SINGLE-CELL RNA SEQUENCING FOR PRECISION MEDICINE

1CellBio and the Open Medicine Institute (OMI) have teamed to investigate the potential use of single-cell RNA sequencing (scRNA-seq) technology in precision medicine applications. Under the terms of this collaboration, OMI will validate 1CellBio's inDrop System as part of a clinical research project that will initially focus on generating predictive data for patients with an undiagnosed immune dysfunction condition. Researchers at OMI will aim to identify putative biomarkers of this condition and to demonstrate how an integrated omics approach improves sensitivity, accuracy, and specificity of complex immune disease diagnosis, in addition to potentially guiding therapeutic decision-making. The study will also use machine learning and additional big data analysis techniques to identify clinically relevant patterns of gene expression in single cells, as well as relationships between disparate omic data types and single-cell expression patterns. Following this pilot project, the two organizations will explore the production of a scRNA-seq-based laboratory-developed test that OMI will offer through its CLIA-certified laboratory.

QIAGEN, NEOGENOMICS TEAM TO SPEED AVAILABILITY OF CANCER CO-DIAGNOSTICS

Qiagen and NeoGenomics are collaborating in an effort to accelerate the availability of companion diagnostics for cancer therapeutics. Building on the Food and Drug Administration's modernized regulatory approach to advanced diagnostics such as next-generation sequencing tests, NeoGenomics will work with Qiagen and its pharmaceutical partners to streamline the synchronized development and launch of targeted drugs and their associated companion diagnostics. As part of this initiative, Qiagen and its partners will provide investigational use only tests to NeoGenomics and other labs, enabling them to verify, set up, and run these companion diagnostics in clinical trials and in anticipation of regulatory approval. "As a leading provider of oncology testing for both clinical trials and patient care, NeoGenomics is uniquely positioned to assist pharmaceutical and biotech companies to develop and commercialize companion diagnostic tests," said Douglas M. VanOort, chairman and CEO of NeoGenomics. "Our collaboration with Qiagen will ensure that patients have access to the most advanced companion diagnostics to target new cancer medicines, as soon as those medicines are approved."

Index to Advertisers

AACC Announces NEW Point-of-Care Testing Professional Certification (CPP)

The exam tests mastery and knowledge of:

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

Applicants must have a four-year degree in a biological or physical science and at least two years' documented experience in point-of-care testing.

JANUARY 14–APRIL 1, 2019: Submit your application to take the exam

MAY 31–JUNE 7, 2019: Sit for the online exam to become a CPP

Submit your application in 2019

Learn more at www.aacc.org/CPP

AACC

Better health through laboratory medicine.

Ask The Expert

Chain of Custody for Urine Drugs of Abuse Testing

EXPERT
Amitava Dasgupta, PhD, DABCC

What is chain of custody?

A: Chain of custody is the movement and location of physical evidence from the time it is obtained until the time it is presented in court, and is used to prove the integrity of a piece of evidence. In order to track chain of custody, a paper trail is maintained so that personnel in possession of the evidence at different times can be identified easily and subpoenaed to testify during trial if needed.

For urine drugs of abuse testing in particular, it is important that the donor identify the specimen and that the urine cup is sealed in front of the donor, followed by the person who collected the specimen signing the chain of custody forms. (In the case of an unconscious patient in the emergency room, the nurse collecting the urine specimen can identify it in the patient's place.) An example of what might happen next is as follows:

Police sergeant A seizes the urine sample collected from the defendant, and police officer B transports the specimen to a crime lab. At the crime lab, staff member C receives the urine specimen and scientist D analyzes it, detecting the presence of benzoylecgonine, the inactive metabolite of cocaine, using gas chromatography-mass spectrometry (GC/MS). Scientist D gives the result to senior scientist E of the crime lab, who confirms the result. A, B, C, D, and E would all need to sign the chain of custody forms, and the prosecution would need to offer testimony by each person in the chain to identify and establish the condition of the evidence showing that the defendant abused cocaine.

Is chain of custody used in both medical and legal drug testing?

A medical urine drug test is conducted when a patient suspected of overdosing is admitted to the emergency department, but this individual has not been involved in an accident or another situation in which he or she could be prosecuted if a drug test were to come back positive. Usually, urine drug screens conducted during medical drug testing are performed using immunoassays. Confirmation using a different analytical method such as GC/MS or liquid chromatography tandem-MS might not be conducted unless the ordering clinician requests it. The result of a positive urine drug screen during medical drug testing is confidential information and cannot be used against the patient for any punitive action, such as reporting the result to his or her employer. Therefore, chain of custody is not needed during medical drug testing.

For urine drugs of abuse testing in particular, it is important that the donor identify the specimen and that the urine cup is sealed in front of the donor.

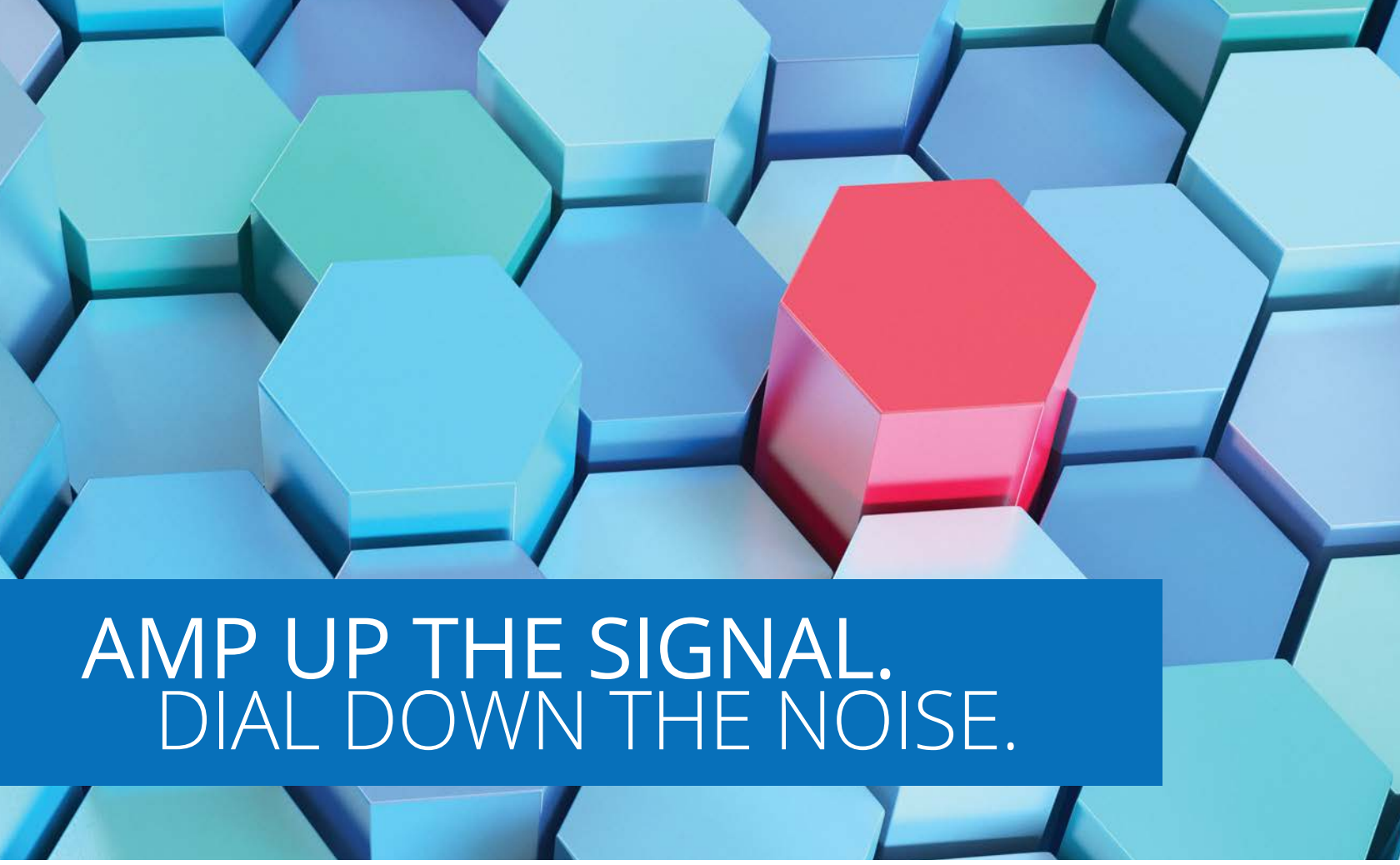
In contrast, confirmation of an initial positive immunoassay result is mandatory during legal drug testing because the result may be presented in court as evidence against the defendant. In these cases, chain of custody is essential.

Chain of custody is also used for newborn drugs of abuse screening, which falls under the category of legal drug testing. Usually, consent is obtained from the mother to conduct this testing. If the mother does not provide consent, however, the hospital legal team must be involved to see if a court order for drug testing of the newborn is necessary.

What about in the case of medical alcohol testing?

Although headspace GC is the standard method for legal alcohol testing, medical testing results for serum alcohol level are sometimes used as evidence to prosecute individuals charged with driving while impaired. However, chain of custody is not maintained in medical alcohol testing and it is up to the judge overseeing the case to decide whether such results can be admitted in a court of law. In these cases, defense teams typically argue that medical alcohol testing results are not acceptable because there was no chain of custody. In such situations, a laboratory scientist should simply confirm that the specimen was not collected following chain of custody and let the prosecution pick up the battle.

Amitava Dasgupta, PhD, DABCC, is a professor of pathology and laboratory medicine at the University of Texas McGovern Medical School in Houston.
+E-MAIL: Amitava.Dasgupta@uth.tmc.edu



AMP UP THE SIGNAL.
DIAL DOWN THE NOISE.

Experience Remarkable Performance

Surmodics IVD sets the bar high with assay components that significantly enhance signal and minimize noise. Our broad portfolio of proven immunoassay and POC solutions improve the performance of a wide range of diagnostic tests, and our skilled scientists can help you specify the right products for your particular needs.

In the end, our goal is your goal: **ensuring accurate and reliable results every time, for every patient.**

PROTEIN STABILIZERS/
BLOCKERS

BIOFX® SUBSTRATES/
STOP REAGENTS

TRIDIA™ SURFACE
COATINGS

DIARECT™
ANTIGENS

DILUENTS/IHC
REAGENTS/BUFFERS

SURMODICS IVD FOR ASSAY SUCCESS.

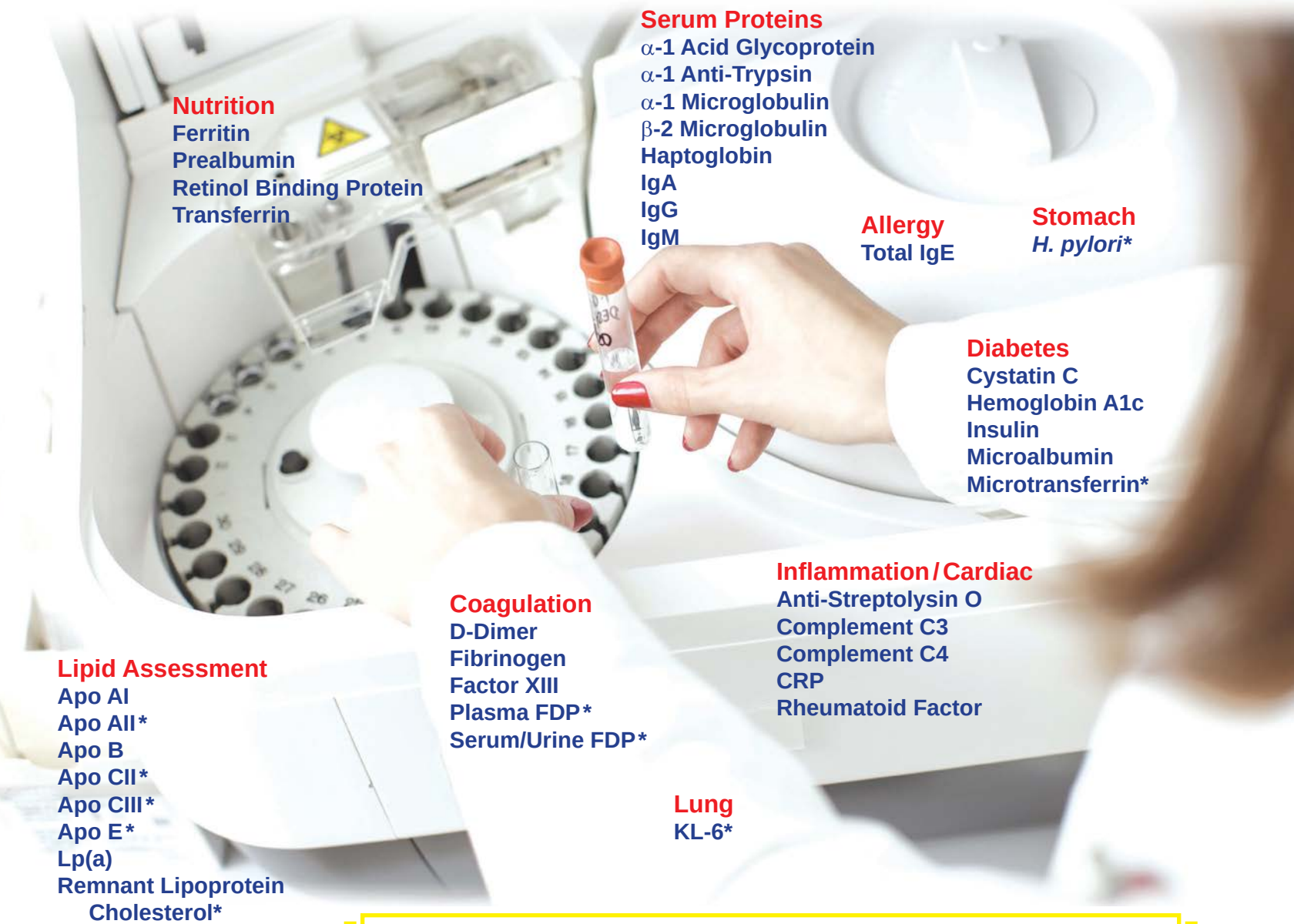
For more information or samples, contact orders@surmodics.com.
952-500-7200 | www.surmodics.com/ivd

SURMODICS

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

Immunoassay Reagents for chemistry analyzers™

Over 37 different assays available



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

Nutrition
Ferritin
Prealbumin
Retinol Binding Protein
Transferrin

Allergy
Total IgE

Stomach
*H. pylori**

Diabetes
Cystatin C
Hemoglobin A1c
Insulin
Microalbumin
Microtransferrin*

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

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

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

Lung
KL-6*

New Products Now Available!!

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

* Research Use Only

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