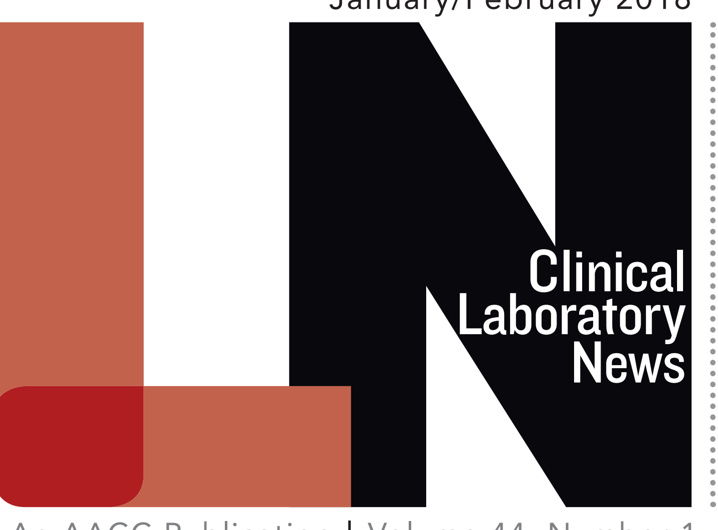
January/February 2018



Clinical Laboratory News

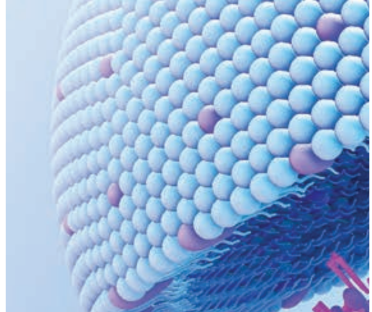
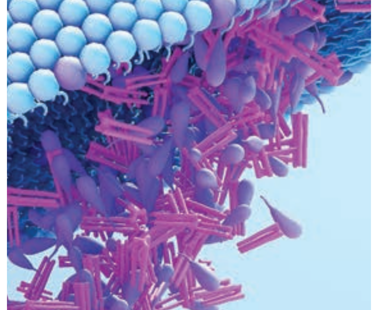
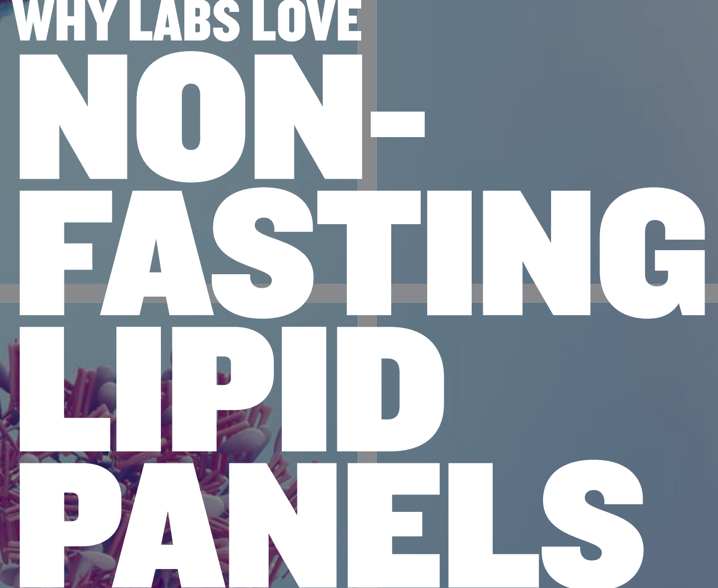
An AACC Publication | Volume 44, Number 1

CONTINUOUS QUALITY IMPROVEMENT

43%

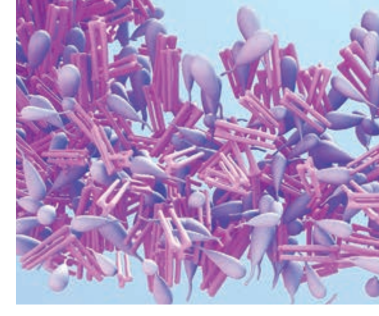
Drop in labor costs for an assay after implementing a new method and QC strategy

PAGE 4

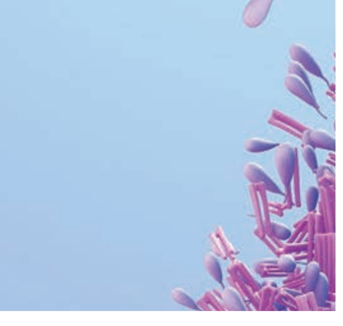
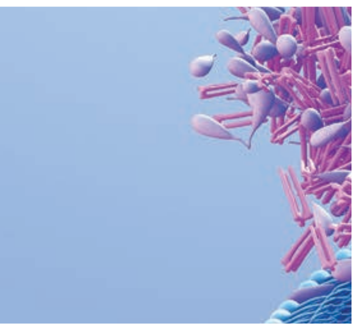
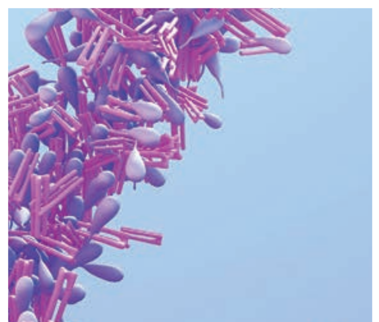
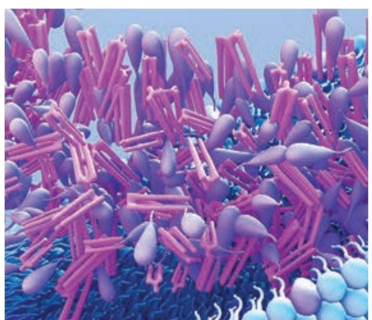
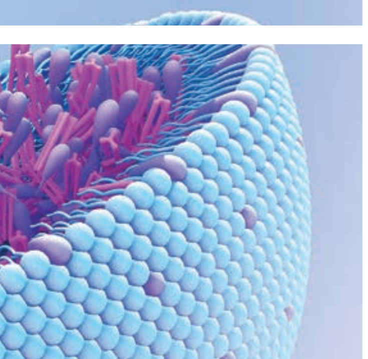




WHY LABS LOVE NON-FASTING LIPID PANELS

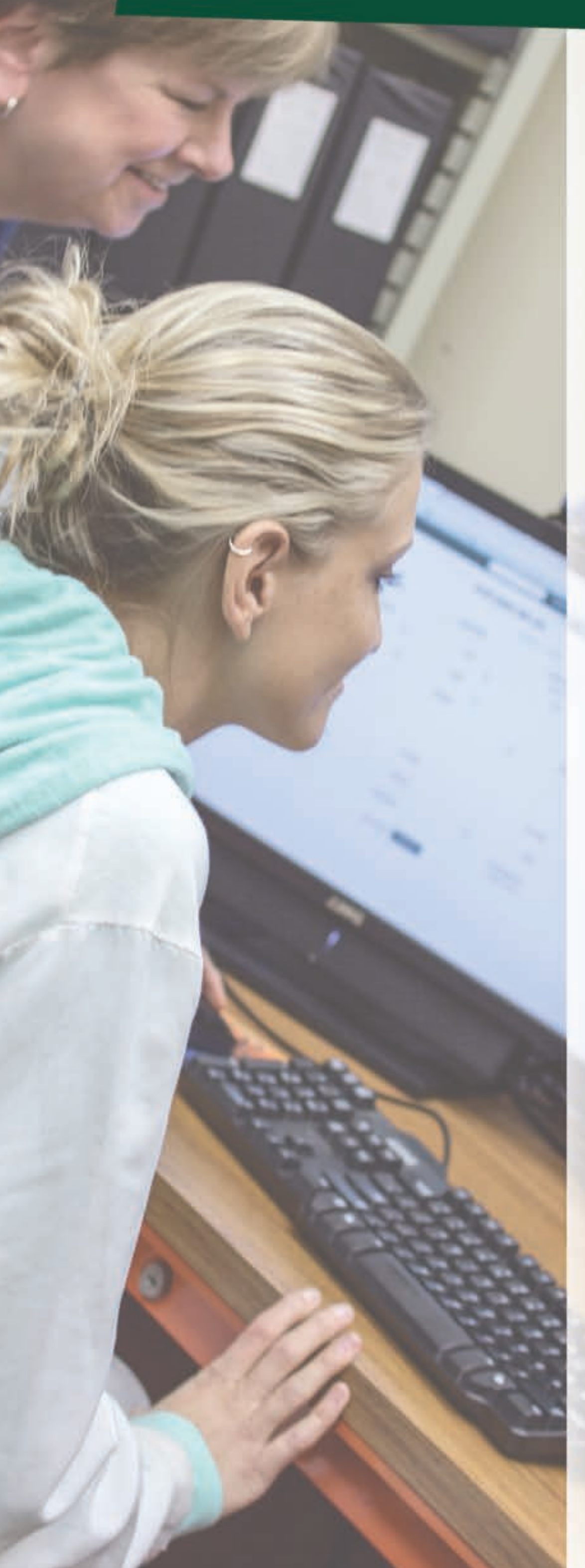
Docs Get Hooked on Drug Testing



The Safe But Unsatisfied Patient

Better health through laboratory medicine.



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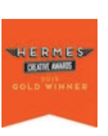

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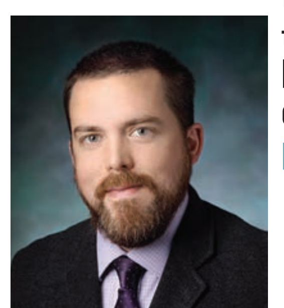
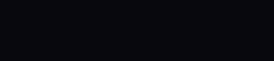


miRNA-based diagnostics are finally entering the clinic...However, these kinds of tests are likely best suited to a companion role.
p36



Federal Insider

FDA, Congress Return Attention to Direct-to-Consumer Genetic Testing

Five years after a crackdown on direct-to-consumer (DTC) genetic testing companies that in 2013 temporarily shut down Google-backed 23andMe in the U.S., the Food and Drug Administration (FDA) is now finalizing a plan to speed regulatory approval of DTC genetic testing that could help fuel a testing boom. The agency is building on its approval of 23andMe's carrier screening test for Bloom syndrome in 2015 and 10 genetic health risk assessment tests in April 2017 that included late-onset Alzheimer's and Parkinson's disease.

However, at the same time that FDA is opting for a lighter touch on DTC genetic testing services, these companies have caught the eye of leaders in Congress. Senate Minority Leader Chuck Schumer (D-NY) has called on the Federal Trade Commission to investigate the privacy policies of DTC companies and ensure that they have "clear, fair privacy policies and standards." He emphasized that some companies have included in their consent agreements permission to share data with third parties.

The senator's comments came after FDA issued a final notice classifying what it calls genetic health risk assessment tests as class II devices. Importantly, FDA now feels confident in expanding this approval to all comers after a one-time, per-company checkup. "The accelerated development of these innovative DTC genetic risk tests paired with the known safety considerations presents unique challenges to FDA regulation, as these technologies don't fit squarely into our traditional risk-based approach to device regulation," said FDA Commissioner Scott Gottlieb, MD, in a statement. Under FDA's new approach, after companies obtain clearance for a genetic health risk assessment test system they will be able to offer new tests directly to consumers without notifying the agency. FDA does spell out, however, detailed requirements for how companies must educate consumers about the benefits and risks of testing, what test results mean, and how to seek the help of a genetic counselor.

The interest in DTC genetic testing comes at a time when companies are expanding sales beyond the niche market in which they began. A discounted kit from 23andMe for health and ancestry testing was in the top five best-selling items from Amazon on Black Friday during the 2017 holiday shopping season, just behind a Wi-Fi smart plug and the Instant Pot pressure cooker. 23andMe, Ancestry, and more than a dozen other companies all sell test kits on Amazon.

WORK REQUIREMENTS COULD SHRINK MEDICAID ROLLS

States will now be free to impose work requirements on Medicaid enrollees, a policy shift intended to move Medicaid away from being an open-ended entitlement program that benefits able-bodied adults, according to Centers for Medicare and Medicaid Services (CMS) Administrator Seema Verma.

In a speech to state Medicaid directors, Verma said the Trump administration views Medicaid as a program that should help able-bodied adults "move on and move out." Verma also announced that CMS will create the first-ever scorecards that will track state and federal Medicaid spending.

Critics say the administration aims to shrink the Medicaid program. According to the National Health Law Program, a legal health advocacy group for low-income and underserved groups, the new policies would "roll back significant progress" in expanding access to Medicaid. For example, Wisconsin has submitted a proposal to put a 4-year limit on benefits and charge premiums and copays to enrollees who earn between 50-100% of the federal poverty level. Other states are considering requiring drug testing, lifetime limits, and lockout periods when enrollees miss premium payments or commit other infractions.

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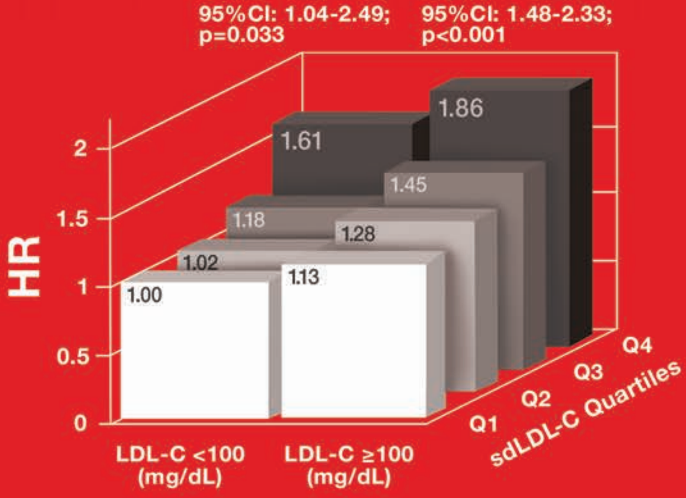
Cardiovascular Disease Prediction by Small Dense LDL Cholesterol

Fully automated assay to quantify small dense LDL cholesterol cleared by US FDA

Small dense LDL can help identifying patients at a higher risk for cardiovascular disease and serve for a better management of the risk, especially for whom LDL cholesterol is moderately low.



Adjusted hazard ratios for incident coronary heart disease consisting of myocardial infarction, coronary heart disease death and revascularization by small dense LDL cholesterol (sdLDL-C) quartiles stratified by LDL-C risk categories. Adjusted for age, sex, and race, smoking, body mass index, hypertension, diabetes mellitus, diabetes mellitus medications, and log high-sensitivity C-reactive protein. CI indicates confidence interval (adapted from Hoogeveen et al. Arterioscler Thromb Vasc Biol. 2014;34:1069-1077 with approval).

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Quality Quotient

A post-mortem analysis of a multiyear quality improvement project

Many clinical labs now are incorporating a continual quality improvement philosophy into their quality management systems, as part of an important evolution away from a reactive problem-solving approach. Ours is no exception, and we hope our experience in analyzing a multiyear initiative will inform and inspire others embarking on this new approach.*

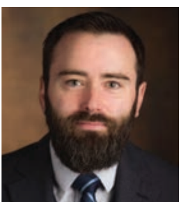
The lab medicine community knows well the concepts, standardized processes, and guiding documents like ISO 15189 and CLSI-QMS01 involved in assessing quality. Labs implement quality measures to produce accurate and precise results and to identify problems during the analytical phase of testing. We fulfill our quality assessment and assurance requirements by establishing quality control (QC) metrics and enrolling in proficiency testing (PT) programs. However, simply monitoring QC doesn't necessarily lead to improvements, especially if labs set quality thresholds simply to meet regulatory requirements.

In contrast, effectively utilizing quality metrics may expose other weaknesses in a laboratory process. When assessing and looking for potential quality improvements for a particular assay, asking three key questions may help bring process limitations to the surface: Do I have the necessary rules in place to achieve sufficient analytical quality assurance for this assay? How much effort does it take to maintain the desired level of test result accuracy and quality? Can we maintain this level if our testing volume increases or we experience a significant change in staffing?

In some scenarios, reducing testing process inefficiencies necessitates improving instrumentation reliability by switching to newer, more reliable platforms and undergoing method improvements aimed at better precision and throughput. Standardizing troubleshooting practices also may reduce run-to-result time variability, which helps improve process consistency. In order to maintain the necessary analytical quality assurance, gurus at Westgard QC advise tailoring an appropriate set of QC multirules. These subsequently may guide troubleshooting practices to reach resolutions faster and independently of users' expertise. Once the finalized plan for improvements is in place, committing to change requires a lot of effort and trust that the change is beneficial to a lab.

*At the time referenced, Dr. Strathmann was employed at ARUP Laboratories.

Valentinas Gruzdys, PhD


Frederick G. Strathmann, PhD, DABCC (CC, TC)

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CASE STUDY LOOK BACK

Our trace and toxic element testing lab, like other labs across the country, is seeing downstream benefits from adopting a proactive strategy that attempts to anticipate future problems associated with lab performance, PT, and accuracy of test results. In our case this involved not only implementing a QC initiative but also going back afterward to assess how

the changes we made affected our lab and whether they were successful.

We carried out a lab quality assessment and focused our efforts on a multi-element urine assay that had higher than desired variability. Routine QC analysis showed the assay's average imprecision coefficient of variation (CV) was 7.5% and exceeded 15% for outlier analytes. Our root cause analysis suggested we needed to take a closer look at the total testing process with a detailed process map. This proved to be illuminating as we documented long and variable run times of 7±6 minutes per sample. We attributed this in part to older and less reliable instrumentation that used inductively-coupled plasma mass spectrometry (ICP-MS) analysis. Troubleshooting for this ICP-MS process often was cumbersome because staff lacked standardized instructions on specific troubleshooting steps and relied on their individual experience to look for solutions to assay problems.

Our improvement efforts included implementing updated instrumentation using the same ICP-MS methodology, redeveloping our analytical method, instigating a robust QC strategy, and installing software that integrated best practices for QC monitoring and troubleshooting. We sought to improve analytical performance, efficiency, and throughput.

Within 2 months we carried out a post-implementation assessment of this initiative as part of our continual improvement efforts and found our changes had yielded substantial productivity gains. In particular, thanks to an approximate 75% reduction in troubleshooting and markedly shorter analytical run times of 5±1.8 minutes per sample, our capacity rose and we were able to efficiently handle greater testing volume without increasing the lab's footprint.

The drop in troubleshooting time—especially by advanced staff trained in this process—reduced our labor costs for this assay by an estimated 43%. The new method also demonstrated reduced imprecision and bias with an average CV of 4.4%, and <12% for most outlier analytes.

As often occurs with operational changes, new bottlenecks emerge once old ones clear. In this case, during the early stages of implementing our new method we identified an area for improvement—double verification processes, arising from increased in-lab turnaround time due to a delay in secondary verification. We mitigated this delay in the later stage of implementing our new method once staff grew more accustomed to when runs became ready for secondary verification.

From our process improvement and associated look back we learned that both offered valuable lessons about new limitations and future areas of focus. As difficult as it may be, maintaining momentum after successful quality improvement initiatives and keeping a lab focused on using its newly gained experience to solve emerging shortcomings is crucial. We also learned that long-term management support is an essential element as labs embrace a philosophy of constantly striving for better clinical testing. Multiyear quality improvement efforts can be a big burden and won't be effective without lab staff's acceptance of the new quality vision. Embracing such ideas takes time, but a robust follow-up study such as ours may demonstrate the value of such effort and philosophy. It may provide confidence for labs that larger-scale implementation improvement initiatives will be worth the time and effort, perhaps even transforming staff attitudes from "we have no control over it" to "we can work to make it better."

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The Sample

Single, Negative Test Might Not Rule Out Zika Virus Infection

Repeat quantitative, reverse transcription polymerase chain reaction (RT-qPCR) testing in pregnant women with confirmed Zika virus infection showed that in some, the viral load in their urine disappeared and later returned (Emerg Infect Dis 2017;23:1891-3). These findings suggest a single negative test might not be sufficient to reassure women about their Zika status.

"These results suggest the virus continues replicating during pregnancy, in the fetus or the placenta, which must serve as a reservoir for the pathogen," said the study's senior author, Maurício Lacerda Nogueira, MD, PhD, a professor in the Medical School of São José do Rio Preto in São Paulo state, Brazil. "However, viral load in the mother's fluids is intermittent and very low, almost at the detection threshold."

Nogueira and his colleagues followed 13 pregnant women who were being treated at the Public Health Authority in São José do Rio Preto. The women were from 4-38 weeks pregnant at the time of enrollment and had positive viral RNA results via urine RT-qPCR, defined as cycle threshold ≤38.5. They had repeat RT-qPCR testing until they delivered their babies.

In five women, the researchers detected viruria after they had no detectible viral load in prior tests. One patient's viruria persisted 7 months. In all the women, no viral load was detected after they delivered. This led the researchers to speculate that virus replication continues in fetal tissues like the placenta, umbilical cord, brain, liver, lung, and spleen. Three babies born to the study participants had complications that probably were Zika-related, including two with hearing loss and one with a brain cyst.

The authors called for further research into understanding the meaning of this viruria and its consequences for newborns.

ALL DETECTABLE LEVELS OF CARDIAC TROPONIN ASSOCIATED WITH NEGATIVE OUTCOMES

Swedish researchers report a strong, graded association between all detectable levels of cardiac troponin measured by a high-sensitivity assay (hs-cTnT) and increased risk of myocardial infarction (MI), heart failure, and cardiovascular- and noncardiovascular-related deaths (J Am Coll Cardiol 2017;70:2226-36). The findings, which build on prior studies with similar outcomes, suggest a need for better evaluation and management strategies to reduce risk in patients with elevated hs-cTnT, according to the researchers.

The study involved 22,589 patients older than age 25 who presented with chest pain at the Karolinska University Hospital emergency department in Stockholm. After excluding patients who had an MI associated with their initial visit or who had acute illnesses that might have affected hs-cTnT, the researchers followed 19,460 patients for a mean 3.3±1.2 years. During this time, 6.9% of patients died, and 62%, 21%, 8.6%, 5.7%, 1.5%, and 0.7% had baseline hs-cTnT levels <5 ng/L, 5-9 ng/L, 10-14 ng/L, 15-29 ng/L, 30-49 ng/L, and ≥50 ng/L, respectively.

The adjusted hazard ratios for all-cause death in comparison to individuals with undetectable hs-cTnT (<5 ng/L) were 2.00, 2.92, 4.07, 6.77, and 9.68 for those with hs-cTnT 5-9 ng/L, 10-14 ng/L, 15-29 ng/L, 30-49 ng/L, and ≥50 ng/L, respectively. The researchers observed similar increased adjusted hazard ratios associated with rising hs-cTnT levels for cardiovascular-related mortality, noncardiovascular-related mortality, MI, and heart failure. However, this graded risk relationship was particularly pronounced in the case of heart failure, with adjusted hazard ratios of 3.66, 6.04, 10.7, 13.1, and 13.3 for those with hs-cTnT 5-9 ng/L,

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10-14 ng/L, 15-29 ng/L, 30-49 ng/L, and ≥50 ng/L, respectively, in comparison to the reference population with undetectable levels of hs-cTnT.

The latter finding and other studies suggesting continuous but small release of cTnT from the myocardium during heart failure may indicate that "chronic troponin release may be mediated by functional and structural heart diseases rather than by ischemic heart disease," wrote the researchers.

SALIVARY MICRORNA SHOW PROMISE FOR DETECTING PROLONGED CONCUSSION SYMPTOMS

In the search for objective tools to identify children at risk of prolonged concussion symptoms (PCS), Pennsylvania State University researchers found that levels of five microRNAs (miRNAs)—miR-320c-1, miR-133a-5p, miR-769-5p, let-7a-3p, and miR-1307-3p—accurately identified patients with PCS on logistic regression, with area under the receiver operating characteristics curve (AUROC) of 0.856 (JAMA Pediatrics 2017; doi:10.1001/jamapediatrics.2017.3884).

This AUROC compared with the accuracy of symptom reporting by affected children and by their parents with AUROCs of 0.649 and 0.562, respectively. Though the findings need to be validated in an independent, larger cohort, they suggest that salivary miRNAs might be used as part of a toolset to improve concussion management, according to the investigators.

The study involved 52 patients with a mean age of 14 who presented for evaluation of a concussion within 14 days of their initial head injury and who underwent follow-up evaluations at 4 and 8 weeks. The researchers took nonfasting saliva samples from the participants and found 437 microRNAs in at least 22 samples with a mean read count of 2.1 x 10^5 reads per sample. They used a two-dimensional partial least squares discriminant analysis to identify 15 miRNAs of interest in discerning acute concussion symptoms from PCS. The investigators also explored the functional targets of these miRNAs and found them involved in signaling cascades related to synaptic development, neuronal migration, and repair, and in gene ontology pathways related to neurotrophin tyrosine receptor kinase signaling, axon guidance, and nervous system development. They deployed multivariate regression analysis to evaluate these 15 miRNAs for PCS classification accuracy. The combination of the aforementioned five miRNAs showed the highest classification accuracy.

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NO LONGER A FINANCIAL WINDFALL, URINE DRUG TESTING BY MASS SPECTROMETRY MAY BECOME A BURDEN FOR SOME PHYSICIAN OFFICE LABS

BY JULIE KIRKWOOD

Bill Diodato / DigitalVision / Getty Images

About 4 years ago, a quirk in insurance reimbursement made drug testing by mass spectrometry a lucrative business. A lab could bill at least $400 to $800 for a single urine sample, sometimes more than $1,000. The opioid crisis had increased the need for urine drug tests, and the financial incentive was so strong that many pain doctors set up their own in-house physician office laboratories (POLs) to claim their share of the profits.

"I'm not going to sugarcoat it, it was relatively disastrous putting these things into physician offices beforehand—not with us, but with a lot of other companies that didn't take it as seriously as they should have," said Gregory Ingle, CEO of Clinical Lab Consulting, a company that has set up hundreds of drug testing laboratories in physician offices.

Consulting practices proliferated, marketing mass spectrometry equipment to doctors. Some unscrupulous companies sold old, used mass spectrometers that were never meant for clinical testing, Ingle said. Some made claims that they could set up mass spectrometry in just a couple of weeks. And because of the insurance reimbursement quirk—that each drug class was reimbursed separately—laboratories were rewarded for running full panels of drug tests on every sample, leading to overuse, said Charles Root, PhD, CEO of CodeMap LLC, a laboratory coding and reimbursement information company. "The doctors especially, since they were the ones who ordered tests as well the ones who performed them, tended to do quite a bit of testing," Root said.

An investigation of billing data by Kaiser Health News published in November 2017 found that spending on urine drug screens and related tests quadrupled from 2011 to 2014 to about $8.5 billion a year, leading to allegations of overuse, whistleblower lawsuits, and settlements. The analysis found that in 2014, Medicare paid more for urine drug tests than on the four most-recommended cancer screenings combined.

The growth of POL drug testing was so widespread that toxicology

reference laboratories felt the pressure. “We actually saw a lot of our business go toward physicians setting up their own labs,” said Andrea Terrell, PhD, DABCC, who was lab director at AIT Laboratories at the time. “We actually struggled to retain business because of the POLs.”

Insurers soon realized what was happening and changed the rules. The Centers for Medicare and Medicaid Services created new codes last year with payment tiers based on the number of analytes tested, capping out at around $200 to $250 per sample. “The rates have been slashed by virtually 80 percent now,” Root said.

A New Era for Physician Office Labs

While the frenzy for opening new POLs has calmed down, these labs have not gone away. Many pain doctors continue to operate their own drug testing laboratories, and some addiction treatment centers are now bringing testing in-house, according to Ingle. “It was primarily greed and monetary-driven in the beginning, but now it’s just become the new standard of care,” he said.

POLs can be successful if a practice invests the time and money to do it right, Ingle noted. For example, Robert B. Wilson, II, MD, board certified in anesthesiology and pain management and founder of Piedmont Interventional Pain Care in Salisbury, North Carolina, runs a successful mass spectrometry laboratory that was set up by Clinical Lab Consulting in 2015. Generating revenue was one reason for bringing testing in-house, he said, but he was not expecting to make hundreds of thousands of dollars in profits as did the early adopters. “I never saw that kind of money, ever,” Wilson said. “When I started doing my billing, it had already been adjusted down.”

Wilson’s decision to bring testing in-house mainly arose out of frustration with reference labs, he said. He felt they were too expensive and they pushed him to order unnecessary full test panels on every patient. His office had to do all the work collecting the urine samples, counseling patients about their results, and referring them to

Bill Diodato / DigitalVision / Getty Images

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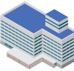

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addiction treatment, as well as all the other facets of ensuring medication compliance such as counting pills—all in an environment of constantly shrinking reimbursements. "[The reference labs] were generating more revenue doing the urine screens than I was sticking needles in [the patients'] spines," Wilson said. "We do all these things based on our clinical judgment that we never get paid to do, and by bringing in the urine screening revenue, it makes it more palatable."

Even at the reduced mass spectrometry reimbursement rates, Wilson's laboratory makes a small profit, he said, and it gives him more control over testing. Now the overuse of this testing is tightly regulated by Medicare and commercial insurance guidelines, Wilson noted. The allowed frequency of testing is based on the morphine milligram equivalents prescribed to patients.

Science Stretched Thin

It is not easy to bring mass spectrometry to a physician office, according to Ingle. While an immunoassay analyzer can be set up and validated in as little as a week, mass spectrometry validation takes months. A mass spectrometer is like a stove, and it's up to the chemist or biochemical engineer to be the chef who creates the recipe, he said. "Everybody has a different way of doing it, and there's a lot of scientific argument over who's right."

The instruments also have special requirements for power, climate control, and custom-made reagents. "Mass spectrometry is the hardest to implement out of any kind of lab testing, and that includes genomic testing, which we do a lot of," Ingle said. "It's because of the special sauce—all of the different things that can go into it."

Physicians also need to hire appropriate staff to run mass spectrometry laboratories, presenting an additional challenge, Terrell said, who left AIT Laboratories and now works with Ingle to set up and advise POLs. "If a physician hires just a PhD analytical chemist who has no clinical laboratory training and experience, they're not going to be successful."

Analytical chemists might not understand the level of regulatory scrutiny involved in a clinical assay, might add tests to a panel without revalidating it, have weak quality control practices, or struggle to maintain the instrument and all the peripheral equipment, she said. Overall, she doesn't recommend physicians run mass spectrometry laboratories. "It can work…but I have not seen it work really well in a physician office setting," she commented.

Marion Snyder, PhD, chief science officer at Luxor Scientific, has the same misgivings and said physicians should not run their own mass spectrometry labs. She co-authored an article in January's *Journal of Applied Laboratory Medicine* about the risks and difficulties of POL mass spectrometry (J Appl Lab Med 2018;2:657-9). "I don't think this type of testing should be done in a setting where the sole driving factor is revenue generation," Snyder said. "Over time, as the reimbursement comes down especially, there's going to be pressure to cut corners in those labs."

Indeed, the market for selling mass spectrometer to POLs has already essentially disappeared, Root said. Reimbursement is only going to get worse as the Protecting Access to Medicare Act takes effect, he said. "With the changes to the Clinical Laboratory Fee Schedule, it looks like it could be cut 10 percent a year further for two to three more years," Root said. "It's not getting any better at this stage."

While POLs are subject to CLIA inspections, the inspectors "haven't traditionally had the expertise or haven't been adequately funded to support inspections of liquid chromatography-tandem mass spectrometry labs," Snyder said. "They're looking for the more basic maintenance procedures and things like that, but they wouldn't necessarily understand if the science behind it is flawed or if errors are being made."

Perhaps there should be a task force that inspects POLs to supplement CLIA or even a requirement that they be subject to a higher level of inspection, she said, adding: "It's something that the lab community should discuss."

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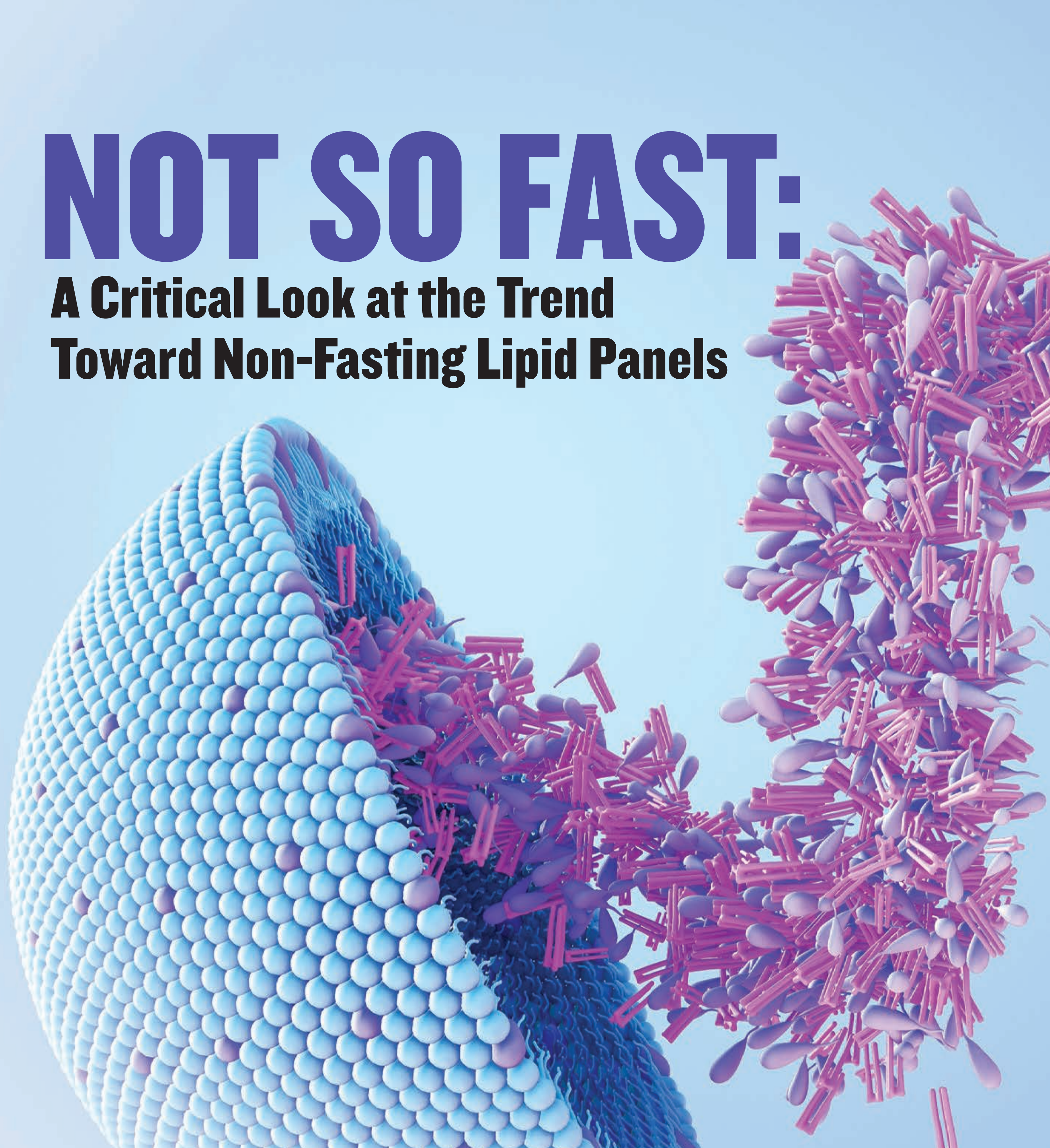
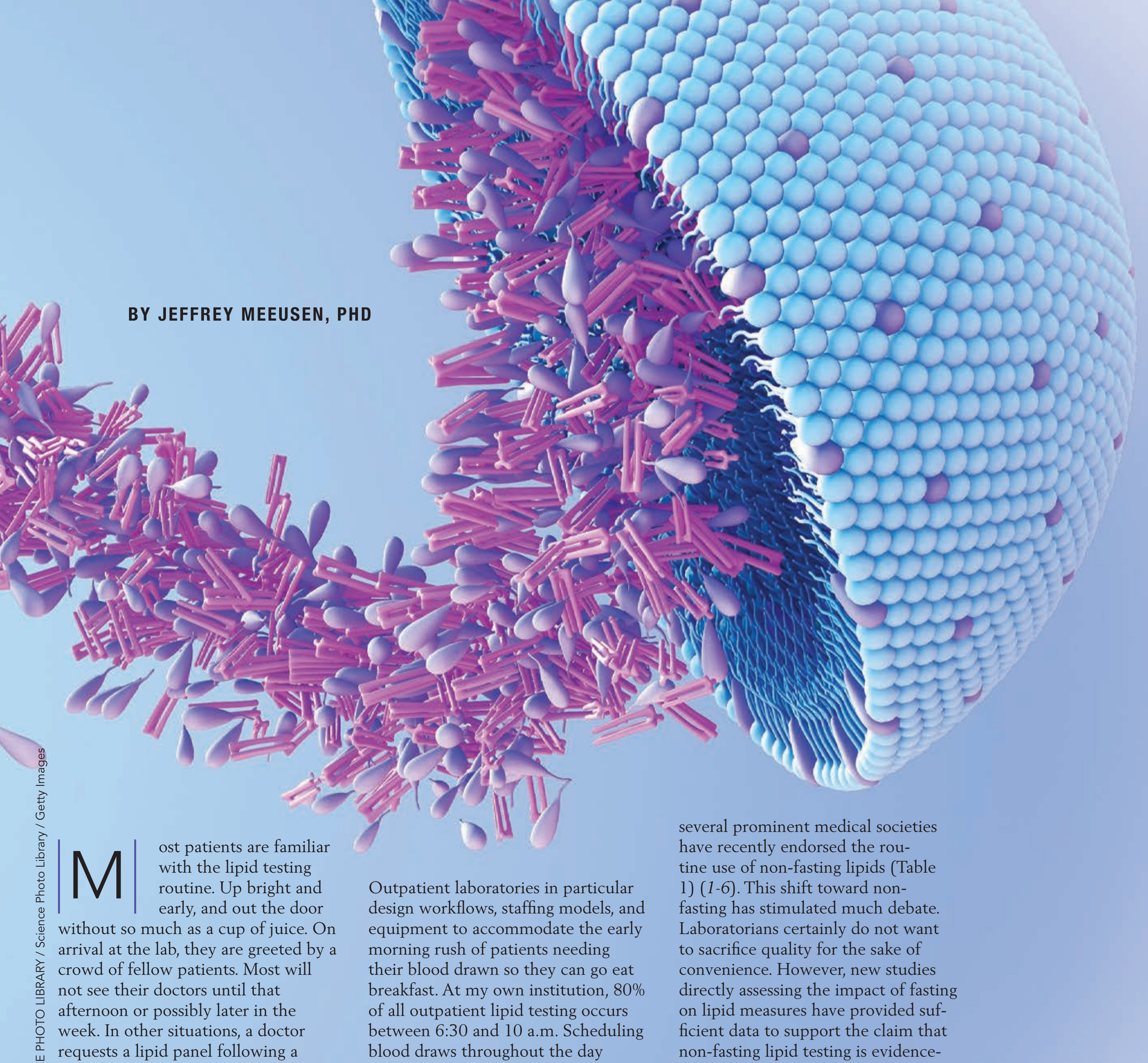


NOT SO FAST:

A Critical Look at the Trend Toward Non-Fasting Lipid Panels



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BY JEFFREY MEEUSEN, PHD

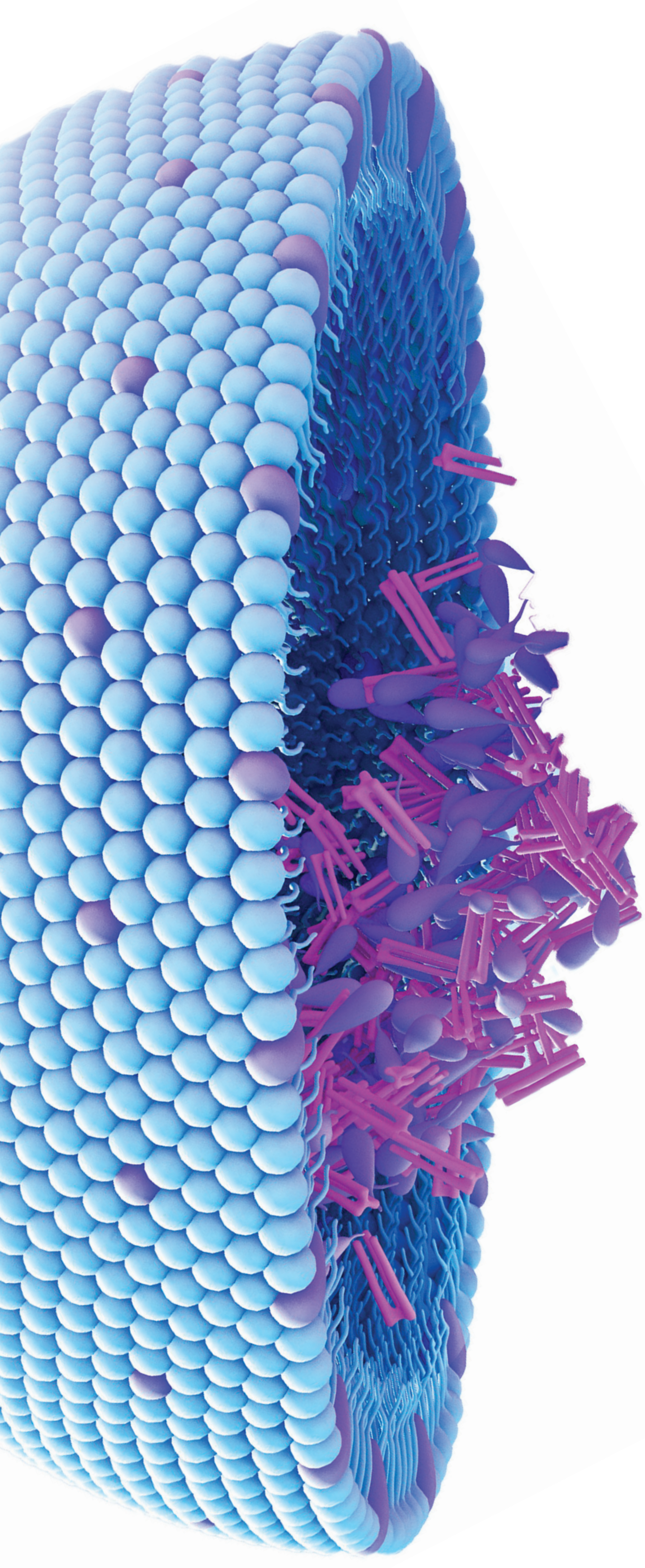
Most patients are familiar with the lipid testing routine. Up bright and early, and out the door without so much as a cup of juice. On arrival at the lab, they are greeted by a crowd of fellow patients. Most will not see their doctors until that afternoon or possibly later in the week. In other situations, a doctor requests a lipid panel following a clinical evaluation, in which case the patient makes a separate return trip after an overnight fast.

Patients certainly shoulder most of the burden surrounding fasting blood draws, but clinical labs are a close second. Clinical laboratorians take pride in minimizing patient wait times and providing the highest quality testing. Outpatient laboratories in particular design workflows, staffing models, and equipment to accommodate the early morning rush of patients needing their blood drawn so they can go eat breakfast. At my own institution, 80% of all outpatient lipid testing occurs between 6:30 and 10 a.m. Scheduling blood draws throughout the day would be much more cost-effective. However, lipids are measured on fasting samples. Everyone knows that. That's the way things have always been. Now, however, the rules might be about to change.

After decades of dogma requiring an overnight fast prior to blood collection for lipid measurements, several prominent medical societies have recently endorsed the routine use of non-fasting lipids (Table 1) (*1-6*). This shift toward non-fasting has stimulated much debate. Laboratorians certainly do not want to sacrifice quality for the sake of convenience. However, new studies directly assessing the impact of fasting on lipid measures have provided sufficient data to support the claim that non-fasting lipid testing is evidence-based medicine that provides superior care for the majority of patients.

Why Do We Measure Fasting Lipids?

Lipids, specifically low-density lipoprotein cholesterol (LDL-C), are measured to assess an individual's risk of coronary artery disease and



monitor a patient's response to lipid-lowering therapy. The association between LDL-C and heart disease is arguably one of the most studied in medicine. Dozens of prospective clinical trials have established that the risk of heart disease is directly proportional to blood levels of LDL-C. Furthermore, interventional trials have shown that lowering LDL-C reduces risk of heart disease. This remains true regardless of baseline LDL-C and has no apparent limit in efficacy—the lower the better.

LDL-C is not a specific molecule, but rather a measure of all blood cholesterol contained in lipoproteins with a density between 1.019 and 1.063 g/L. Separating blood via density gradient is time-consuming, laborious, and expensive. The most common laboratory method estimates LDL-C according to the Friedewald formula: LDL-C = [Total Cholesterol] – [HDL-C] – [Triglycerides/5]. Although it was derived from a small number of subjects and intended for research purposes, the Friedewald formula made possible the rapid and ubiquitous adoption of LDL-C measures as standard clinical care.

In Friedewald's highly cited original publication, the authors mention that fasting samples are necessary to reduce the variability observed in measured triglycerides (*7*). Indeed, it is well established that triglyceride concentrations transiently increase following a meal due to the presence of chylomicrons (*8*). Furthermore, the degree of triglyceride elevation is related to the amount of fat consumed (*9*) and the patient's baseline triglyceride concentration (*1*). "Aha!" exclaims the discerning clinical laboratorian. "Not fasting alters measured results. Case closed. The absurdity of non-fasting lipid panels is put to rest." But there's more to the story.

The Clinical Significance of Increased Non-Fasting Triglycerides

On closer inspection, the most recent data suggest that triglyceride changes observed due to non-fasting are clinically negligible in most patients. In one study of >140,000 individuals, 80% of subjects had non-fasting triglyceride concentrations <195 mg/dL (*10*). Another study of >33,000 subjects found that the median concentration of non-fasting triglycerides was 124 mg/dL, while 75% of patients had values <185 mg/dL (*8*). These findings are supported by the Very Large Database of Lipids (n=1.4 million patients). This study found a median non-fasting serum triglyceride concentration of 125 mg/dL with 75% of patients having a non-fasting triglyceride value <182 mg/dL (*11*).

The fact that most patients have relatively normal concentrations of triglycerides (<150 mg/dL) even in the non-fasting state is good news. As noted previously, post-prandial elevation of triglycerides is directly proportional to fasting triglyceride concentrations: The higher a patient's fasting triglycerides, the larger the increase will be following a meal. This phenomenon was recently affirmed in a study of 5,538 patients with matched lipid panels measured immediately before and 3 to 5 hours after a meal (*12*). The median post-prandial increase in triglycerides was 50-75% among patients with fasting triglycerides >250 mg/dL. However, patients with fasting triglycerides <130 mg/dL had an average increase of 6 mg/dL or less following a meal (<5%). In larger studies, the median peak post-prandial triglyceride increase was 26 mg/dL, or 21% from the median baseline of 124 mg/dL (*8*).

The biological variability of fasting triglycerides is reported to be 20-30%, and the intra-individual variability ranges from 5% for people with average fasting triglycerides <100 mg/dL to 75% for those with average fasting triglycerides >250 mg/dL (13). Consequently, a triglycerides increase of 6 mg/dL, 26 mg/dL, or even 36 mg/dL based on a non-fasting sample is well within the noise of typical biological variations.

There is an apparent disconnect between these studies and the historical understanding of fasting influence on triglycerides. A possible explanation is that many historical studies measured triglycerides following an intentionally high fat meal (50 g or more). A typical meal containing approximately 17g of fat maximally increases triglycerides by <20% (*9*). Obviously, if a patient reports for a blood draw after an all-American lunch of a cheeseburger,

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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

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T1 Endorsement of Routine Non-Fasting Lipid Panels

Year	Society	Non-Fasting Triglycerides cutoff*	Risk Assessment (Prior to Therapy)	Lipid Assessment on Treatment
2016	European Atherosclerosis Society and European Federation for Laboratory Medicine	>400 mg/dL	Non-fasting lipid panel is appropriate.	Non-fasting lipid panel is acceptable.
2014	National Clinical Guideline Center and Joint British Societies	>400 mg/dL	Non-fasting lipid panel is appropriate.	Non-fasting lipid panel is acceptable.
2013	American College of Cardiology / American Heart Association	>200 mg/dL	Fasting lipid panel is preferred *but not required*.	Fasting lipid panel recommended prior to statin initiation. Non-fasting is acceptable on treatment follow-up.

*Repeat measure of triglycerides using fasting sample is recommended following elevated non-fasting triglycerides.

fries, and a milkshake, there will be a significant increase in measured triglycerides. For these reasons, the American Heart Association recommends that any non-fasting triglycerides >200 mg/dL be followed up with a fasting lipid panel (*14*). Clinicians and laboratorians could also partner to deal with this issue by targeting patients for fasting who have a history of hypertriglyceridemia or through patient education. Requesting that patients avoid fatty meals a few hours prior to a blood draw is a very different request than a complete fast for 8-12 hours.

Non-Fasting Triglycerides and Risk of Heart Disease

Interestingly, while the association between fasting triglycerides and risk of heart disease is minimal, growing evidence suggests that non-fasting triglyceride concentrations confer significant risk. One study followed 26,509 U.S. women over 12 years for myocardial infarction, ischemic stroke, coronary revascularization, or cardiac death. The risk of having an adverse cardiac event was double (hazard ratio (HR) 1.98 [95% confidence interval (CI) 1.21-3.25]) for women in the highest tertile of non-fasting triglycerides (≥171 mg/dL) after adjusting for age, blood pressure, smoking, and blood cholesterol. In contrast, the investigators found no additional risk for women in the highest tertile of fasting triglycerides (HR 1.09 [95% CI 0.85-1.41]) (*15*). Another study of 1,337 patients with type 2 diabetes mellitus found a significant increase in cardiac events among patients with elevated non-fasting triglycerides (*16*). Multiple studies have reported similar findings for non-fasting triglycerides (*8, 10, 17-19*).

What About Estimated LDL-C?

Even if the fasting influence on triglycerides is debatably minimal, an 800-pound gorilla remains in the room. Triglycerides are part of the Friedewald equation. Any increase in triglycerides will result in a decrease in the reported LDL-C.

Several large studies have set aside the fasting rule and estimated LDL-C by the Friedewald formula in non-fasting blood samples (*1, 8, 20, 21*). Figure 1 shows that Friedewald estimated LDL-C and measured LDL-C are not significantly different when tested in non-fasting samples from a general population study (n=470) (*1*). In one cohort of 586,481 patients with median triglyceride concentrations of 125 mg/dL (interquartile range (IQR) 87-182), the median ultracentrifuge-measured LDL-C was 115 mg/dL (IQR 91-142), while the median Friedewald estimated LDL-C was 112 mg/dL (IQR 87-139) (*11*). Another study comparing fasting and non-fasting LDL-C (estimated by the Friedewald formula in both cases) among 209,180 community outpatients showed an average decrease of 4 mg/dL LDL-C due to non-fasting (*22*).

Two factors help minimize the impact of fasting on estimated LDL-C. First, as explained above, the typical increase in triglycerides is less than previously assumed. Second, estimated LDL-C is only reduced by 1 mg/dL for every 5 mg/dL increase in triglycerides. Since most patients have at most a non-fasting increase of 25 mg/dL triglycerides, then LDL-C estimates are only expected to vary by 5 mg/dL.

The Clinical Significance of Decreased Non-Fasting LDL-C

Clinicians use LDL-C to establish a patient's risk of cardiovascular disease and to monitor the impact of therapeutic interventions. The primary tools used to assess a patient's risk of cardiovascular disease are the Framingham Score, the American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equation, the Reynolds score, and European Systematic Coronary Risk Evaluation Score. All of these calculations incorporate age, sex, blood pressure, smoking status, total cholesterol, and HDL-C. None formally include triglycerides or LDL-C: The endorsed means of risk assessment are completely independent of a patient's fasting status.

Data from 8,270 patients enrolled in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) confirm the rationale for excluding these measures. In ASCOT, investigators found greater than 95% concordance between fasting and non-fasting lipids using the 2013 ACC/AHA Pooled Cohorts equation (*23*). Incidentally, this study found that non-fasting LDL-C was a stronger indicator of

future cardiac events within 3 years when compared to fasting LDL-C.

Previous strategies supported lower target LDL-C for higher risk patients. In order to achieve lower target LDL-C, clinicians treated high-risk patients more aggressively and these individuals received much more benefit. Patients who had borderline high lipids were prescribed a weaker dosage of lipid-lowering drugs or none at all.

These days lipid management strategies no longer endorse a target LDL-C or titrated dosage of lipid-lowering medications. Rather, the new ACC/AHA recommendations call for prescribing a specific dosage of statins based on a patient's baseline risk (*24*). This recommendation is based on data from dozens of randomized clinical trials and is in agreement with the concept of "the lower the better." ACC/AHA do recommend a fasting lipid panel prior to starting statin therapy or adjusting dosages. However, initial screening and long-term monitoring of lipid lowering are minimally affected by non-fasting.

As a thought experiment, consider two lipid scenarios for a hypothetical patient (Table 2). In the first scenario, a fasting sample has a calculated LDL-C of 162 mg/dL (high by conventional terminology). As triglycerides increase due to non-fasting, the calculated LDL-C is reduced. Assuming this is an initial screen, then calculated risk is the criterion of interest, and fasting has no impact. If this were an annual follow-up for a patient on therapy, even a triglyceride increase of 50% would result in a reported LDL-C of 143 mg/dL (borderline high). This difference is of questionable clinical import. Furthermore, a non-fasting triglyceride >200 mg/dL would trigger a request for a follow-up fasting lipid panel.

In the second scenario, the fasting sample has a calculated LDL-C of 194 mg/dL, suggesting familial hypercholesterolemia. Calculated LDL-C falls to 188 mg/dL if triglycerides increase 20% (the median increase) for a non-fasting sample. In this worst case scenario, the calculated LDL-C falls below the diagnostic threshold due to the non-fasting elevation. However, the reported LDL-C in non-fasting

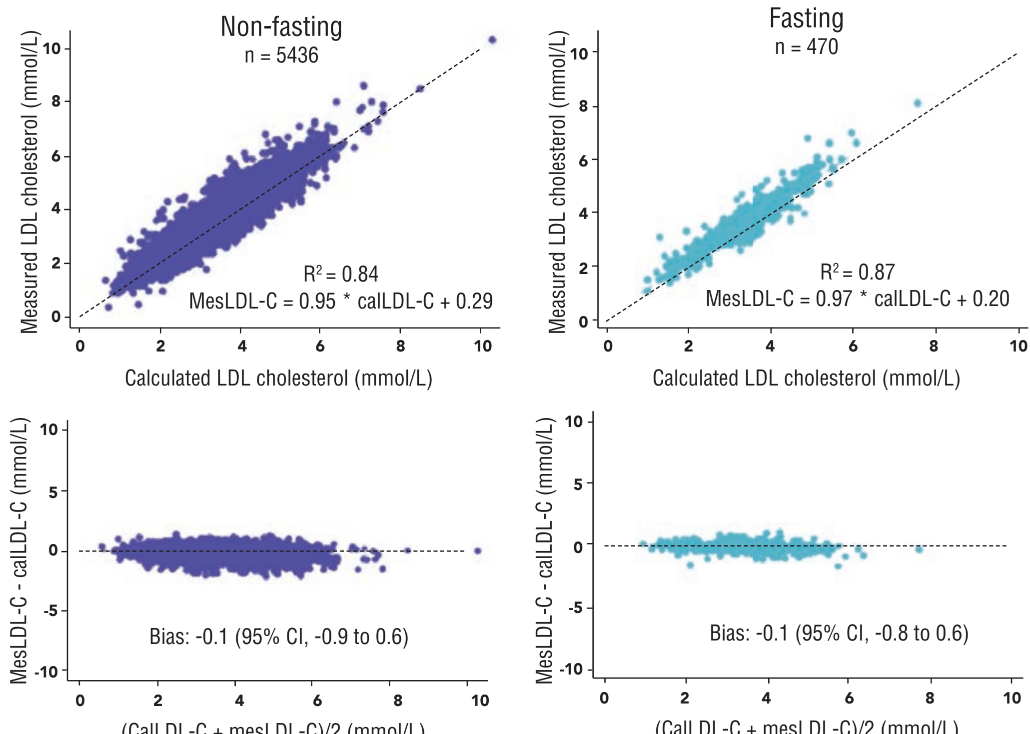
T2 The clinical impact of non-fasting lipids on cardiovascular risk assessment

	Δ Triglycerides	Total Cholesterol (mg/dL)	HDL-C (mg/dL)	Triglycerides (mg/dL)	LDL-C* (mg/dL)	Non-Fasting LDL-C Change (mg/dL)	Non-Fasting LDL-C Change %	Framingham 10-yr Risk**	Pooled Cohort**
Scenario 1	0% (Fasting)	240	39	195	162	-	-	9.0%	3.9%
	+10%			215	158	-4	-2.4%		
	+20%			234	154	-8	-4.8%		
	+50%			293	143	-19	-12.0%		
Scenario 2	Δ Triglycerides	Total Cholesterol (mg/dL)	HDL-C (mg/dL)	Triglycerides (mg/dL)	LDL-C* (mg/dL)	Non-Fasting LDL-C Change (mg/dL)	%	Framingham 10-yr Risk**	Pooled Cohort**
	0% (Fasting)	250	30	132	194	-	-	11.4%	5.0%
	+10%			145	191	-3	-1.3%		
	+20%			158	188	-5	-2.7%		
	+50%			198	180	-13	-6.7%		

*LDL-C estimated by the Friedewald formula

**Risk scores calculated using a hypothetical 58-year-old female non-smoker with systolic blood pressure of 125 mmHg and C-reactive protein of 1.0 mg/L.

F1 Comparison of Friedewald estimated LDL-C and measured LDL-C (homogeneous direct method) in samples from fasting and non-fasting subjects.



Source: Nordestgaard BG, Langsted A, Mora S, et al. Fasting is not routinely required for determination of a lipid profile: Clinical and laboratory implications including flagging at desirable concentration cutpoints-a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. Clin Chem 2016;62:930-46.

state is within 2.7% of the fasting value. This variation is within the biological noise and even within the analytical noise of measured cholesterol. Thus, a similar change in values could be seen in serial fasting measures.

Non-Fasting LDL-C and Risk of Heart Disease

While it is true that most studies to date have used fasting measures of LDL-C to establish cardiovascular risk, several prospective studies have reported on the utility of non-fasting LDL-C *(1, 15, 25, 26)*. The Emerging Risk Factors Collaboration reported a meta-analysis of 68 prospective studies and found no difference in the association of lipids with risk of heart disease within the 20 studies that used non-fasting lipids (*25*). Among these 20 studies, three were randomized clinical trials demonstrating the efficacy of statin interventions in nearly 43,000 patients.

Similarly, a 2014 report followed 8,598 participants from the National Health and Nutrition Examination Survey with fasting or non-fasting baseline LDL-C (estimated by Friedewald formula in both cases) (*26*). Cardiovascular mortality was significantly higher among patients in the highest tertile of LDL-C (>130 mg/dL) regardless of fasting status. The prognostic value of non-fasting LDL-C was identical to fasting LDL-C, each with a C-statistic of 0.62 (95% CI 0.60-0.66).

Another prospective study measured non-fasting lipids in 9,319 patients followed for 14 years (*8*). Non-fasting LDL-C (estimated by Friedewald formula) was significantly associated with increased cardiac events. Risk conferred by non-fasting LDL-C remained significant after adjusting for age, blood pressure, smoking, diabetes mellitus, body mass index, and C-reactive protein.

Laboratory Implementation of Non-Fasting Lipid Panels

From the laboratory perspective, it would be prudent to report non-fasting triglycerides and LDL-C differently from fasting samples. This would enable laboratories to use a unique abnormal flag for non-fasting triglycerides at the recommended 200 mg/dL cutpoint and automatically appended a comment suggesting repeat testing after an 8-12 hour fast. Due to the novelty of reporting non-fasting Friedewald estimated LDL-C, including an appended comment that suggests values may be decreased when triglycerides are >200 mg/dL would also be reasonable.

In conclusion, multiple independent and highly powered studies suggest that non-fasting lipids are similar (or better) than fasting measures for predicting risk of cardiovascular disease. Furthermore, routine non-fasting lipid panels can accommodate a majority of patients without the need for separate fasting visits. Thus, routine non-fasting lipids are not only convenient, but also evidence-based. These findings empower laboratories to build a new paradigm for lipid testing that better accommodates most patients while maintaining high-quality care for special cases of dyslipidemia.

From the laboratory perspective, it would be prudent to report non-fasting triglycerides and LDL-C differently from fasting samples.

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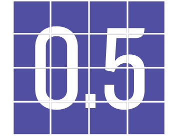

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MASS SPECTROMETRY

FOCUS ON

BY STEFANI N. THOMAS, PHD, AND WILLIAM CLARKE, PHD

Alternative (but Believable) Truths

Calibration Strategies for Clinical LC-MS Assays

As the use of liquid chromatography-mass spectrometry (LC-MS) has increased, clinical laboratories have sought to improve efficiency by employing alternative calibration strategies to reduce the number of calibration standards. While CLIA guidelines require biannual calibration at a minimum, no regulation requires that labs generate a calibration curve with every assay. This is in stark contrast to what has become common practice in clinical laboratories.

Generating a calibration curve for every batch of runs can be a significant expense, due in large part to the high cost of stable isotope-labeled internal standards (IS). One group estimated that abiding by a conventional calibration scheme at six concentration levels results in more than 5,000 calibration points per year (*1*). Indeed, it has been proposed that clinical laboratories employing LC-MS assays use more calibration standards than necessary (*2*), and that conventional calibration methods are wasteful because they do not capitalize on the rich information contained within recent calibrations (*3*).

Labs have recently developed several approaches to reduce the cost and burden associated with preparing several calibration standards with every batch of samples—without sacrificing analytical quality. These efforts have found that reduced calibration standard strategies not only conserve time and cost but also are more robust than conventional multi-point calibration schemes (*4*, *5*). In fact, redundant multi-point calibration can actually result in excessive quantitative bias or the unnecessary failure of analytical runs using conventional methods (*1*), due in part to process changes such as the degradation of IS stock solution concentration and/or poor IS preparation (*6*).

One of the first alternative calibration strategies in clinical LC-MS used a single-point (linear through zero) calibration for quantifying the immunosuppressant tacrolimus (*7*). A subsequent study by the same group expanded the repertoire of abbreviated calibration curves and evaluated the performance of these curves in quantifying sirolimus (*8*). The results of this study demonstrated that single-point, linear through zero, and two-point alternative calibration schemes yielded acceptable inaccuracy (-6.7%-1.2%) and imprecision (3.7%-8.2%).

Internal Calibration

In 2007, the concept of internal calibration was introduced as a means of direct quantification in bioanalytical LC-MS methods. In this approach, labs calculate the results directly from an analyte/internal standard area ratio and a pre-determined response factor (*9*).

The validated data indicate linearity and good precision and accuracy over the analytical measurement range. Four conditions must be met for this strategy to be successful: 1) the relative response should not be concentration dependent; 2) the relative response should be constant between batches/days; 3) the level of analyte in the IS should not be detectable; and 4) there should be no influence from naturally occurring isotopes of the analyte on the IS peak area.

Response Ratio and Response Factor Approaches

Researchers have also expanded on the concept of response ratio (RR)-based calibration by using the measurement of the RR corrected by

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the response factor (RF). The authors of one study compared contemporaneous RF (cRF) and sporadic RF (sRF) measurements with clinical results obtained by interpolation on a calibration curve (*10*). cRF and sRF calibration in a clinically validated LC-MS assay for therapeutic drug monitoring yielded results analytically and clinically comparable to those produced by interpolation with a calibration curve.

Another variation of alternative LC-MS assay calibration compares provisional RF (pRF) to a historical RF (hRF) in order to calculate a current RF (referred to as contemporaneous RF in the study conducted by Olson et al.) that relies on a weighting factor to stabilize the CRF against random fluctuations (*1*). This strategy is amenable to clinical settings that use the same analytes and method routinely over a prolonged period. Indeed, CLSI document C43-A2 indicates that historical calibration curves can be used if they are shown to be linear over time (*11*).

More Alternatives

Other published strategies employ a different tack. A particularly notable one used a single-point calibration with a calibrator close to the center of the full calibration range as a feasible alternative to full calibration (*4*). In this study, the authors compared the bias and precision from multiple-point and single-point calibration in six validated multi-analyte assays for quantifying drugs in human plasma. Of particular merit, this study included the retrospective analysis of assays encompassing several variables, such as various sample preparation strategies, acidic and basic analytes, and assays in which stable isotopically labeled analogs were used as IS for the majority of analytes, some analytes, or no analytes at all.

Another alternative calibration strategy that does not use stable isotope-labeled IS is termed threshold accurate calibration (TAC). In this approach, labs spike analytes of interest into the sample as IS to achieve a 100% of cut-off or threshold concentration as added standards. A TAC ratio is calculated for each analyte using the following equation: (peak area of analyte in neat sample)/(peak area of analyte in the spiked sample – peak area of analyte in neat sample). The TAC ratio is then calibrated by analyzing a specimen containing the threshold concentration of each analyte. Although this approach requires that each sample be injected twice, the method is adaptable to accurate, high-volume screening, and it normalizes matrix effects.

Deciding on the Best Strategy

Although research has shown that the analytical performance of the aforementioned alternative LC-MS calibration strategies is at least equivalent to that of conventional calibration methods, clinical laboratories should evaluate several considerations prior to deciding which strategy to adopt. The best strategy is fit-for-purpose and takes in to account factors such as a laboratory's sample volume, the number of different assays in a laboratory's testing menu, and the availability of dedicated LC-MS platforms.

In the current healthcare environment, laboratories would do well to improve their efficiency in ways that translate to cost-savings within the scope of laboratory operations. While alternative LC-MS calibration is one such approach, targeted cost-benefit analyses have not been conducted. Such analyses that demonstrate clear cost-savings would provide the final piece of evidence to demonstrate that alternative LC-MS calibration strategies are not simply alternative truths: They are valid, comprehensively vetted truths for clinical laboratories.

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MASS SPECTROMETRY

FOCUS ON

BY LORI BOURASSA, PHD, MPH, D(ABMM)

MALDI-TOF MS Quality Control in Clinical Microbiology

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) has revolutionized clinical microbiology laboratories. Numerous studies have demonstrated the superiority of MALDI-TOF MS systems over conventional methods in identifying a wide range of microorganisms. Since a large number of clinical microbiology laboratories have adopted MALDI-TOF MS as a primary method, labs absolutely need to implement sufficient quality control (QC) practices to ensure they report accurate identifications.

Until recently, few guidelines for using MALDI-TOF MS in clinical microbiology existed. However, in April 2017, the Clinical and Laboratory Standards Institute (CLSI) published a document, Methods for the Identification of Cultured Microorganisms Using Matrix-Assisted Laser Desorption/Ionization Time-of-Flight (M58-Ed1), which lays out comprehensive recommendations for MALDI-TOF MS in clinical microbiology laboratories. This CLSI document, as well as recommendations from instrument manufacturers and regulatory agencies, all agree on the need for robust internal and external QC designed to account for the unique performance and limitations of MALDI-TOF MS.

Internal QC

Laboratories must perform internal QC before using MALDI-TOF MS to identify microorganisms. Internal QC consists of an automatic instrument calibration using a manufacturer-specified calibration standard. Depending on the system, calibrators include a manufactured extract of *Escherichia coli (E. coli)* or a specific *E. coli* calibration strain. Laboratories should ensure that they follow manufacturers' specifications for preparing, using, and storing calibrators.

During calibration, the calibrator generates and automatically analyzes a mass spectrum to check the spectrum baseline and ensure the expected calibration peaks are present. Laboratories use these parameters to confirm their instrument settings are appropriate and their instruments will automatically adjust if necessary. The calibrator spectrum is also run against the reference database to ensure the correct identification is given with a level of confidence that meets the manufacturer's specifications. Laboratories must perform calibration before every run.

In addition to ensuring a successful calibration, the College of American Pathologists (CAP) Microbiology Checklist requires that labs run a calibrator control each day of patient testing, when a new target is used, or more often if the manufacturer recommends it. The CAP checklist also requires that labs maintain a written procedure for operating and calibrating the instrument as well as all calibration records.

It is important for labs to not only document calibration results but also promptly investigate calibration failures. Spectral acquisition cannot occur until calibration is successful. Calibration failures often result from user error, typically due to improper application of the calibrator. Labs can assess potential user error by reapplying and reanalyzing their calibrator. Calibration failure also occurs when the calibrator has been prepared improperly or when problems crop up with the matrix, reagents, target, or instrument.

External QC

Laboratories should perform external QC using appropriate positive and negative controls. While most manufacturers do not, CAP requires that positive controls (either an appropriate control microorganism or calibrator) be tested each day of patient testing.

For positive controls, labs should test well-characterized strains using the same methodology they use for patient isolates. For example, yeast typically require extraction prior to analysis, so labs should process yeast QC organisms using the same extraction methodology. Most laboratories should, at a minimum, test a bacterial QC organism on each day of testing. If laboratories are using MALDI-TOF MS to identify yeast, mycobacteria, *Nocardia*, or molds, appropriate QC organisms for each organism type should be run each day they test for these microorganisms. Labs must obtain correct, high-confidence identifications for all QC organisms. If a lab fails to identify a QC organism, it must investigate and suspend patient testing until the problem is resolved. If a Food and Drug Administration (FDA)-cleared platform is used, manufacturers may recommend specific American Type Culture Collection strains for use as positive controls.

CAP also requires that labs use manufacturer-recommended control microorganisms for FDA-approved platforms. While there are no specific QC organism recommendations for laboratories operating research-use-only platforms, laboratory directors should ensure appropriate control organisms are tested each day. Results of QC testing should be documented and periodically reviewed to assess not only instrument performance but also testing consistency among users.

Labs should also include a negative control with each run. Typically the negative control consists of reagents spotted directly on the target plate or slide. Matrix should be applied to a random blank spot on each target plate or slide to ensure there is no reagent contamination and, for systems that use a reusable target plate, to ensure that the target plate has been adequately cleaned between runs.

CAP requires labs that operate platforms with reusable targets test a blank negative control to ensure adequate cleaning of the target. If an extraction is performed, the reagents used for the extraction can be spotted and overlaid with matrix to ensure no false-positive results are produced due to reagent contamination. Because of the implications of reporting organism identifications directly from blood cultures, labs should test lysis buffers and other reagents used for sample preparation to ensure they are free of contamination. Currently, there are no regulatory requirements for testing reagents on a routine basis.

Ensuring Spectral Quality

Once controls are satisfactory, testing of patient samples can begin. To ensure they produce high-quality spectra, labs must follow recommendations for optimal culture conditions and sample preparation, as well as manufacturers' recommendations for approved media types. If necessary, labs should validate additional media types. They should also use fresh isolates whenever possible. Spectral quality depends on placing an optimal quantity of microorganism on the target plate, and special spotting techniques and extractions might be necessary to identify certain microorganisms. Labs should consider analyzing all isolates in duplicate and have procedures in place to help resolve discordant results between spots.

In addition, since MALDI-TOF MS cannot identify all organisms in polymicrobial cultures, labs should ensure cultures are pure. Ensuring purity is particularly important when microorganisms are identified directly from liquid cultures: Labs should report results as preliminary until purity can be confirmed. A robust training and competency assessment program is also essential to ensure testing staff are competent in performing identifications of commonly encountered microorganisms and in using and maintaining the instrument.

Reporting Identifications

Another important QC consideration involves interpreting and reporting of MALDI-TOF MS identifications. Spectral databases differ in composition depending on the manufacturer and whether they are FDA-cleared. Users also can develop custom databases. While manufacturers validate identifications from their FDA-cleared platforms and these identifications have been cleared for reporting, laboratories still must determine how to report them. Laboratories face choices such as reporting the identification to the genus, species, or complex level.

Reporting also may differ based on specimen source. For example, reporting species-level identifications for coagulase-negative staphylococci from certain sites may lead to clinicians attributing a higher degree of significance to a culture result.

A major challenge for laboratories operating research-use-only platforms is how to report unfamiliar or uncommon identifications. If these laboratories do not independently validate them, such identifications should always be confirmed with supplemental testing. However, validating targets for rarely encountered organisms is especially difficult due to problems obtaining an adequate number of isolates for validation studies.

In addition, labs should familiarize themselves with the identification limitations of their MALDI-TOF MS platform by reviewing technical bulletins, comments provided by the software, and from periodic review of the scientific literature. Unless they extensively validate lower confidence thresholds, labs should adhere to the manufacturer-recommended thresholds for genus and species-level identifications.

In light of the numerous considerations for interpreting and reporting of MALDI-TOF MS identifications, labs should develop reporting guidelines for their bench technologists to ensure accuracy and consistency in reporting. Labs also should participate in external proficiency testing programs to ensure they are proficient in correctly generating and reporting identifications.

MALDI-TOF Limitations

While MALDI-TOF MS is a robust system for microorganism identification, it is not infallible. For example, MALDI-TOF MS cannot discriminate reliably between closely related microorganisms, and incorrect identifications can occur from user error (such as spotting the organism on the wrong spot on the target plate), analysis of mixed cultures, and other reasons.

Due to these limitations, labs should consider MALDI-TOF MS results as one component of the overall testing system for identifying microorganisms. Results should always be reviewed by a trained microbiologist and correlated with other characteristics, including growth requirements, colony morphology, and Gram-stain. In addition, labs should ensure they maintain their instruments and update their database in keeping with manufacturers' recommendations and retain all maintenance records in the laboratory.

As more laboratories abandon traditional methods in favor of MALDI-TOF MS, those that make the switch absolutely need to follow best practices for quality control by adhering to recommendations given by instrument manufacturers, regulatory agencies, and other guidelines.

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PATIENT SAFETY FOCUS

BY SHARON MARKHAM GEAGHAN, MD

Blood Glucose Test Strips: Another Shared Diabetic Supply Demonstrated to Harbor Bacterial Contamination

When you or a family member are admitted to the hospital, you expect that the room will be cleaned and disinfected thoroughly. You do not expect to find half-used tissue paper boxes or leftover bandages from the previous patient. To the contrary, patients expect that hospitals will take all necessary precautions to avoid spreading disease, including disposing of patients' medications when they are discharged from a facility.

Perhaps the only exception to the current practice of single-use, single-patient hospital supplies is blood glucose test strips. Hospitals and other institutions often procure blood glucose test strips in 25- or 50-count vials and bring them from patient to patient and room to room for testing purposes. Testing sites range from acute care hospitals, outpatient clinics, skilled nursing facilities and long term care facilities to prisons, shelters, surgery centers, schools, and camps.

Regardless of testing site, this practice of multi-strip vial use has come into focus as yet another potential source of contamination for patients undergoing blood glucose testing, along with the well-documented risks of sharing blood glucose meters and capillary puncture devices (*1*).

CDC and FDA Guidance on Shared Diabetic Supplies

The position of the Centers for Disease Control and Prevention on shared diabetic supplies is clear: Unused supplies such as blood glucose test strips taken to a patient's bedside should not be used for another patient because of possible inadvertent contamination (*2*).

The Food and Drug Administration (FDA) regulates these test strips as medical devices. In the home testing market, FDA advises consumers to buy only unopened vials of glucose test strips designed for their meter and never to purchase "pre-owned" test strips (*3*), which often are sold at a discount. FDA advises against their use because consumers would not be able to determine several factors, such as whether the strips were stored properly, expired, or contaminated by the previous owner. Of course, this guidance is directed at consumers. But given that assisted blood glucose testing has many of the same elements of risk as self-blood glucose testing—such as capillary blood testing spatter and potentially shared test strips in vials—these warnings also are noteworthy for healthcare professionals.

Bacterial Contamination of Blood Glucose Test Strips

In 2011, an independent U.K. study found serious contamination of test strips: 38 of 148 strips (25.7%) from 50-count vials in use at an acute care hospital tested positive for bacteria. Pathogens included enteric and skin flora but no multidrug-resistant pathogens. Importantly, there was not a statistically significant association between multi-patient vial use (non-intensive care units) and single-patient vial use (intensive care units) and contamination. This lack of association suggested that the key contamination step occurs when caregivers repeatedly enter a vial to retrieve a strip—the same process in single-patient and in multi-patient vial use. Strips from only one manufacturer and a single institution were included in this study. Unopened vials were not found to harbor bacteria (*4*). Vials are currently manufactured under nonsterile conditions.

The following year, a study of strips from opened vials in use at five hospitals and from three manufacturers confirmed the previous findings. The majority of opened vials from two manufacturers of strips-in-vials (vendors not previously studied in the first paper) had bacterial contamination of strips. The percentage of strips contaminated within each vial varied. One colony-forming unit (CFU) per strip was considered a positive result. Strips were contaminated by fecal and skin flora, including *Enterococcus faecium* and *Staphylococcus aureus*. The authors tested unopened vials as a control, finding a 4% contamination rate.

The authors also retrieved individually wrapped strips from a third manufacturer in use at one hospital and found a 3% bacterial contamination rate. Of note, this was an industry-sponsored study from the singly packaged strip manufacturer (*5*).

In 2013, investigators in Spain compared bacterial contamination between individual, single-use packets at one hospital versus multi-use vials of 50- and 100-count in two hospitals. They used unopened vials from each hospital as controls. A number equal or higher than two CFU per strip was considered a positive result. Of 423 glucose test strips collected and cultured,

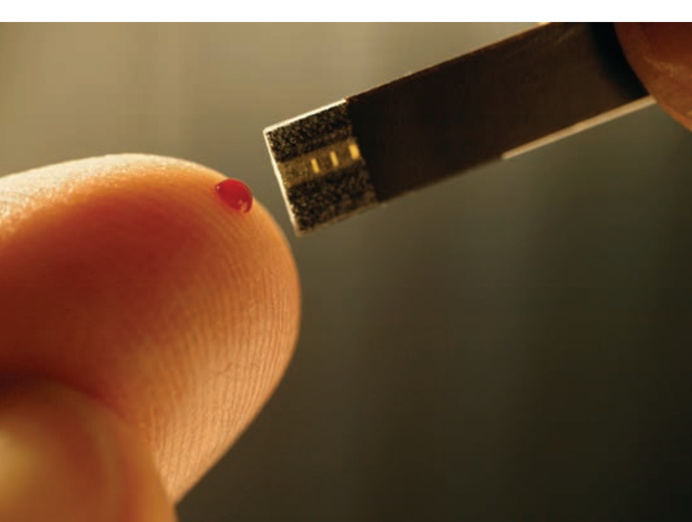
the authors found that 7% of individually packed strips were contaminated versus 45% of strips packed in multi-use vials ($p < .001$). Pathogens included skin flora and a high percentage of methicillin-resistant species, including *Staphylococcus epidermidis* and *Staphylococcus hemolyticus* (*6*).

Despite the differences in technical methods in these studies, the researchers replicated the findings of widespread bacterial contamination in glucose test strips from multi-strip vials in use in hospitals. These diverse investigations also found enteric and skin flora—including resistant strains.

The Issue of Glucose Strip Wastage

If vials were designated for single-patient use, unused strips would represent wastage when discarded, akin to pharmaceutical wastage. The financial consequences of discarding unused test strips are unique to any given facility depending on the vial count, patient length of stay, patient volumes, percentage of patients being tested, and other variables.

One independently developed model of the costs of test strip vial wastage projected costs of strip wastage for one healthcare facility comparing 50- and 25-count vials and found that the former more than doubled wastage. The authors underscored that vial count and offering of individually wrapped strips could influence vendor selection if healthcare facilities adopted the practice of one vial: one patient (*7*).



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Glucose Test Strip Handling Hazards

The practice of a designated glucose test strip vial for each patient may not deal with the root cause of the contamination issue, as suggested by the findings from the U.K. study. In that study, the investigators did not see any reduction in contamination with a single-patient vial designation (*4*).

The opening of a strip vial is small relative to the size of two fingers needed to grasp a single test strip. This leads to repeat touching of strips in the vial, attempts to shake out a strip, and accidental strip spillage onto nearby contaminated surfaces or floors. Equipment in intensive care units can harbor bacteria with the same antibiotic susceptibility profiles of patient isolates (*9*). Yet most hospitals do not have protocols for what to do with spilled strips, so spilled, contaminated strips may be returned to the vial. One manufacturer has developed a spill-proof vial in response to patient dissatisfaction with home testing options (*8*).

The impact of vial count has not been studied as an independent factor in strip contamination. The percentage of strips remaining in the vial does not appear to be a statistically significant predictor of contamination (*4*).

Perhaps most importantly, the practice of repeatedly entering a vial and touching the test strips under nonsterile conditions yields repeated opportunities for contamination in both directions. Caregivers contaminate their hands after direct patient contact and also after touching surfaces and equipment. Inadequate hand hygiene before and after entering a patient zone and performing blood glucose testing may result in cross-transmission of pathogens and patient colonization or infection (*9*). Until improved system design—such as glucose biosensors or touchless testing systems—eliminates current testing processes so fraught with contamination risk, the best prevention is meticulous hand hygiene.

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PATIENT SAFETY FOCUS

Patient Satisfaction Is Not the Same as Patient Safety

Q&A with Michael Astion, MD, PhD

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I work in a hospital lab, and the hospital has goals for both patient satisfaction and patient safety. I am finding that these are sometimes in conflict, but my boss told me that they don't have to be. Is my boss right or wrong?

Your boss is right *and* wrong. Patient satisfaction and patient safety do not have to be in conflict, but when they are, resolution is challenging.

The Agency for Healthcare Research and Quality defines patient safety as "freedom from accidental or preventable injuries produced by medical care" (*1*). In this definition, patient safety is considered a characteristic of healthcare institutions seeking to eliminate harm caused by medical care. Despite this noble aim, however, patient safety as an organizational goal can still conflict with other organizational objectives such as risk management, patient satisfaction, employee engagement, fiscal responsibility,

client satisfaction (e.g., physicians in laboratory outreach), and environmental stewardship.

In a series of talks to laboratory outreach directors 10 years ago, I outlined the conflicts between client satisfaction and patient safety. For example, some physicians were unhappy when laboratories forbade relabeling a mislabeled specimen, even though a restrictive specimen relabeling policy is a quintessential part of patient safety. Similarly, some physicians were unhappy when they could no longer order some of their favorite tests, which had become obsolete because they were replaced by better tests. When client satisfaction and patient safety did not align, conflicts arose between clients and laboratory quality managers, as well as between laboratory sales staff and quality managers.

Satisfaction Versus Safety

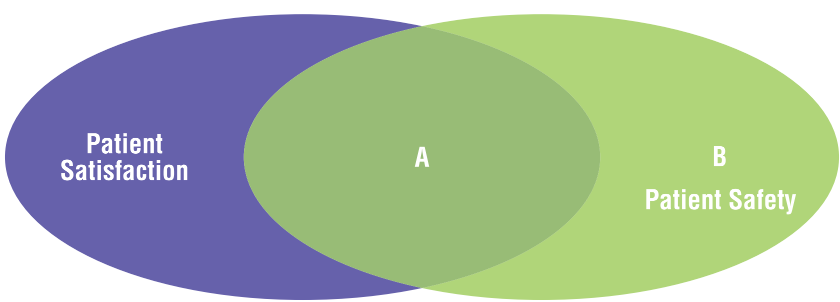
The relationship between patient satisfaction and patient safety can be even more complicated than the lab's relationship with physicians (Figure 1). Patient satisfaction itself has become a moving target complicated by several interrelated trends: the Googlefication of healthcare, the direct-to-consumer healthcare movement, the amplification of both information and misinformation through social media, and the emphasis by healthcare organizations on patient experience.

Considered the basis of patient satisfaction, patient experience is defined as "the sum of all interactions, shaped by an organization's culture, that influence patient perceptions across the continuum of care" (*2*). The desire to enhance patient experience can be challenging when some direct their own healthcare in ways that clash with organizational goals.

Resolving Conflicts

Rarely do conflicts between patient safety and patient satisfaction have easy answers. However, both care providers and laboratory staff can find a way forward by empathizing with patients and explaining that their healthcare facility is patient-centered, but not patient-directed when it comes to clinical laboratory services. Many times a sincere, judgment-free, fact-based conversation leads to a reasonable result. At the end of the day, when a conflict arises between patient safety and patient satisfaction, patient safety must remain paramount.

F1 Overlapping, but Not Identical, Goals
The Complicated Relationship Between Patient Safety and Patient Satisfaction



Region A refers to examples of quality practices and improvements in the laboratory that are associated with both enhanced patient satisfaction and patient safety:

- Decreasing the time until patients receive their lab results
- Helping physicians properly order, retrieve, interpret, and communicate results to patients
- Decreasing laboratory errors known to be associated with patient harm such as mislabeling
- Increasing the accuracy and precision of a test
- Enabling a smaller volume of blood to be used for a laboratory test
- Making blood collection less painful

Region B refers to laboratory practices that improve patient safety, but which may make patients dissatisfied. Sample cases include:

- A patient goes to a low-quality direct access testing provider and his blood sample is labeled with one identifier. The patient is angry when the laboratory refuses to accept the specimen. The patient says: "I saw them label it, and I do not know what you mean by the two-identifier rule."
- After Googling her symptoms, a patient pressures a family practice physician into ordering an expensive genetic test for a disease that the patient is exceedingly unlikely to have. The laboratory informs the family practitioner that this test must be approved by a medical geneticist. After a phone consult with the family practitioner, the medical geneticist does not approve the test order. The patient is bitter, but the family practitioner is relieved.
- A patient demands unconventional testing not on the laboratory's test formulary (e.g., IgG allergy testing) and feels dissatisfied when the laboratory will not send out the test.
- After negative results by a lab's automated, Food and Drug Administration-approved method, a patient demands that her Lyme disease test be sent out to a lab that is banned by the lab's medical director because it nearly always produces positive results.

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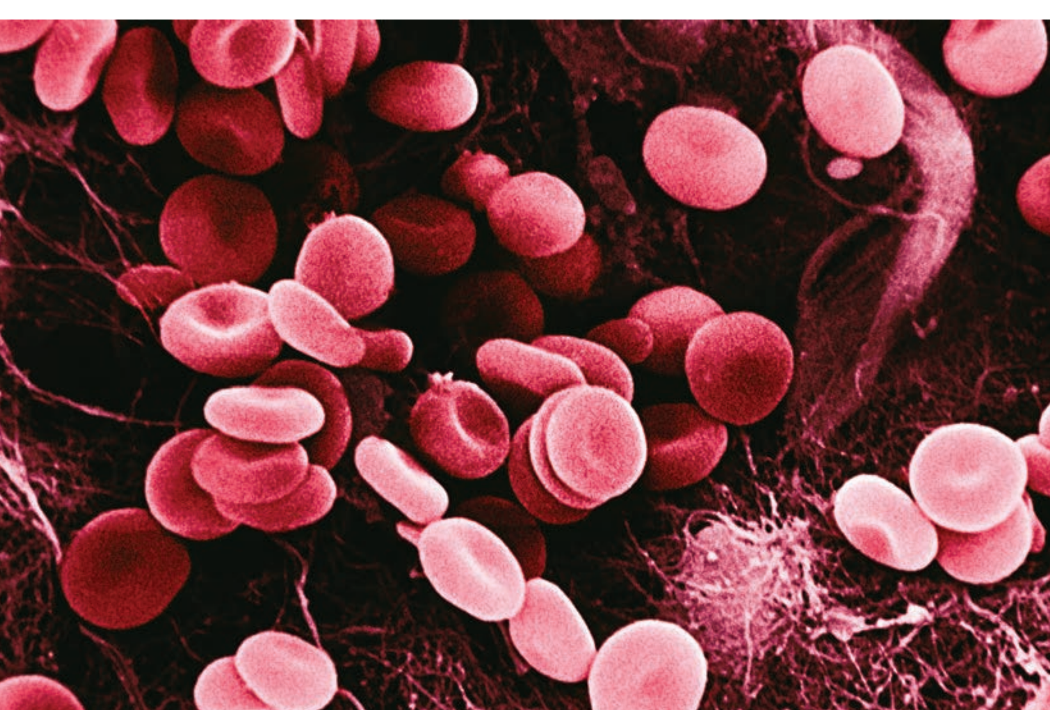
Regulatory Roundup

Sysmex CBC Test Becomes First to Receive CLIA Waiver

The Food and Drug Administration (FDA) has granted premarket clearance and a CLIA waiver to Sysmex America for its complete blood cell count (CBC) test, the XW-100 Automated Hematology analyzer. This is the first CBC test to receive a CLIA waiver, enabling non-traditional laboratory sites, such as physicians' offices, and nonmedical staff to perform it. The XW-100 Automated Hematology analyzer is intended for use in patients 2 years of age and older who require a whole blood cell count and white blood cell differential. FDA reviewed the device through the Dual Submission pathway, which is a streamlined regulatory pathway for both 510(k) clearance and CLIA Waiver by Application. To support the use of this device in CLIA-waived settings with untrained operators, the analyzer provides simple instructions for what to do when results are flagged or outside of a specified range. The number of hematology parameters has also been reduced to 12 to eliminate results that are most susceptible to inaccuracy or require additional testing.



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FDA CREATES STREAMLINED REGULATORY PATHWAY FOR NGS-BASED CANCER PROFILING TESTS

The Food and Drug Administration (FDA) has unveiled a more efficient process for authorizing next-generation sequencing (NGS)-based cancer profiling tools that aims to reduce the burden on test developers and spur innovation. As a first step in establishing this new regulatory pathway, the agency has accredited the New York State Department of Health (NYSDOH) as an FDA third-party reviewer of in vitro diagnostics. Moving forward, if manufacturers have received NYSDOH approval for an NGS-based tumor profiling test, they will no longer need to submit a separate 510(k) application to FDA. Instead, developers may choose to request that New York state forward their NYSDOH application, as well as the state's review memorandum and recommendation, to FDA for consideration. In the future, other accredited, third-party FDA reviewers also may become eligible to conduct such reviews and make clearance recommendations to the agency.

In addition, FDA is establishing a class II regulatory pathway for the review of NGS-based tumor profiling tests. Class II designation makes these tests eligible to go through FDA's 510(k) clearance process, either via an application submitted directly to the agency or through an accredited third-party reviewer.

MEMORIAL SLOAN KETTERING GETS FDA AUTHORIZATION FOR

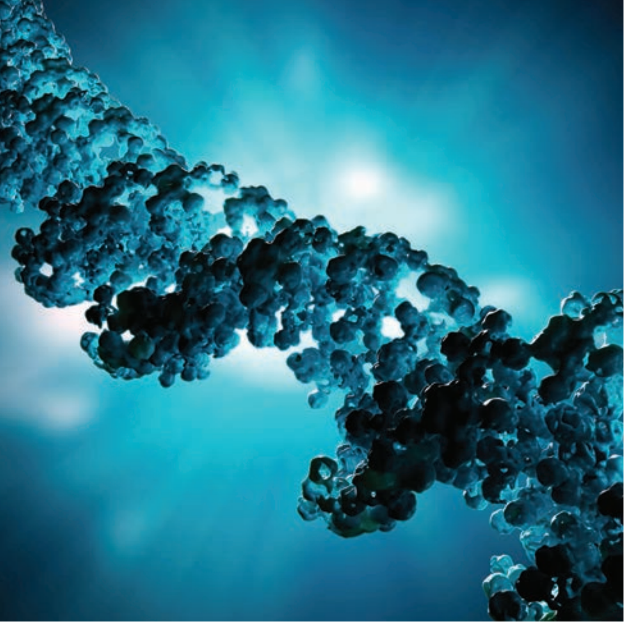
GENOMIC TUMOR PROFILING TEST

The Food and Drug Administration (FDA) has authorized Memorial Sloan Kettering Cancer Center's (MSKCC) tumor profiling test IMPACT, which stands for integrated mutation profiling of actionable cancer targets. The IMPACT test compares tumor tissue to a sample of normal tissue from the same patient to detect genetic alterations that might help guide treatment options. Using next-generation sequencing, the test rapidly identifies mutations in 468 unique genes—a higher number of oncogenic mutations than any test previously reviewed by FDA—as well as other molecular changes in the genomic makeup of a person's tumor.

FDA evaluated the test through the de novo premarket review pathway for precision, accuracy, and limit of detection. Results indicated that the assay performs with greater than 99% accuracy and is capable of detecting a mutation at a frequency of approximately 5%. Additionally, when compared to traditional methods, IMPACT's detection of microsatellite stability was concordant more than 92% of the time across multiple cancer types in 175 cases.

FDA READY TO ENFORCE NEW SPECIAL CONTROLS FOR CERTAIN RAPID FLU TESTS

On February 13, 2017, the Food and Drug Administration (FDA) reclassified rapid influenza virus antigen detection test systems (RIDTs) that were regulated as influenza virus serological reagents from class I into class II with special controls. For antigen based RIDTs that were legally marketed prior to February 13, 2017, FDA delayed enforcing these special controls in order to give manufacturers time to ensure their devices meet minimum performance criteria and to submit 510(k) applications for significantly changed or modified devices. The new special controls for previously marketed RIDTs will now go into effect on January 12, 2018. The special controls require that RIDTs meet minimum sensitivity and specificity criteria; that manufacturers compare device performance with FDA-accepted methods; and that RIDTs undergo analytical reactivity testing with contemporary influenza strains as well as flu strains for which Health and Human Services has declared an emergency or potential emergency.



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DRAFT GUIDANCE ON CLIA WAIVER APPLICATIONS RELEASED BY FDA

The Food and Drug Administration (FDA) has published two draft guidance documents to help in vitro diagnostic manufacturers apply for and receive CLIA waivers. The first draft guidance document encompasses the appropriate use of comparable performance between a user in a waived facility and a user in a moderately complex laboratory to demonstrate accuracy. When finalized, this content will update Section V of the 2008 guidance, "Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices." The second draft guidance document, "Recommendations for Dual 510(k) and CLIA Waiver by Application Studies," describes the agency's expectations regarding study designs for generating data that supports both 510(k) clearance and CLIA Waiver by Application. FDA hopes that increased use of this dual pathway will speed up the process of bringing diagnostic devices to CLIA waived settings.

FDA is seeking feedback on both draft guidance documents through January 29, 2018. Comments can be submitted at www.federalregister.gov.

FDA APPROVES GRIFOLS' GENETIC ALPHA-1 ANTITRYPSIN DEFICIENCY TEST

Grifols, a diagnostic company based in Barcelona, Spain, has received Food and Drug Administration approval for a new genetic test to diagnose alpha-1 antitrypsin deficiency. This marks the first time the agency has approved a molecular assay for this condition. Known as the A1AT Genotyping test, it analyzes in a single reaction 14 mutations in the *SERPINA1* gene that comprise the majority of the most prevalent known genetic alterations that cause alpha-1 antitrypsin deficiency. The test can be performed on 192 samples simultaneously per kit and is designed for use with DNA extracted from venous blood samples as well as from dried blood spots. Developed by Progenika Biopharma, a Grifols subsidiary, the A1AT Genotyping test previously received CE marking in December 2016.

CureOne, Washington University Collaborate on Genomic Cancer Database

CureOne has partnered with the Washington University School of Medicine in St. Louis to consolidate and standardize genomic cancer data. Under the terms of the agreement, CureOne will work with the university's clinical next-generation sequencing (NGS) laboratory, Genomics and Pathology Services (GPS), to achieve this goal through the N1 Registry. CureOne created the N1 Registry to serve as an open-access database that links NGS data with information about molecular or immunological testing and treatments, as well as clinical outcomes data. The N1 Registry also acts as a conduit for enrollment in clinical trials and collects information on the growing number of patients who receive NGS testing.

Washington University School of Medicine is the first academic organization to collaborate with CureOne, and CureOne plans to leverage the university's extensive experience helping other laboratories and regulatory partners to understand and build clinical NGS tests for cancer. "In collaboration with CureOne, we'll provide high-quality, mutational profiles for patients enrolled in [the N1 Registry], hopefully across many different cancer types," said Jon Heusel, MD, PhD, chief medical officer at GPS. "As the N1 Registry grows, we expect it will include many thousands of cases [including rare cancers] where the genomic data, patient phenotypic data, and clinical outcomes data are all aligned and high-quality … which are essential to drawing significant conclusions that can inform precision cancer treatments."

QUEST BUYS CLINICAL LAB NETWORK IN SOUTHERN CALIFORNIA

Quest Diagnostics has acquired certain assets of California Laboratory Associates (CLA), a clinical lab network serving patients and providers in the greater Los Angeles area. CLA's operations and patients were previously supported by caregivers and the laboratory at Providence Saint Joseph Medical Center in Burbank, California. Quest will now add several CLA patient service centers to its network in Los Angeles County, while Providence Saint Joseph will continue to operate its lab for hospital patients and certain outside physician services. "We look forward to bringing Quest's insights and innovations to more individuals and providers in Southern California," said Steve Rusckowski, chairman, president, and CEO of Quest. "This acquisition will deepen our presence and ability to serve the region, while advancing our strategy to accelerate growth and drive operational

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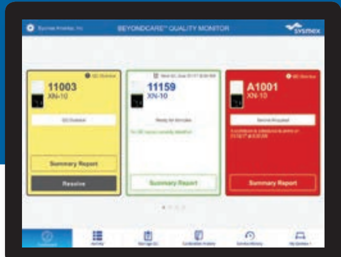

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UT AUSTIN LAUNCHES INTEGRATED DEPARTMENT OF DIAGNOSTIC MEDICINE

Dell Medical School at The University of Texas in Austin has created a new Department of Diagnostic Medicine, which is developing partnerships with local clinical practices and community physicians to improve accuracy in diagnoses, make testing more convenient and efficient, lower costs, and broadly integrate patient health data with electronic medical records. Most medical schools have separate departments for pathology, radiology, and laboratory medicine, but the new department at Dell Med will integrate these three specialties. Key partners include local Central Texas organizations such as Austin Radiological Association (ARA) and Clinical Pathology Associates (CPA), as well as other major Dell Med collaborators such as Seton Healthcare Family. Through these partnerships, diagnostic testing will be performed in in-patient facilities managed by Seton or outpatient clinical sites jointly operated by Dell Med and Seton. Specialty physicians in ARA and CPA will supervise and interpret the tests, and the results will be available to regional referring physicians and their patients.

ROCHE TO ACQUIRE LABORATORY BUSINESS ANALYTICS COMPANY

Roche has signed an agreement to buy Viewics, a privately held software company focused on laboratory business analytics. Roche said the acquisition will expand its offerings for integrated core labs and enable labs to make faster, data-driven decisions in their operations. Viewics software provides automated data extraction, cleansing, and augmentation architecture and is designed to resolve problems that laboratory IT staff encounter when using generic business intelligence solutions, traditional data warehousing, or extraction methodologies. As a cloud-based product, it is infrastructure-agnostic, interactive, and accessible from mobile devices and desktop computers. "The Viewics platform generates insights that can inform real-time decisions about costs, laboratory performance, and many other areas affecting today's modern healthcare organizations," said Keith Laughman, CEO of Viewics. "We are looking forward to working with our Roche colleagues in helping to support the lab's critical role in healthcare delivery."

PATHOQUEST, MEMORIAL SLOAN KETTERING TO VALIDATE NGS PATHOGEN BLOOD TEST

PathoQuest, a spinoff of Paris' Institut Pasteur, has joined forces with Memorial Sloan Kettering Cancer Center (MSKCC) to establish the company's proprietary iDTECT Blood test in MSKCC's microbiology lab. Using next-generation sequencing technology, iDTECT Blood offers a culture-free, agnostic metagenomics approach to pathogen detection. It also features a proprietary sample preparation process that applies to several types of samples, as well as a proprietary pathogen genome sequence database and automated analysis pipeline. The partnership aims to compare iDTECT Blood with standard methods used to identify microorganisms responsible for infections in patients presenting with febrile neutropenia. "This study will add to the clinical evidence we have accumulated to date which demonstrates the improved ability to identify bacteria and viruses from blood samples using next-generation sequencing technology in combination with our proprietary iDTECT Blood sample preparation process and bioinformatics solution," said Jean-Francois Brepson, PathoQuest's CEO.

BGI GENOMICS, GENOKS TEAM TO EXPAND GENETIC TESTING IN TURKEY

BGI Genomics and the Turkish genomics healthcare company Genoks have inked a new memorandum of understanding (MOU) broadening their existing partnership in the field of noninvasive prenatal testing. The updated MOU commits BGI Genomics to provide full technical and strategic support to Genoks in an effort to expand the clinical genetic testing market in Turkey. In addition, both companies will collaborate on next-generation sequencing services for general research and drug development for the Turkish population. "Our wide portfolio of genetic tests, many years of sequencing expertise and proprietary sequencing platforms uniquely position BGI to meet the diverse business needs of our local genomics partners," said Matt Poulter, global marketing manager of BGI Genomics. "We have worked closely with Genoks for more than five years and are pleased to expand this partnership to take advantage of the significant potential that the Turkish market offers in the field of clinical genomics and sequencing services for research."

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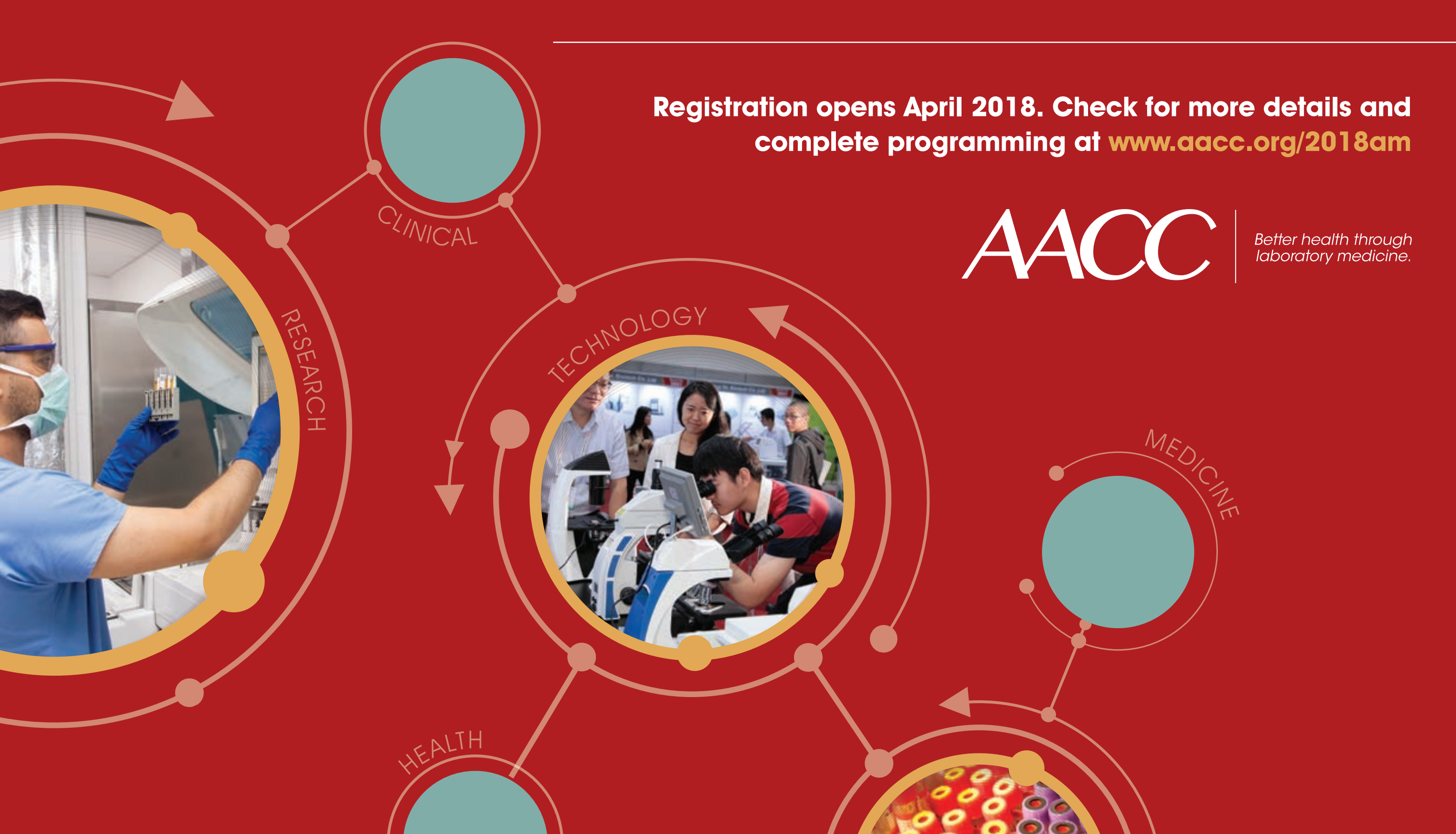

The Challenges of Tests for miRNA Markers

EXPERT
Kenneth Witwer, PhD

What standard methods are currently used to measure microRNA (miRNA) biomarkers?

A: Typically, miRNA biomarkers are measured with quantitative polymerase chain reaction (qPCR) after the RNA is converted to complementary DNA (cDNA). Since miRNAs are only about 20-25 nucleotides in length, though, before they are converted to cDNA a longer molecule is generated that will work as a qPCR substrate. Valid strategies for accomplishing this include poly-adenylation, adapter ligation, and application of miRNA-specific stem-loop reverse transcription primers. Our group and many others rely on the latter method, which was described in the scientific literature more than 10 years ago (Nucleic Acids Res 2005;33:e179). Why? Stem-loop qPCR efficiently discriminates between the unprocessed precursor miRNA and mature miRNA, uses a fluorescently labeled hydrolysis probe that imparts additional specificity, and achieves better technical reproducibility compared with other systems we have tested.

What challenges do clinical laboratories face when using miRNA biomarkers?

miRNA-based diagnostics are finally entering the clinic. To give an example, qPCR miRNA assays are now available to help endocrine surgeons better classify thyroid cancers. However, these kinds of tests are likely best suited to a companion role. In contrast with DNA or RNA-based tests that indicate the presence of a mutation(s), miRNA tests produce results that are difficult to interpret. Most miRNAs are expressed widely in a non-cell-specific manner, and they do not differ drastically in level between cases and controls. In fact, a truly disease-specific miRNA probably does not exist, whether in cancers or in non-neoplastic diseases. Many miRNAs proposed as biomarkers for one disease have been found in association with a bewildering variety of other conditions (PLoS One 2014;9:e89565).

Although very stable, miRNAs also contain little information. As a result, successful miRNA-based tests must often measure ten or more miRNA species with varying weights assigned to each. In particular, liquid biopsies in which blood, urine, or other fluids are gathered present special difficulties compared with tissue sampling, as miRNA levels are very sensitive to pre-processing and post-processing factors.

Most miRNAs are expressed widely in a non-cell-specific manner, and they do not differ drastically in level between cases and controls.

Data processing steps come with challenges as well, including normalization or adjustment to invariant miRNAs or other analytes. When selecting tools for miRNA test data analysis, clinical labs should ensure strict standardization of the entire process, from obtaining and processing the sample through results reporting. This is the key to reproducible and potentially informative miRNA results, no matter what technology is used.

Could emerging assays facilitate clinical labs' adoption of miRNA testing?

Recent innovations in miRNA detection include amplification-free technologies, assays that do not require extensive RNA purification, detection of signal by flow cytometer, and departure from traditional cDNA generation, such as using the miRNA itself as a primer. These developments may simplify adoption of miRNA testing in clinical laboratories. An established technology, digital PCR (dPCR), also provides a quasi-absolute readout or copy number for miRNAs, at least for assays that have been thoroughly validated. dPCR thus eliminates the need for standard curves as well as the influence of normalization strategies. However, even with these advances, the other challenges of miRNA biomarkers still remain.

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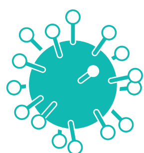

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