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 identify 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 (sLDL-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).
Few studies have examined the validity of haptoglobin as a marker of in vivo hemolysis. The studies that do exist have shown varying degrees of sensitivities and specificities for haptoglobin depending on the cutoff concentration used.
For the first time since the insurance exchanges established by the Affordable Care Act (ACA) were established in 2014, premiums for the lowest cost plans will drop in 2019, with an average reduction of 1.5%. According to the Centers for Medicare and Medicaid Services (CMS), average individual market premiums more than doubled from $2,784 per year in 2013 to $5,712 on HealthCare.gov in 2017, an increase of 105%.

In addition, many insurers had dropped out of the federal exchange, but this trend is reversing as well. Some 23 insurers have said they will add plans to the exchange, and the number of counties with only one insurer has dropped from 56% in 2018 to 39% in 2019.

However, a study by the Kaiser Family Foundation found that premiums would be significantly lower if not for changes made to private insurance markets since 2016. According to the Kaiser analysis, plans on the exchange will cost an average of 16% more than they otherwise would due to the loss of ACA cost-sharing reduction payments, the repeal of the individual mandate penalty, and the administration’s expansion of looser regulated plans.

Beginning in 2017, CMS allowed physicians to bill for services related to home monitoring, which includes devices that track and digitally share data on blood pressure, blood glucose, and other parameters. In 2019, however, home health agencies will be able to bill for the actual monitoring instruments and services themselves. This will foster adoption of emerging home monitoring and testing technologies, and encourage greater data sharing and coordination of care among patients and providers, according to CMS.

CMS also is focusing on home-based care in the Medicare Advantage proposed rule. Medicare Advantage, in which Medicare pays a single capitated payment for private managed care, has grown enrollment 71% since 2010, attracting more than a third of Medicare beneficiaries. The proposed telehealth benefits for 2020 would expand these services beyond narrowly defined situations like rural areas and special telehealth centers that fee-for-service Medicare traditionally allowed, making telehealth a part of core “basic benefits” under Medicare Advantage rules.

In a final rule setting payment for home healthcare in 2019, and in a proposed rule for Medicare Advantage plans in 2020, the Centers for Medicare and Medicaid Services (CMS) is adding new reimbursement for remote patient monitoring technology and expanding telemedicine options for providers. The home healthcare rule also implements a payment model that focuses on groups of patients with certain medical needs rather than the volume of services.

“Using new technology … will provide home health agencies and doctors what they need to give patients a personalized treatment plan that will result in better health outcomes,” said CMS Administrator Seema Verma.

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The GAO report found that in states that expanded Medicaid, 9% of low-income adults delayed medical care, compared to 20% in non-expansion states. The gap narrowed somewhat for specific preventive services. For example, 49% in expansion states received a blood cholesterol check within the last year versus 42% in non-expansion states. Low-income adults in expansion states were only slightly less likely to visit the emergency department, 27% versus 28%.

Overall, 5.6 million low-income adults were uninsured in 2016. Of these, an estimated 1.9 million resided in expansion states, compared with an estimated 3.7 million in non-expansion states.

Most people on Medicaid are children or people with a disability or who are elderly. Currently 31 states and the District of Columbia have expanded Medicaid eligibility under the ACA, and this new population now makes up 20% of the Medicaid rolls. Most work, with 16% unemployed across all states.
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Toxicology services are in high demand, but even as startup labs focused on toxicology break into the market and established clinical labs look to expand their offerings, maintaining the highest standards of testing while also running efficient operations remain essential given the far-reaching consequences of toxicology testing. Before labs dive (or dive deeper) into the booming drug testing market, they will do well to conduct a strategic cost-benefit analysis to ensure better financial performance and long-term success.

Whether a lab is just starting toxicology testing or expanding its offerings, the driving consideration in determining the most appropriate solution turns on this question: What purpose will the toxicology lab serve?

GETTING CERTIFIED
The purpose and complexity of testing dictate the certifications and practices labs must follow. For example, toxicology evaluations in clinical settings may have legal implications under certain circumstances, especially when it comes to pregnant women, children, and newborns. However, unless ordered by law enforcement or the judicial system, toxicology testing in clinical laboratories falls under CLIA regulations. Some states or institutions may have additional requirements.

Non-forensic toxicology testing such as for pain management and non-Department of Transportation workplace screenings also fall under CLIA regulations. Labs can elect to use chain of custody forms and abide by other restrictive procedures consonant with legal system standards—like setting cutoff concentrations for positive results—but aren’t under regulatory requirements to do so. In contrast, labs that perform strictly forensic toxicology testing are CLIA-exempt. Even so, they may be subject to some accreditation requirements, such as the College of American Pathologists Forensic Drug Testing program, which provides accreditation for laboratories performing workplace drug testing.

WHAT’S ON THE MENU?
A lab’s test menu also needs to reflect the overall purpose of its toxicology services. Clinical laboratories that perform limited toxicology testing for diagnostic, management, and prognostic purposes already understand the concept of an essential toxicology menu. This menu usually includes screening for the major classes of abused drugs (amphetamine, barbiturates, benzodiazepines, cocaine, opiates, propoxyphene, and tetrahydrocannabinol), alcohol, and common therapeutic drugs like acetaminophen, salicylates, digoxin, antidepressants, and aminoglycosides. Laboratories offering advanced testing services may extend this core menu to hundreds of drugs and metabolites. A lab’s director ultimately determines how deep its testing menu should be, based on the testing volume and financial considerations for each drug of interest.

FROM SCREENING TO CONFIRMATION
The testing menu in turn imposes needs for specific instrumentation and methodologies. Point-of-care drug tests are broadly available and include immunoassay-based devices for rapid qualitative urine-based evaluation of commonly abused drugs, together with limited evaluation of a specimen’s quality. However, these devices generally are only suitable for settings with low test volumes.

Labs with higher testing volumes need to consider carefully their throughput and instrumentation for screening. Although toxicology screening can be accomplished very quickly, considering immunoassays’ limited specificity and
cross-reactivity issues, the results are considered presumptive and need to be confirmed with a more sensitive and specific method less prone to interferences, such as various mass spectrometry (MS) technologies. MS offers many advantages, including accurately quantifying drugs, discriminating between different compounds in the same drug class, discerning therapeutic versus abuse level concentrations, and detecting compounds at very low concentrations. Nevertheless, the confirmatory process not only involves more sophisticated instrumentation, but also is more labor intensive and has a longer turnaround time.

Most small and large laboratories find drug screening clinically and financially feasible, but confirmatory and advanced toxicology testing for these facilities is more challenging. Many use reference laboratories for these purposes; however, larger laboratories serving broad population bases need to consider the turnaround time of outsourcing. This underscores the necessity of a cost-benefit analysis for labs considering confirmatory and advanced toxicology services.

**TIME FOR AN MRO?**

To meet the highest standards of toxicology testing, labs need to not only render analytically accurate results but also interpret those results correctly. The latter, in the context of a patient’s clinical presentation and medical and medication history, can be very challenging. While qualified laboratory personnel can assure high quality analytical performance, procedures for interpreting toxicology results often require a higher level of expertise. Both the Substance Abuse and Mental Health Services Administration and Department of Health and Human Services highly recommend involving medical review officers (MRO), who have training, certification, and knowledge regarding the pharmacology and toxicology of illicit drugs, testing, and instrumentation. MROs not only ensure correct interpretation of toxicology reports, but also support lab efforts to provide quality toxicology services. They review all positive, adulterated, substituted, and invalid test results before the final results report, represent a link between all participants in the drug testing process—donor, collector, testing lab, and ordering institution—and also play a key role in interfacing with the legal system as needed.

The decision to engage an MRO, along with choice of testing menu, appropriate regulations to follow, and choice of test menu, instruments, and methods all flow from the crucial question of a lab’s purpose.

Alina G. Sofronescu, PhD, NRCC-CC, FACB, is medical director of clinical chemistry and the toxicology laboratory and an associate professor of pathology and microbiology at the University of Nebraska Medical Center in Omaha.

*EMAIL: alina.sofronescu@unmc.edu*

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**EPILEPSY**

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**URINE DRUG TESTS**

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**ANTIRETROVIRAL**

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**ANTI-INFECTIVES**

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LIQUID BIOPSY DETECTS MORE TARGETABLE MUTATIONS IN LUNG CANCER THAN TISSUE BIOPSY ALONE

A study designed to test the clinical utility of liquid biopsy in non-small cell lung cancer (NSCLC) found that in comparison to tissue biopsy this method—plasma-based circulating tumor DNA (ctDNA) next-generation sequencing (NGS)—nearly doubled the number of targetable mutations detected (JAMA Oncology 2018; doi:10.1001/jamaoncol.2018.4305). The findings "argue for incorporation of plasma-based genotyping into routine clinical management of patients with NSCLC," according to the authors.

Of the 323 patients with metastatic NSCLC enrolled in this prospective cohort study conducted at the University of Pennsylvania (Penn), the investigators identified targetable mutations in 113 (35%), 94 of whom had ctDNA NGS testing only. Out of these 94, 31 (33%) had a targetable mutation detected and did not need to undergo tissue biopsy. In the 229 patients who underwent concurrent ctDNA NGS and tissue biopsy or who were unable to undergo tissue biopsy, the investigators identified by tissue biopsy a therapeutically targetable mutation in 47 (20.5%). However, adding ctDNA NGS increased to 82 (35.8%) the number of the targetable mutations identified.

The authors also reported that 85.7% (42) of patients who received targeted therapy based on ctDNA NGS achieved a complete or partial response, or maintained a stable disease status.

Immunome of Healthy Subjects: Tool for Advancing Research, Treatment

A new open-access data tool, the 10,000 Immunomes Project (10KIP), offers researchers and clinical immunologists a standardized reference dataset of normal human immunity (Cell Reports 2018;25:513-22). Compiled using data from 83 publicly available studies involving 10,344 individuals which the investigators manually curated and harmonized, the 10KIP aims to accelerate discovery in immunology. “We believe that integrating these datasets and presenting them as a fully open resource will pay dividends in terms of both basic research and the precision and robustness of ongoing translational efforts in immunology,” they wrote.

The data come from a diverse population, split evenly between men and women, and with racial and age diversity, including 1,000 subjects younger than age 18 and 1,300 older than age 65. The data were robust enough that the researchers were able to create a custom control group of women ages 18 to 40 to compare against 56 pregnant women who participated in a study of immunologic changes in pregnancy.

The authors standardized analyte names and units of measure, divided data by sample type, and corrected for sample dilutions. The inaugural dataset includes 10 data types in standardized tables, such as enzyme-linked immunosorbent assay (ELISA), multiplex ELISA, and flow cytometry and gene expression from both whole blood and peripheral blood mononuclear cells, as well as common blood tests like complete blood count, comprehensive metabolic panel, and fasting lipid profile. The authors deployed a model used in genomic analyses to compensate statistically for batch effects of multiplex ELISA data.

In analyzing the data, the researchers found that 20% of the 50 commonly measured cytokines, chemokines, and metabolic factors measured by multiplex ELISA differed significantly by race. For example, African-Americans have significantly higher levels of C-X-C motif chemokine 5 compared with other races. They also learned that 19 of these analytes vary significantly with age.

Analysis of serum cytokine measurements showed that some in this normal healthy population fall in a relatively tight range, but others, like C-C motif chemokine 4, have quite a wide range.

“These findings affirm the benefit of maintaining and growing a diverse common control population for the future of clinical and precision immunology,” according to the investigators.
The clinical laboratory at Penn’s Center for Personalized Diagnostics conducted the tissue biopsy NGS starting with a 47-gene panel, and then using Agilent Technologies’ 153-gene panel. Guardant Health performed the ctDNA NGS using its Guardant360 panel, which increased from 70 genes to 73 during the study. The panels tested for therapeutically targetable driver and resistance mutations in \textit{EGFR}, \textit{ALK}, \textit{MET}, and others.

“These findings show that liquid biopsy is increasing the detection of mutations we can target and improving patient outcomes, and when you combine that with the reality that liquid biopsy is less invasive for patients and, in some cases, may be the only option for patients, the clinical impact is very clear,” said co-lead author Charu Aggarwal, MD, MPH, an assistant professor of hematology-oncology at Penn.

\textbf{NOVEL POINT-OF-CARE TROPONIN ASSAY OFFERS AMI RULE-OUT DISCRIMINATION COMPAREABLE TO LAB-BASED TEST}

An observational study at an emergency department (ED) in New Zealand has found that a novel point-of-care (POC) cardiac troponin (cTn) assay produces results within 15 minutes of blood sampling and has comparable discriminatory ability to a lab-based high-sensitivity (hs) cTn assay for ruling out suspected acute myocardial infarction (AMI) after a single blood test (JAMA Cardiology 2018; doi:10.1001/jamacardio.2018.3368). The study was designed to assess the clinical accuracy of the new test, and these findings suggest that if the test were used in ED settings it might facilitate earlier decision-making, thereby expediting safe discharge of low-risk patients, according to the authors.

POC cTn tests render results quickly, but so far have lacked sufficient precision at low concentrations to enable clinicians to safely rule out AMI based on a single sample. For this reason, EDs still rely on lab-based hs-cTn assays, which, though accurate at low concentrations, have longer turnaround times.

The researchers evaluated a novel “high precision” POC cTn assay, the Abbott Point of Care TnI-Nx test. They emphasized that this assay has not yet been established as high-sensitivity, which requires a coefficient of variation <10% at the 99th percentile of a healthy population and that the assay measures cTn between the level of detection and the 99th percentile in at least 50% of healthy individuals.

In 354 patients assessed for suspected AMI, 16.1% actually experienced AMI. A TnI-Nx result <11 ng/L identified 56.7% as low risk, with both a sensitivity and negative predictive value (NPV) of 100%, respectively, and a TnI-Nx result <3 ng/L identified 43.5% of patients as low risk, also with sensitivity and NPV of 100%.

The authors speculated that this assay might be most useful in rural hospitals with limited rapid access to lab-based cTn assays.

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Redefining Diabetes
For many of the 425 million people worldwide with diabetes, managing their disease and forestalling its serious complications remain frustratingly out of reach. Patients with type 2 diabetes in particular present with a wide range of disease and respond quite differently to treatments. Researchers and clinicians have long recognized that the current labels of type 1 and type 2 diabetes don’t accurately capture this heterogeneity. Ongoing research aims to better elucidate the underlying mechanisms behind hyperglycemia from either too little insulin or insufficient insulin effectiveness. Along this line of investigation, researchers in Sweden have proposed a new classification system for diabetes consisting of five subtypes rather than the current two (Lancet Diabetes Endocrinol 2018;6:361-9).
“Treatment of type 2 diabetes has not been very successful,” said Leif Groop, MD, PhD, senior study author and a physician and professor of diabetes and endocrinology at Lund University Diabetes Centre in Malmö. “Lumping all patients together makes it very difficult to individualize the right treatments.”

If verified, the research group’s proposed classifications could enable physicians to offer better tailored therapies, he suggested, something the entire field is striving for. “The real question we need to address is how do we figure out what drug to give to what person versus another,” stressed Zachary T. Bloomgarden, MD, MACE, clinical professor of medicine at the Icahn School of Medicine at Mount Sinai in New York City and editor of the Journal of Diabetes.

Beyond Types 1 and 2
Diabetologists readily acknowledge that the type 1/2 dichotomy is not sophisticated enough, but whether Groop’s and his colleagues’ proposed classification will ever make its way into practice remains to be seen, said Clare J. Lee, MD, MHS, assistant professor of medicine in the division of endocrinology, diabetes, and metabolism at Johns Hopkins Medicine in Baltimore. “I don’t think this one article is going to change the way we classify things tomorrow, but I think it certainly lays the foundation for looking deeper into a better understanding of the heterogeneity within diabetes that’s not quite captured by just differentiating as type 1 versus type 2.”

Groop and his colleagues conducted a cluster analysis of 8,980 patients with newly diagnosed diabetes from the All New Diabetics in Scania cohort. To create their clusters, the scientists assessed glutamic acid decarboxylase antibodies (GADA), age at diagnosis, body mass index, hemoglobin A1c, and homeostasis model assessments of β-cell function (HOMA 2-B) and insulin resistance (HOMA-IR) based on C-peptide concentrations. They also used patient records to evaluate prospective data on complications patients developed and on their prescriptions.

The investigators replicated this process in nearly 6,000 patients from three other Scandinavian-based cohorts. Their analysis revealed three subgroups representing relatively more severe disease, and two large subgroups in which most patients have mild disease that does not substantively progress, said Groop (see Box, below).

The Complications Equation
This research provides some insight into which patients are more likely to develop complications and could help physicians better determine who needs closer screening for retinal versus kidney damage, said Lee. The

Five New Diabetes Classifications
Researchers in Sweden have proposed five new subgroups of diabetes based on longitudinal analysis of more than 13,000 newly diagnosed diabetics.

1. **Severe Autoimmune Diabetes**
   - Associated with severe autoimmune disease, corresponding to type 1 diabetes and latent autoimmune diabetes in adults.
   - Patients typically developed disease at a young age, had poor metabolic control, impaired insulin production, and glutamic acid decarboxylase antibodies.

2. **Severe Insulin-deficient Diabetes**
   - Individuals in this group had high hemoglobin A1c, impaired insulin secretion, moderate insulin resistance and the highest incidence of retinopathy.

3. **Severe Insulin-resistant Diabetes**
   - Patients in this group tended to be obese and have severe insulin resistance. They also had the highest incidence of kidney damage.

4. **Mild Obesity-related Diabetes**
   - This group included obese patients diagnosed with diabetes at a relatively young age.

5. **Mild Age-related Diabetes**
   - About 40% of the study population fell into this category, a less severe form of diabetes that might be managed successfully with the drug metformin and lifestyle modifications.
20 Critical Analytes

Blood gases
- pH
- PCO₂
- PO₂
- SO₂\%

Electrolytes
- Na⁺
- K⁺
- Ca²⁺
- Mg²⁺
- Cl⁻
- TCO₂

Metabolites
- Gluc
- Lac
- Urea
- Creat

Hematology
- Hb
- Hct

CO-Oximetry
- O₂Hb
- HHb
- COHb
- MetHb

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- Width: 14.2 inches (35.6 cm)
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article also notes that people with age-related diabetes generally don’t develop sequelae, “so perhaps we could reduce the diabetes-related complications screening frequency for this group,” she said.

Potentially, doctors could redirect resources in diabetes care from individuals with mild forms of disease to those in more severe subgroups who need it, said Groop.

In a commentary accompanying the study, Robert Sladek, MD, proclaimed it “compelling” that simple parameters assessed at the time of diagnosis might reliably stratify patients according to prognosis, but he cautioned in an interview that potentially relaxing therapy in a group of patients categorized as having a less aggressive clinical course based on one study, “is probably not a good thing to be doing,” Sladek, an associate professor of medicine and human genetics at McGill University and the Genome Quebec Innovation Centre in Montreal, also expressed hope that Groop’s and other investigators’ research might offer solutions for one of the most vexing clinical challenges today, that current diabetes therapies may reduce disease symptoms but not the risk of developing complications. This is why researchers and clinicians are interested in looking for diabetes treatments that reduce blood sugar and also prevent the development of cardiovascular disease or eye and kidney complications, he said.

**Genetic Analysis and Clustering**

A genetic association analysis Groop and his colleagues conducted that supported the proposed five subtypes could help with the latter. “I think the paper supports the idea that genetic variances may be helpful in understanding one’s risk for diabetes-related complications,” said Lee. “There’s some justification for looking in future studies at genetic differences that put some patients at a higher risk for, say, eye versus kidney complications.”

If a genetic classification system could be developed, patients would not change subgroups as they aged, said Sladek. Genetic data from randomized controlled trials for diabetes treatments also could be analyzed to identify subgroups of patients who respond and who don’t respond to therapy. He pointed to another recent analysis that found five novel clusters of type 2 diabetes genetic loci: two associated with insulin production and processing in pancreatic beta cells and three related to mechanisms of insulin response (PLoS Med 2018;15:e1002654).

Genetic analysis will help scientists find genes, proteins, or cellular processes to target, said Sladek. Researchers also need to find a genetic or blood test that determines whether an individual patient will respond to that therapy or not, he added.

While further classifying genetic features of diabetes could be helpful in categorizing patients, “it’s only part of the answer,” stressed Loren Wisnser Greene, MD, MA, an endocrinologist and clinical professor of medicine at NYU Langone Health in New York City. Autoantibodies, particularly GADA status, are also important in understanding patients’ treatment needs, she noted.

**The Journey to Personalized Care**

As intriguing as Groop’s and other researchers’ proposed classifications might be, they will require considerably more vetting to advance into use clinically, cautioned Andrew Ahmann, MD, a professor of medicine and director of the Harold Schnitzer Diabetes Health Center at Oregon Health and Science University in Portland. One challenge with reclassifying diabetes is that none of the new systems are anywhere near universally accepted, he said. They also don’t yet meet the test of clinical practicality for the physicians caring for these millions of patients.

Although the Swedish researchers evaluated six relatively simple variables, using them in clinical practice would be much more complicated and require a new laboratory approach and clinical interpretation for diagnosis, added Ahmann. “We do not routinely obtain all of the tests used to characterize the proposed clusters,” he said.

Because Groop and his colleagues evaluated a mostly white Scandinavian group of patients, research data need to be replicated in other populations, said Lee. If validated, then clinicians would need to consider whether baseline fasting glucose and fasting insulin, as well as other study measures, need to be adopted, she said. Groop agreed with the need to validate his team’s model in more diverse populations. He and his colleagues are planning to launch more extensive diabetes classification research in populations in India, China, and Mexico.

Ultimately, the Swedish analysis and others to come will, according to Ahmann, “eventually lead to precision medicine approaches that will make a difference, particularly as technology matures.”

Heather Lindsey is a freelance medical writer in Maplewood, New Jersey.

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Create for Others
PUTTING THE PIECES TOGETHER TO BATTLE ANTI-MICROBIAL RESISTANCE
Antibiotic resistant bacteria are not just a $2.2 billion healthcare industry problem: They’re a modern-day health crisis that has continued to build a dangerous momentum. “Antibiotics have revolutionized medicine and our ability to care for patients because they allow us to treat not just bacterial infections but to make other medical inventions such as surgery, transplantation, childbirth, even just growing up safe,” said Robin Patel, MD, director of the infectious disease research laboratory and chair of the division of microbiology at the Mayo Clinic in Rochester, Minnesota. “When you run into a problem with an infection or, in the case of surgery, when you need to prevent an infection, we use antibiotics for that. We have all just historically assumed that they’re going to work.”

Are new technologies and testing strategies needed?

BY JEN A. MILLER
Antibiotic resistance may seem like a new problem in medicine, but that’s only because the drugs are still relatively new themselves, compared to billions of years of evolution among bacteria. “We’ve only been using antibiotics in clinical practice since the 1940s,” Patel said. “We’re putting a lot of pressure on bacteria, and they’re just doing what they do naturally when they evolve to be resistant. The more you expose the bacteria to antibiotics, the more they pull out their resistance mechanisms.”

One way to lengthen the life span of antibiotics is to use them only when evidence shows they will be effective, and not when a physician doesn’t know for sure that bacteria and not a virus or fungus is making a patient sick. Better and faster testing can help.

“Diagnosis of bacterial infections by culture and production of susceptibility tests is somewhat time consuming,” noted Sheldon Campbell, MD, PhD, professor of laboratory medicine at the Yale School of Medicine and director of laboratories at the VA Connecticut Healthcare System in New Haven, Connecticut. “Cultures typically take one to two days to grow, and susceptibility testing can take one to two days after that.” That doesn’t seem like a long time, but in practice, four days can seem like an eternity to a sick patient—or the parent of a sick patient—especially one who is used to being given an antibiotic no matter what.

Advances in molecular diagnostics, notably matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, greatly shorten the time to identify organisms and resistance. The disseminating technology also gives quite accurate data—in places where it has been implemented. “Matching is so precise that it can tell you exactly what that organism is and can tell you not just the name of the bacterium but whether it’s a yeast and the name of the yeast—or the parent of a sick patient—especially one who is used to being given an antibiotic no matter what.

New research shows that the danger is not limited to what physicians consider major infections in hospitalized patients, either. Mild conditions easily treated by antibiotics are showing resistance too, and without treatment, could lead to life-threatening illnesses.

Researchers at Alameda Health System Highland Hospital in Oakland, California found that nearly 6% of urinary tract infections (UTI) analyzed during a 1-year period were extended-spectrum beta-lactamases (ESBL) resistant, meaning they are resistant to most beta-lactam antibiotics, including penicillin, cephalosporins, and monobactams aztreonam (Ann Intern Med 2018;72:449-56).

“ESBL has traditionally been considered the kind of resistance you see inside the hospital, not in a community setting like an emergency department,” said Bradley W. Frazee, MD, attending physician at the Alameda Health System Highland Hospital and lead author of the study. “Here, almost half were patients without risk factors for harboring bugs with ESBL.”

A major concern for these patients, he said, is that a mild infection could unexpectedly become extraordinarily dangerous. “A society without working antibiotics would be like returning to preindustrial times, when a small injury or infection could easily become life-threatening,” he said.

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“We’re putting a lot of pressure on bacteria, and they’re just doing what they do naturally when they evolve to be resistant.”

– ROBIN PATEL, MD
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to run, so it’s less costly than the way we’re used to identifying bacteria with panels of biochemicals. As soon as we have something growing on a plate, we can submit it to MALDI-TOF and identify what it is and report it out.”

While clinical laboratories can use MALDI-TOF to name the organism that’s growing, it can’t identify which antibiotics will work against it. That takes another day, Patel said, “but knowing what the organism is can give you some hint as to whether it’s a clinically significant organism actually causing the patient’s infection or whether it’s their normal microbiome.”

Clinicians can also look at data generated by other labs to identify what has traditionally worked against that specific infection and guide drug deployment.

“There’s no one single test that will be the solution. They’re all just pieces that will do better,” she said.

A System-Wide Approach
Combating antibiotic resistance will take a combination of wide access to quick, effective testing and a paradigm shift away from treating antibiotics like a never-ending resource, according to experts. “We haven’t had perfect ways of differentiating these different types of infections. We’ve come to expect that when we’re sick with something that looks like an infection, we’ll take an antibiotic because that’s what’s been done in the past,” said Campbell.

Frazee sees multiple pieces forming the solution, including wider use of culture in relatively mild disease, monitoring trends by geographic site, publishing hospital antibiograms stratified by clinical site (emergency departments versus intensive care units, for example), and developing rapid testing for resistant organisms.

“The problem we have today is that testing isn’t available for all kinds of infections, and that there’s a high rate of false alarms due to colonization. Sometimes you identify a bacteria in a 2-year-old, and every 2-year-old is going to have it whether they’re sick or not. We carry these bacteria when we’re healthy,” he said. Pathogens can change quickly, too.

MeMed believes it can work around these issues in two ways. The first is MeMed BV, an immune-system instead of pathogen-based test for distinguishing between bacterial and viral infections. “The immune system is perfect machinery, so we decided to just listen to the immune response,” said Eden. “We knew we were probably not going to find one magic bullet, one biomarker. Instead, we combined several biomarkers together to measure the immune response.”

That leads to the second part of testing: MeMed Key, a proprietary point-of-care protein measurement platform that runs the MeMed BV test.

MeMed, a private medtech company, received a new round of funding in September, bringing total financing of the project to $70 million. That influx builds on two grants MeMed has already received from the U.S. Department of Defense for test development. So far, the system has been evaluated in double-blind studies in 13,000 patients with results published in *The Lancet, Pediatrics,* and *PLOS One.*

Campbell sees a need to build more efficient systems, “not just doing one-offs but working through antibiotics stewardship programs, infectious disease experts, and laboratories, and optimizing both the use of the data and the use of it,” he said. “There’s pretty good data now that shows a system-wide approach is having an impact on antibiotic overuse. It’s not just the laboratory saying this, but a data-driven institutional process for reporting in a way that results in appropriate antibiotic use.”

The one thing we cannot do is go back. The days of antibiotics working in every case, every time, are over. “There is no way to get rid of antibiotics resistance permanently or go back to an era where all we have is fully susceptible bacteria, because we’re dealing with evolution,” Patel commented. “There are infections for which we need antibiotics, and if that wasn’t the case, we wouldn’t be in this crisis.”

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The Food and Drug Administration (FDA) has approved Grifols’ ID Core XT, a molecular-based assay designed for use in transfusion medicine, to help determine blood compatibility. The assay identifies blood donor and patient non-ABO red blood cell types by detecting 29 polymorphisms that determine 37 non-ABO blood group antigens. It is the second molecular assay approved for use in transfusion medicine and the first to report genotypes as final results. Grifols hopes that a molecular test will improve upon traditional serological blood typing assays, which can be limited by factors such as the availability of antisera. In particular, this test could improve blood matching for patients who receive repeated transfusions and who are more likely to develop antibodies to non-ABO antigens in addition to the main ABO blood group antigens.

As part of the FDA approval process for this test, a study was conducted to compare the typing results of the ID Core XT with licensed serological reagents, the first FDA-approved molecular blood typing assay, and DNA sequencing tests. The results demonstrated comparable performance among all the methods.
cause of bacterial pharyngitis, in 6 minutes or less, with positive results as early as 2 minutes. No culture confirmation is required for negative results for the Strep A 2. Both assays have been granted a CLIA certificate of waiver and are currently available on the ID NOW (formerly Alere i) platform. The ID NOW, a CLIA-waived point-of-care molecular platform, uses Abbott’s isothermal nucleic acid amplification technology.

**ANSH LABS GETS FDA AUTHORIZATION FOR MENOPAUSAL STATUS TEST**

Through the de novo premarket review pathway, the Food and Drug Administration (FDA) has permitted marketing of Ansh Labs’ PicoAMH enzyme linked immuno-sorbent assay (ELISA) kit to aid in determining a patient’s menopausal status. The test is designed for use in conjunction with other clinical assessments and laboratory findings to help inform decisions on preventive care for conditions such as osteoporosis or cardiovascular disease, for which women are at increased risk after menopause. To determine whether a woman is approaching or is likely to have reached her final menstrual period, the PicoAMH ELISA measures the amount of anti-Müllerian hormone in her blood. Healthcare providers should carefully evaluate these results in the context of a full clinical work-up to ensure that contraceptives are not discontinued in women who have not yet reached menopause and that uterine bleeding due to endometrial cancer is not dismissed as a diagnosis, FDA noted. The PicoAMH test should also not be used to assess a woman’s fertility status or to monitor fertility treatments.

**GENEPOC EARNHS HEALTH CANADA APPROVAL FOR C. DIFFICILE TEST**

Health Canada has approved the GenePOC CDiff assay, a molecular diagnostic test for the qualitative detection of *Clostridiodes difficile* (*C. difficile*). This test detects the toxin B (*tcdB*) gene of toxigenic *C. difficile* in unformed stool specimens obtained from patients suspected of having *C. difficile* infection. It is designed to run on the revogene instrument, a fluorescence-based real-time polymerase chain reaction platform that employs single-use microfluidic cartridges. The GenePOC CDiff allows throughput of up to eight samples in one 70-minute run. After completion of a run, the revogene system computes the results using measured fluorescent signals and embedded calculation algorithms. The resulting data can be displayed on a touch-screen, printed, or saved. The test also features embedded process control to monitor sample processing and ensure optimal quality.

**CE MARK GRANTED TO HOLOGIC FOR BORDETELLA TEST**

Hologic has received the CE mark for its Panther Fusion Bordetella assay. This fully automated test uses real-time polymerase chain reaction (PCR) to detect *Bordetella pertussis* (*B. pertussis*) and *Bordetella parapertussis* (*B. parapertussis*) from nasopharyngeal swab specimens collected from symptomatic patients. The test is intended to aid differentiation between *B. pertussis*, the primary cause of whooping cough, and *B. parapertussis*, which is responsible for a whooping-cough-like disease that is not easily distinguished from *B. pertussis* infection by symptoms alone. Hologic’s test runs on the Panther Fusion platform and features ready-to-use, unit-dose lyophilized reagents, which have 60-day onboard stability. The Panther Fusion is available either as a full system or as a module that can be attached to existing Panther systems in the field. As a module, the Panther Fusion extends testing capabilities to include PCR assays in addition to tests based on transcription-mediated amplification.

**CHINA FDA APPROVES MORE DIAGNOSTICS IMMUNOSUPPRESSANT DRUG CONTROLS**

The U.S.-based company More Diagnostics has received approval from the China Food and Drug Administration for its Rap/Tac/CsA controls in a whole blood matrix. Labs can use these controls for calibration checks when performing therapeutic drug monitoring of the immunosuppressants rapamycin, tacrolimus, and cyclosporine. The controls for each drug—available at four clinically significant concentration levels—are designed to be run side by side with a patient sample through all phases of an assay. A value sheet provided with the control set gives expected recovery ranges for many chemistry analyzers as well as liquid chromatography tandem-mass spectrometry testing. Additionally, the controls do not require reconstitution because they are in frozen form. They have a shelf life of 4 years when stored at less than -14°C and 45 days when thawed and stored at 2-8°C. Also included with this set is a control for the drug everolimus, but as an unassayed analyte.
Siemens, Healthy.io Team on At-Home Test for Chronic Kidney Disease Monitoring

Siemens Healthineers and Healthy.io have joined forces to help broaden access to albumin-to-creatinine ratio testing and to make it easier for patients to comply with chronic kidney disease monitoring. Periodic albumin-to-creatinine ratio testing to monitor kidney function is traditionally performed in a clinician’s office. This partnership aims to offer patients a home testing option by integrating Siemens Healthineers’ albumin-to-creatinine ratio urinalysis reagents into Healthy.io’s smartphone-based urinalysis system. Healthy.io’s urinalysis system is CE marked and ISO 13485 certified in the EU, and is currently awaiting Food and Drug Administration 510(k) clearance in the U.S.

The system uses a traditional urinalysis dipstick that the patient takes a picture of with his or her smartphone. Healthy.io’s computer vision algorithms and calibration method then compensate for lighting conditions and the settings of the patient’s smartphone camera to enable accurate reading of the dipstick. Healthy.io’s app guides the user through the entire testing process step by step, and at the end automatically sends the results to the patient’s electronic medical record for clinical follow-up.

“Healthy.io is a pioneer in using computer vision and machine learning to transform the smartphone camera into a clinical grade medical device for improved patient access and convenience,” said Yonatan Adiri, founder and CEO of Healthy.io. “Healthy.io and Siemens Healthineers share a vision for a future of healthcare, which sees consumers take greater control of their healthcare in a way that complements the existing clinician workflow.”

Beckman Coulter, Johns Hopkins Enter Broad Partnership to Develop New Tests

Beckman Coulter Diagnostics and Johns Hopkins Medicine are collaborating to develop and commercialize in vitro diagnostic devices that address unmet clinical and technical healthcare needs. Through this partnership, Johns Hopkins’ faculty, students, and startup community are expected to benefit from Beckman Coulter Diagnostics’ experience with the global commercialization of diagnostic products. In turn, Beckman Coulter hopes to benefit from observing Johns Hopkins researchers and clinicians as they work to develop new technologies. The company will also be able to test solutions on-site with Johns Hopkins experts, which the partners hope will help to accelerate the translational process from research to healthcare application. “It is critical to explore and test new and innovative solutions with clinicians working in actual clinical settings to determine real-world quality and effectiveness,” said John Blackwood, senior vice president and general manager of products and services at Beckman Coulter Diagnostics. “This will help us to address clinical challenges in a rapidly changing environment.”

Mayo Clinic, Helix Start Direct-to-Consumer Genetic Testing Service

Together with the personal genomics company Helix,
Mayo Clinic has launched a new service called the Mayo Clinic GeneGuide that provides healthy individuals with genetic testing in addition to educational materials to help them understand their results. The GeneGuide test covers genetic markers for complex illnesses and hereditary genetic conditions as well as indicators of how the body processes certain medications and anesthesia. When an individual orders GeneGuide, the process begins with a Mayo-affiliated physician reviewing the individual’s health history. If GeneGuide is appropriate for the individual, the physician then orders the test through Helix’s clinical lab and Helix ships a saliva collection kit to the individual within 2 days. Once Helix receives the saliva sample and sequences the DNA, Mayo Clinic interprets the results and makes them accessible via the Mayo Clinic GeneGuide web application.

**U.K. EPILEPSY SOCIETY, CONGENICA STUDY GENETICS OF SUDDEN UNEXPECTED DEATH IN EPILEPSY**

The U.K.’s Epilepsy Society has entered a partnership with Congenica, a diagnostic decision support platform provider, to improve the prediction and treatment of sudden unexpected death in epilepsy (SUDEP). As part of a joint study, the partners will carry out whole genome and exome sequencing analysis on samples from a cohort of 100 SUDEP clinical cases to better understand the underlying genetic causes of this condition. The study will use Congenica’s Sapientia diagnostic decision support platform, which is based on technology developed at the Wellcome Trust Sanger Institute, and will be led by a multidisciplinary research team including scientists from the Epilepsy Society and Congenica, as well as from University College London. “This important study may help us find and understand some possible risk factors for SUDEP,” said Sanjay Sisodiya, PhD, director of genomics at the Epilepsy Society.

“Collaborating with Congenica will ensure analyses of the data are robust and comprehensive, optimizing the chances of discovery.”

**ALMAC, TP THERAPEUTICS TO DEVELOP NGS-BASED CANCER CO-DIAGNOSTIC**

Almac Diagnostic Services is partnering with TP Therapeutics to develop and commercialize a companion diagnostic for repotrectinib, TP Therapeutics’ investigational therapy designed to target ROS1, NTRK1-3, and ALK gene fusions in advanced solid tumors. Currently in the investigational stage, repotrectinib is a low molecular weight, macrocyclic tyrosine-kinase inhibitor that is designed to overcome clinically acquired resistance mutations to other ROS1, TRK family, and ALK inhibitors, especially gatekeeper and solvent front mutations. Using ArcherDx Anchored Multiplex polymerase chain reaction chemistry, Almac will develop a next-generation sequencing test that detects the gene fusions repotrectinib targets and will submit the test for regulatory approval. Once developed, the co-diagnostic will initially be performed by Almac’s CLIA-accredited laboratory in Durham, North Carolina. “Almac provides us with deep experience in the development and regulatory approval of next-generation sequencing diagnostic assays, which will enable the selection of patients who may not otherwise have access to a targeted therapy like repotrectinib,” said J. Jean Cui, PhD, founder, president, and chief scientific officer of TP Therapeutics.

**RTI INTERNATIONAL, ASURAGEN COLLABORATE ON NEWBORN SCREENING FOR RARE CONDITIONS**

RTI International and Asuragen have validated a new screening technology to test for fragile X syndrome in newborns that will now be used in the North Carolina-based Early Check study. Led by RTI International, Early Check is designed to identify children with rare health conditions before symptoms appear and study the benefits of early interventions. After receiving the mother’s consent, Early Check reuses the same blood sample taken for regular newborn screening to test for additional rare conditions free of charge. The new test developed with Asuragen’s technology will enable the study to include fragile X syndrome screening, which has previously been limited by the lack of an accurate high throughput method that works for both boys and girls. “We are proud to partner with RTI International on Early Check,” said Gary Latham, PhD, senior vice president of research and development at Asuragen. “We hope that the use of this technology in such a large-scale study will help to drive how testing of newborns for many genetic disorders can be realized in the future.”

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**Index to Advertisers**

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Denka Seiken Co., Ltd. .......................................................... C2
www.denka-seiken.jp

DiaSorin Inc. ........................................................................ 17
www.diasorin.com

Kamiya Biomedical Company ............................................. C4
www.k-assay.com

Nova Biomedical .................................................................. 11
www.novabiomedical.com

Preco, Inc. ........................................................................... 13
www.precoinc.com

Sysmex ............................................................................... 3-19
www.sysmex.com
When a sample is hemolyzed, why is it important to distinguish in vivo from in vitro hemolysis?

A: In vivo hemolysis happens due to numerous biochemical, physical, chemical, and immunological mechanisms, and/or infections that occur within the body prior to blood being drawn. Correctly identifying it is of great clinical importance because it is a sign of many different underlying pathological conditions, some of which could be life-threatening if left untreated. Potential causes include: 1) autoimmune hemolytic anemia and hemolysis following incompatible blood transfusion; 2) intrinsic red blood cell defects (e.g., hemoglobinopathies, thalassemias, and various enzyme defects such as glucose-6-phosphate dehydrogenase deficiency and pyruvate kinase deficiency); 3) mechanical hemolysis (e.g., from a mechanical heart valve); and 4) microangiopathic hemolysis (e.g., disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome). In vivo hemolysis can be further sub-characterized into intravascular or extravascular hemolysis depending on the mechanism and site of red blood cell destruction.

In vitro hemolysis, on the other hand, occurs outside of the body and is most often the result of preanalytical factors such as blood drawing, specimen handling, specimen delivery to the laboratory, or specimen storage.

How does hemolysis affect laboratory tests?
The most common effects of hemolysis on chemistry tests include: 1) increases in analyte concentration due to the release of red blood cell constituents (affected analytes include potassium, magnesium, aspartate aminotransferase, and lactate dehydrogenase [LDH]); 2) increases in analyte concentration due to assay interference (affected analytes include cholesterol, triglycerides, and creatinine kinase); and 3) decreases in analyte concentration due to assay interference (affected analytes include bilirubin, insulin, and albumin).

What are the pros and cons of using haptoglobin as an indicator of in vivo hemolysis?
Decreased concentrations of haptoglobin in serum and free hemoglobin in urine are the most pronounced laboratory indicators of in vivo hemolysis. In more severe cases haptoglobin may be undetectable, whereas with in vitro hemolysis the concentration of haptoglobin is usually not affected. However, few studies have examined the validity of haptoglobin as a marker of in vivo hemolysis. The studies that do exist have shown varying degrees of sensitivities and specificities for haptoglobin depending on the cutoff concentration used.

One used a haptoglobin cutoff of less than 25 mg/dL and demonstrated 83% sensitivity and 96% specificity for intravascular hemolysis (JAMA 1980;243:1909-11). Another used a haptoglobin cutoff of less than 28 mg/dL and noted 91.8% sensitivity and 98.4% specificity for intravascular hemolysis (Eur J Clin Invest 2006;36:202-9).

In general, there is no gold standard test to confirm in vivo hemolysis, and most often labs rely on other clinical factors (e.g., increased reticulocyte count) and correlation with other laboratory markers (e.g., complete blood count, LDH, and indirect bilirubin) in addition to a patient’s history.

What other clinical factors influence the concentration of haptoglobin?
A variety of factors aside from hemolysis influence haptoglobin concentrations. For example, haptoglobin is often considered to be a nonspecific acute phase reactant and elevated haptoglobin concentrations occur in many inflammatory conditions, including severe infection, inflammation, tissue destruction, acute myocardial infarction, burns, and some cancers.

On the other hand, haptoglobin concentrations can also decrease in the absence of hemolysis. Pathological conditions associated with decreased haptoglobin concentrations include liver cirrhosis, pulmonary sarcoidosis, and elevated estrogen states. Congenital anhaptoglobinemia is a relatively benign condition that results in the absence of haptoglobin. In addition, hemodilution and blood transfusions can lead to falsely reduced haptoglobin concentrations. Differentiating hemolysis from all these conditions is difficult given that both intravascular and extravascular hemolysis can cause reduced haptoglobin concentrations. Consequently, clinicians as well as laboratorians need to be aware of haptoglobin’s limitations and interactions, and interpret this test in the context of a patient’s clinical scenario.
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