

# CLIN

Clinical  
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News

An AACC Publication | Volume 46, Number 1

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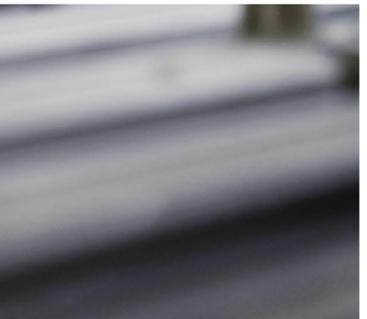
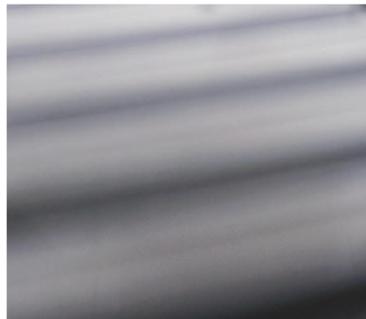
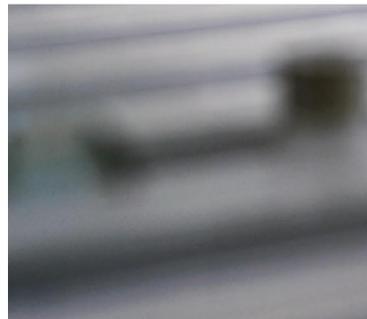
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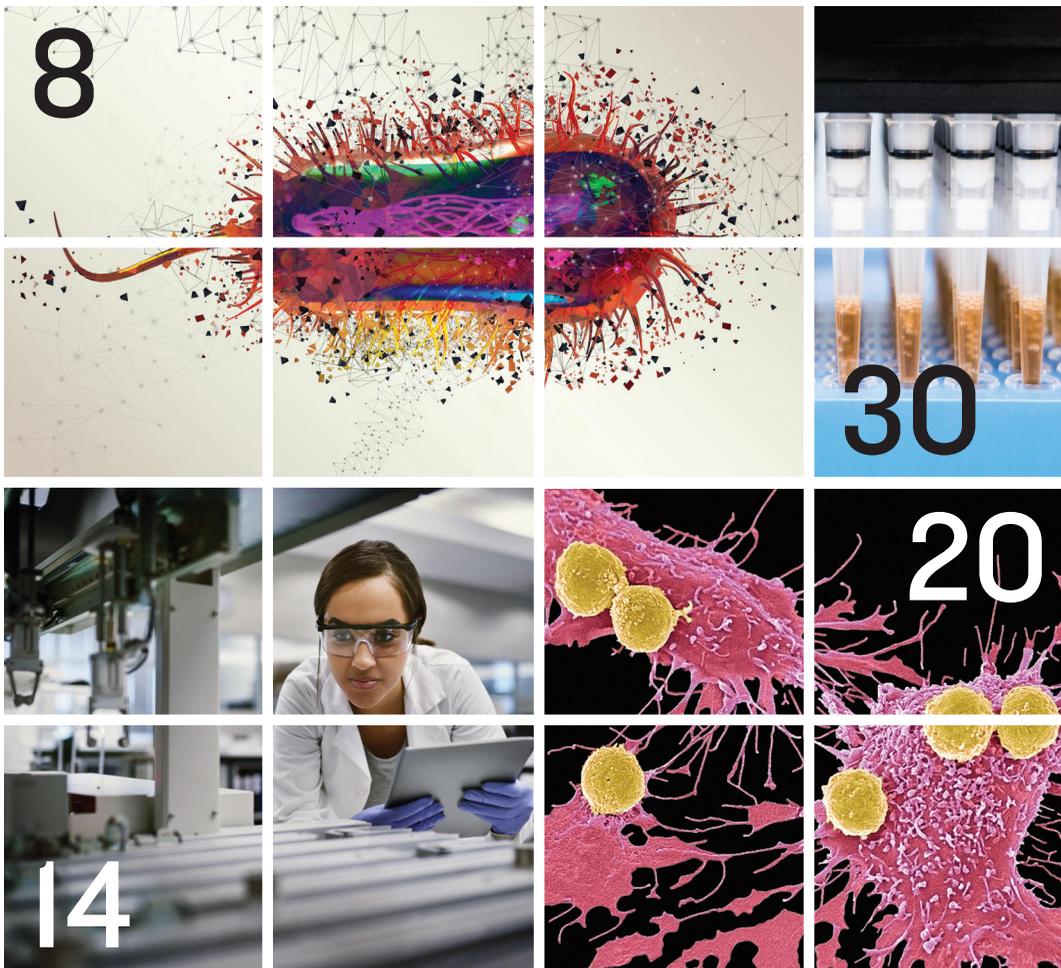
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Hereditary thrombophilia testing is generally reserved for children with unprovoked thrombotic episodes and a family history of thrombosis. It is usually not recommended if a thrombotic episode is provoked by strong risk factors.

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## Federal Insider

## Hospitals Challenge Price Transparency Rule

Hospital groups took legal action to oppose a new rule from the Centers for Medicare and Medicaid Services (CMS) that greatly expands price information available to consumers for everything from laboratory tests to surgeries. Notably, the rule requires that hospitals not only publish online their standard charges for all services but also all payer-specific negotiated rates for their services, which the American Hospital Association (AHA) said will confuse patients.

“Today’s rule mandating the public disclosure of privately negotiated rates between commercial health insurance companies and hospitals is a setback in efforts to provide patients with the most relevant information they need to make informed decisions about their care,” AHA and several other hospital groups wrote in a joint statement. The legal challenge from AHA and hospitals argues that the rule exceeds the administration’s authority.

According to CMS administrator Seema Verma, however, the rule will increase competition and reduce healthcare costs for consumers. “Under the status quo, healthcare prices are about as clear as mud to patients,” she said. “Today’s rules usher in a new era that upends the status quo to empower patients and put them first.”

The final rule will require hospitals to make prices public in two ways beginning in 2021. Hospitals will have to make public all charges—including payer-specific negotiated charges—via a comprehensive machine-readable file that includes billing codes. This will allow anyone with the proper software to easily analyze and publish data for use by consumers.

In addition, hospitals will have to display online so-called shoppable services in a consumer-friendly manner, including payer-specific negotiated charges, the amount the hospital is willing to accept in cash from a patient, and the minimum and maximum negotiated charges for 300 common shoppable services.

Shoppable services are those that the consumer could schedule in advance, such as laboratory testing or a bundle of services like cesarean delivery.

The rule also gives CMS enforcement tools including monitoring, auditing, corrective action plans, and the ability to impose civil monetary penalties of \$300 per day.

### AACC CALLS FOR IMPROVED COVERAGE OF CERTAIN CANCER TESTS

**A**ACC is calling on the Centers for Medicare and Medicaid Services (CMS) to make significant changes to its proposed national coverage determination for next-generation sequencing (NGS) for Medicare beneficiaries with advanced cancer. The CMS proposal would limit Medicare payment for breast and ovarian cancer tests to those cleared by the Food and Drug Administration (FDA).

In a comment letter to CMS, AACC noted that currently FDA has not cleared nor approved any NGS tests for hereditary risk assessment of either condition. “We are also concerned that

this proposal, if adopted, would further limit the ability of patients to obtain appropriate, evidence-based assessment of their hereditary risk for breast or ovarian cancer,” the association said.

In addition AACC is concerned with the agency’s decision to consider breast and ovarian cancers together as if they were synonymous. AACC commented that “many clinical trials assess only one cancer type without the other. It is important to note that although breast and ovarian cancer have similarities with respect to gene mutations and hereditary risk, there are important differences in how the two cancers originate and develop within individuals.”

The association also took issue with the CMS decision in the proposal not to cover NGS testing if a patient has

previously been tested with this method, which would limit somatic cancer testing. “While repeat testing of genes for hereditary risk of cancer should not be covered, NGS testing to assemble a somatic profile of a patient’s cancer is appropriate and should be covered,” AACC wrote. “Determining the molecular profile of an advanced cancer can specifically dictate treatment and several FDA-approved treatments necessitate biomarker measurement.”

Finally, AACC recommended that CMS focus on the clinical indications with sufficient evidence based on published practice guidelines rather than a specific laboratory technology. CMS should use existing guidelines to establish the coverage policy for cancer type, genetic alteration, and treatment option.



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## Bench Matters

# How to Keep Multisite Multi-Analyzer Validations on Track

In multisite healthcare organizations, a patient might present for testing at different laboratory sites during a single healthcare episode or between healthcare visits, healthcare providers might practice at multiple locations, and individual laboratory sites might require operational backup. For each of these scenarios, laboratory results are expected to be sufficiently comparable to ensure optimal care. Multi-analyzer, multisite validation to ensure comparable patient results is not only a good laboratory practice, but also a regulatory requirement.

Thorough planning, well-documented validation protocols, a multidisciplinary team effort, and detailed communications to all stakeholders will keep a complex multisite multi-analyzer validation on track. Here, we describe the approach we took in planning the validation of three automated platforms across five Ontario sites at LifeLabs, the largest community laboratory in Canada. Our validation at two large central sites each with 15,000 to 20,000 daily test volume and three regional sites each with 1,000 to 6,000 daily test volume included 23 analyzers covering 45 assays from a single chemistry platform, and 28 analyzers covering 27 assays across two immunoassay platforms. We also validated two automation lines at two central laboratories.

### THE PROTOCOL

A documented validation protocol outlines the planned validation studies, and we advise having a single validation protocol for each platform that is to be validated. The protocol should be comprehensive and specific, including detailed step-by-step procedures for each study. This eliminates variability in how the studies are performed and allows for adequate comparisons across the sites. The protocol should include defined acceptance criteria for each study, as decided by the lab director. We also recommend that each protocol be discussed and formally approved by internal stakeholders at each site, since large scope validation studies come with a significant resource commitment and substantial cost. In our experience it also helps to share validation protocols with vendors to make them aware if the validation acceptance criteria are different from vendor-stated ones and to ensure easier, faster troubleshooting.

As part of our validation protocol, we also decided which assays to validate at which sites and on which analyzers—this is sometimes referred to as “assay mapping.” Some important

considerations for assay mapping include testing volume and required turnaround time for the test, specimen stability, and potential for sample and reagent carryover.

### THE TEAM

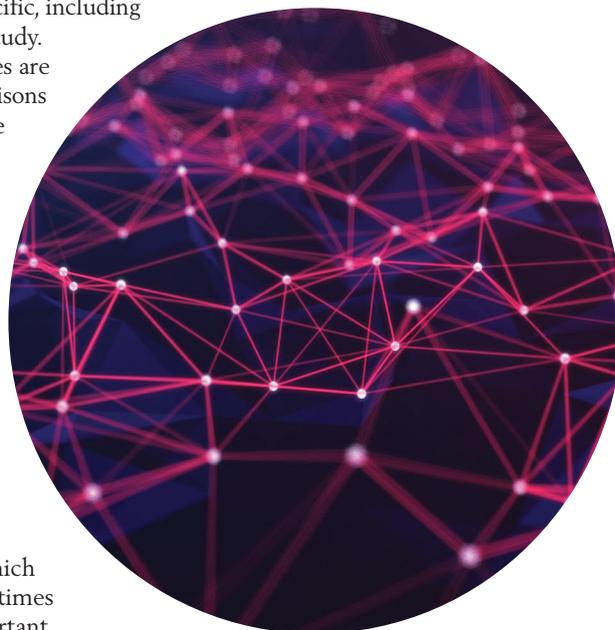
Our core validation team members included staff who perform the studies, and those who manage the data, review, and approve results. We gained from the knowledge and experience of some team members who work at a single site and others who perform duties at several sites, such as clinical biochemists and IT specialists. The complexity of implementing many analyzers at multiple sites also requires significant involvement from other teams, like facilities, procurement, automation specialists, and vendors. We found it particularly helpful to designate a project manager who had insights into the operations at all locations and who knew our validation and implementation requirements. This individual planned the project



Danijela Konforte, PhD, FCACB



Kika Veljkovic, PhD, FCACB





Paul Bradbury / Caiaimage / Getty Images

timelines, ensured team communications and the pace of validation and, in a way, kept the whole team accountable throughout the validation.

Using a staggered validation approach, in which one site performs validation prior to another site, reduces the number of staff required for validation at any one time and puts less stress on laboratory operations overall. This strategy also enabled us to promptly discover and mitigate issues before we moved on to validations at other sites. To ensure the entire project has adequate resources, we suggest identifying key operators for each platform and group of analyzers. The in-depth training they receive from vendors can be leveraged for internal training of the remaining operators at all sites.

### **VALIDATION SAMPLES AND DATA MANAGEMENT**

We advise labs to start collecting validation samples early—including patient samples, proficiency testing materials, reference materials, and spiking materials—that will be needed based on each validation protocol. Plan sufficient

sample volumes for the number of analyzers to be validated and studies to be completed. Sample concentrations should cover the analytical measurement range. Aliquots might need to be prepared, stored, and transported between sites while preserving sample stability. Since there could be several dozen assays and several analyzers validated simultaneously, we recommend using inventory spreadsheets to log available samples and concentrations for each assay.

Data management can be a big validation bottleneck. In multi-analyzer validations, there could be thousands of data points from a single validation study, so labs should plan to automate data management as much as possible. For example, data can be exported from analyzers into validation spreadsheets in .csv files. We also recommend that labs take advantage of statistical software packages like Excel with Analyse-it, EP Evaluator, and R.

### **COMMUNICATION**

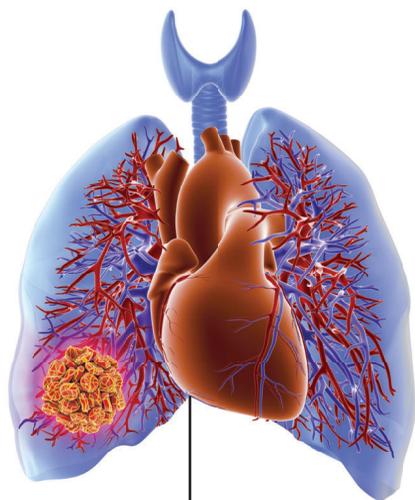
Communication matters with any validation, but even more so when

multiple sites are involved. In addition to daily or weekly touch-point meetings, we used validation progress spreadsheets to show visually where sites were in process, assigning colors to validation steps—for example, study in progress (yellow); study completed (green); follow-up needed (red); etc. In addition, we sent automatic emails to inform all team members each time a validation stage changed. This enabled prompt engagement of the accountable team members at each validation stage.

These activities, although requiring considerable time and effort, allow for a well-coordinated and successful multisite multi-analyzer validation. This enables adequate assessment of test result comparability, ensuring standardized, high-quality patient care across all sites of the organization.

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## Raising D-dimer Threshold Cuts Need for Chest Imaging by 30% in Suspected Pulmonary Embolism

Raising the D-dimer threshold for patients with low or moderate clinical pretest probabilities of pulmonary embolism (PE) effectively rules out PE and reduces the need for chest imaging by one-third (N Engl J Med 2019; 381:2125–34).

The primary goal of diagnostic testing for suspected PE is to determine which patients should be treated with anticoagulants and which should not, according to investigators in the Pulmonary Embolism Graduated D-Dimer study. Current practices generally rule out PE in patients with low clinical pretest probabilities when they have D-dimer results <500 ng/mL. However, only about one-third of patients being evaluated for PE fit this picture, and chest imaging with computed tomography (CT) is expensive, exposes patients to radiation and contrast reactions, and can be time-consuming.

The authors evaluated a strategy that prospectively ruled out further testing in patients who had a low clinical pretest probability and D-dimer results <1,000 ng/mL or moderate clinical pretest probability and D-dimer results <500 ng/mL. In all, the study enrolled and evaluated 2,017 emergency or outpatients at university-based clinical centers in Canada and followed them for 90 days to determine whether they developed venous thromboembolism (VTE). Physicians used the Wells clinical prediction rule to assign pretest probabilities; patients with low or moderate pretest probabilities had their D-dimer results measured via locally available assays, including STA-Liatest, HemosIL HS 500, Innovance, Triage, Hemosil HS, and Roche Cardiac Reader.

In all, 1,325 patients had either a low clinical pretest probability of PE and D-dimer results <1,000 ng/mL (1,285) or a moderate clinical pretest probability and D-dimer results <500 ng/mL (40). None of these individuals developed a VTE, and just one person had VTE out of 1,863 who received neither an initial diagnosis of PE nor anticoagulant therapy. This diagnostic strategy led to CT imaging in 34.4% of patients. In comparison, a strategy that would have ruled out PE in patients with a low clinical pretest probability and D-dimer results <500 ng/mL would have resulted in CT imaging in 51.9%.

### ■ KRATOM, MARIJUANA DRIVE INCREASED CALLS TO POISON CONTROL CENTERS ABOUT NATURAL PSYCHOACTIVE SUBSTANCES

Exposures to marijuana, nutmeg, and kratom led a statistically significant 74% increase in rate of exposure to natural psychoactive substances that occurred between 2000 and 2017, rising from 17.6 to 30.7 per million population (Clin Toxicol 2019; doi.org/10.1080/15563650.2019.1688341). While the rate of exposure to marijuana increased over this period by 150% and

nutmeg by 64%, the rate of exposure to kratom increased by a remarkable 4,948.9%.

The investigators, who analyzed 67,369 calls to poison control centers in the U.S. related to natural psychoactive substances, also found kratom had the highest proportions of healthcare facility admissions and serious medical outcomes (25.7% and 47.1% of single-substance cases, respectively), and was associated with seven deaths from 2016 to 2017.

Kratom, the authors note, is currently classified as a dietary supplement,

but because its main active alkaloid, mitragyline, interacts with opioid receptors, concerns have been raised about its addictive potential. “The continued rise in kratom usage coupled with the serious medical outcomes identified in our study support the need for federal regulation of kratom along with further research on this public health problem,” they wrote.

Exposure rates to other substances, including hallucinogenic mushrooms, anticholinergic plants, morning glory plants, peyote, kava kava, salvia species, absinthe, and khat, all declined.

**SEPSIS DIGITAL ALERT SYSTEM IMPROVES 3 KEY OUTCOMES**

Implementation of a digital sepsis alert system in a multisite U.K. hospital network was associated with improved outcomes—including lower odds of 30-day mortality across all patients (0.76 odds ratio)—and shorter hospital length of stay and more timely start of antibiotics for patients who alerted in emergency departments (0.93 and 1.71 odds ratios, respectively) (*J Am Med Inform Assoc* 2019; doi:10.1093/jamia/ocz186).

This natural experiment involving phased implementation of the alert system without randomization across 27,000 hospital stays is the largest undertaken to date and the first to show an association between use of an alert system and better care outcomes, according to the authors.

Imperial College Healthcare NHS Trust incrementally rolled out the alert

system, which is based on Cerner's St. John Sepsis Algorithm. Initially this integrated part of Imperial's electronic health record (EHR) ran in silent mode, during which alerts were not visible to clinical staff, then was switched to live mode. The implementation started in inpatient units, before spreading to emergency departments, hematology units, and finally all other inpatient units.

Coupled with the alert system, Imperial implemented a novel multidisciplinary care pathway that would launch when a clinician confirmed suspicion of sepsis.

The alert system has two levels of alerts, suspicion of sepsis and suspicion of severe sepsis. The five parameters for the former include white blood cell count >12,000 cells/mm<sup>3</sup> or <4,000 cells/mm<sup>3</sup> or 10% immature (band) forms, glucose >141 mg/dL or <200 mg/dL, temperature >38.3°C or

<36°C, and heart rate >95. When at least three of the criteria were met, an alert would fire.

Similarly the system would fire an alert for suspicion of severe sepsis when two or more of these criteria were met along with at least one criteria indicative of organ dysfunction, including: serum creatinine increase over baseline ≥0.5 mg/dL (72 hr lookback); total bilirubin ≥2.0 mg/dL or <10.0 mg/dL (30 hr lookback); serum lactate >2.0 mmol/L (12 hr lookback); and systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg.

"This study has clearly shown that the introduction of a network-wide digital screening tool embedded in EHRs is associated with improvement in patient outcomes, demonstrating that digital-based interventions can be successfully introduced and readily evaluated," the authors concluded.





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# META





# GENOMIC

## NEXT-GENERATION SEQUENCING

### Modern Tool for Diagnosing Infectious Diseases

BY DEBORAH LEVENSON

When culture, serology, and polymerase chain reaction (PCR) can't identify the cause of a patient's infection, inappropriate therapy, excess healthcare costs, or even the individual's death all are possibilities. In contrast to these tests that generally look for one pathogen at a time, metagenomic next-generation sequencing (mNGS) analyzes a broad spectrum of microorganisms at once, potentially providing quicker diagnoses and avoiding untoward outcomes.

A clinical mNGS test is expensive—sometimes more than \$2,000. But it might be worthwhile when routine tests don't provide information, for immunocompromised patients infected with pathogens that do not affect healthy people, or for patients who can't tolerate invasive diagnostic procedures, said clinical laboratorians who use the test.

"It's exciting to think about how mNGS can help us improve care. There's a lot of promise in these methods," said David Peaper, MD, PhD, an assistant professor of laboratory medicine at Yale University and director of clinical microbiology at Yale New Haven Hospital in New Haven, Connecticut. However, these tests are limited by risk of contamination, designs geared to specific types of pathogens, bioinformatics challenges, and databank deficiencies, said Peaper and others.

#### Diverse Pathogen Detectors

Clinical mNGS typically involves extracting cell-free (cf) DNA, cfRNA, or both from a body fluid, amplifying the nucleic acids via PCR, generating libraries, and shotgun sequencing nucleic acids at a very high depth. Genomic laboratories use software to analyze the millions of reads generated in each sample and identify those that align to nucleotide sequences of pathogens in various databases, such as the National Center for Biotechnology Information (NCBI) GenBank.

A \$2,200 University of California, San Francisco (UCSF) test analyzes both DNA and RNA to diagnose causes of meningitis and encephalitis from bacteria, viruses, fungi, and parasites found in cerebrospinal fluid.

UCSF software analyzes reads, identifies those that align to pathogens in GenBank, and issues a qualitative report noting the pathogens present in the sample, along with interpretive clinical notes. A sequencing board, modeled on a tumor board, discusses results in real time with treating physicians and may make recommendations about additional testing. Turnaround time from shipping samples to delivery of a qualitative report is generally within a week, said Charles Chiu, MD, PhD, a key developer of the UCSF test and a professor of laboratory medicine and director of the clinical microbiology laboratory at UCSF.

The test performs well in head-to-head comparisons with routine clinical testing and can make diagnoses usual microbiology tests cannot, according to recent research (NEJM 2019;380:2327–40). Among 204 pediatric and adult patients in eight hospitals, the UCSF test detected 58 infections in 57 of the patients. Hospitals' routine tests missed 13 or 22% of these infections. Among seven of those 13 diagnoses made solely by mNGS, results guided targeted treatment with clinical effect.

Redwood City, California-based Karius matches sequences from cfDNA in blood plasma to a curated company database of 21,000 reference microbe genomes and delivers reports that show species occurring in greater than expected concentration. Turnaround is fast—typically about 48 hours from blood draw, including shipping. A team of on-call infectious diseases specialists review results with clinicians, particularly for challenging cases, said Timothy A. Blauwkamp, PhD, Karius's co-founder and chief scientific officer.

The \$2,000 Karius test helps diagnose acute infections in immunocompromised patients, invasive fungal infections, and cardiovascular-related infections, according to the company. A recent study showed that the test identified responsible pathogens in 86% of 15 children with pneumonia and resulted in changes in antibiotics for almost half of them. Meanwhile, standard methods diagnosed only 46% of the children (Diagn Microbiol Infect Dis 2019;94:188–91). Other

published data on the first 100 tests used at a children's hospital showed that sensitivity and specificity of the test for a clinically relevant infection were 92% and 64%, respectively (Open Forum Infect Dis 2019;6:pii:ofz327).

Published evidence is emerging on using the Karius test for diagnosing endocarditis, including a case in which the test helped identify a *Coxiella burnetii* infection (Open Forum Infect Dis 2019;6:ofz242). The company's website lists several unpublished abstracts it says support use of the test in diagnostic and management algorithms.

Karius is planning to use the test to discern sepsis causes, often missed by culture. A paper describing validation of the test for this purpose compared Karius test results to standard of care on 350 patients with suspected sepsis. The Karius test identified responsible pathogens at a rate about three times higher than blood culture, and 28% higher than all microbiology testing combined. Results from Karius agreed with blood culture 93.7% of the time (Nat Microbiol 2019;4:663–74).

The UCSF and Karius tests may be the most prominent in the mNGS space, but they aren't the only ones. San Francisco-based IDbyDNA, in partnership with ARUP Laboratories, offers a \$500 test of DNA and RNA detecting 200 pathogens in samples from respiratory disease patients. The company delivers results within 29 hours after receiving samples. Robert Schlager, MD, PhD, MPH, IDbyDNA's chief medical officer and co-founder, attributed the quick turnaround to data analysis via the company's Exemplify platform, which it markets to other labs.

Tests from Scottsdale, Arizona-based Fry Laboratories use blood and sequence a region of the *16S* or *18S rRNA* gene found in bacteria, archaea, fungi, protozoa, amoeba, and algae. Tests, which do not use shotgun sequencing, cost \$1,495 and generally take a week with shipping, said Jeremy Ellis, PhD, Fry Laboratories' chief scientific officer. Fry Laboratories compares findings to "a curated NCBI 'nt' and '16s' database" about these organisms, added Ellis, who also serves as chief

scientific officer at BioID Genomics, a biotechnology company that specializes in sequencing and software solutions to identify and characterize microbes.

### Challenges Ahead

mNGS involves many challenges, according to recent reviews of the technology (Clin Infect Dis 2018;66:778–88; Nat Rev Genet 2019;20:341–55). These include sample contamination with nucleic acid during collections and from sequencing reagents, and design of tests for particular pathogens. For example, a test must process RNA to detect RNA viruses. So mNGS pneumonia assays that do not test for RNA might miss respiratory syncytial virus, an RNA virus that commonly causes pneumonia, Chiu said.

Meanwhile, tests do not detect all pathogens equally. For example, mycobacteria might be more difficult to detect because lysing them for nucleic acid release requires more significant cell wall disruption. Also, a negative result might only reflect high leukocyte count of a sample (corresponding to high human DNA and/or RNA host background) or low sequencing depth of a specimen, rather than the absence of a pathogen.

Databases also may contain mislabeled information and include pathogen strains that do not infect humans. Other challenges include differentiating colonization from infection, lack of method standardization, bioinformatic data storage, and patient privacy.

### mNGS in Practice

Alexander McAdam, MD, PhD, director of the infectious diseases diagnostic laboratory at Boston Children's Hospital (BCH) and an associate professor of pathology at Harvard Medical School, said that it's difficult to fit mNGS into current microbiology testing paradigms built on tests costing less than \$100. However, his lab has integrated mNGS into its normal battery of tests. McAdam regularly sends mNGS tests to Karius and UCSF, but only after preliminary negative results on routine tests and approval from a BCH laboratory director.



“People are showing what’s possible with mNGS. We still have to fit it into existing systems in a way that’s realistic about resources available and the value provided.”

— ALEX GRENINGER, MD, PHD

**“It’s exciting to think about how mNGS can help us improve care. There’s a lot of promise in these methods.”**

– DAVID PEAPER, MD, PHD

The BCH lab works with ordering clinicians to ensure they understand the tests’ utility and the workflow involved.

At Yale, Peaper occasionally uses mNGS tests for scenarios including diagnostic conundrums, critically ill immunosuppressed patients with tissue-based infections, brain lesions

and deep-seated liver abscesses that can’t be biopsied, and suspected endocarditis when valve replacement is not an option. Before ordering, Peaper and clinicians discuss how positive, inconclusive, and negative results would affect care. More data from select patient populations would make decisions easier, he added.

Sometimes results show zero or few reads of the true culprit, so diagnosis requires another method. Peaper recalled recent encephalitis cases detected by antibody, not the UCSF test. Chiu recollected seeing too few reads of *Mycobacterium tuberculosis* to call a test positive for it. A different test confirmed *M. tuberculosis*.

Current mNGS tests can identify diagnostic gaps in hospital lab testing and remind physicians about the breadth of organisms covered in differential diagnoses, said Alex Greninger, MD, PhD. The sensitivity of mNGS is much less affected by antibiotics than that of culture, added Greninger, who participated in early development of the UCSF test and is now developing an mNGS test at University of Washington, where he is an assistant professor of laboratory medicine and associate director of virology.

Greninger pointed out that no mNGS tests have been cleared by the Food and Drug Administration (FDA). Draft FDA guidance issued in 2016 gives labs developing tests an idea of “what validation should look like for a test that’s very different from traditional tests,” he added.

Noting that now-commonplace PCR was new and labor-intensive in the 1980s, Greninger envisions a day when mNGS could become a usual test. “People are showing what’s possible with mNGS,” he said. “We still have to fit it into existing systems in a way that’s realistic about resources available and the value provided.” ■

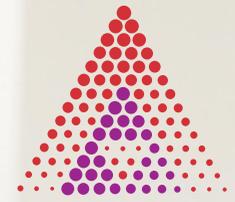
*Dr. Chiu has a patent on algorithms used in automated software developed by UCSF to analyze and interpret metagenomic sequencing data.*

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# Developing an Innovative New Assay?



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# NO WRONG TURNS

How Clinical Laboratory Scientists Shape Careers to Match Their Passions



BY KIMBERLY SCOTT

**W**ith the job outlook for clinical laboratory scientists (CLS) expected to grow much faster than for other professions, the career possibilities for people just entering the field appear limitless. From working at the bench to focusing on research to performing data analysis, CLS professionals have a wide range of potential career paths from which to choose.

According to the Bureau of Labor Statistics, the job market for clinical laboratory technologists and technicians is expected to grow by 11% between 2018 and 2028, compared to 5% for the average growth rate for all occupations. This growth is being driven, in part, by an increase in the aging population and an increase in the number of laboratory tests being ordered by clinical providers.

CLS staff members, also known as medical technologists, earn a bachelor of science degree and then typically complete a 1-year training internship program before sitting for a comprehensive written exam. Once certified, CLS professionals can pursue a variety of career trajectories. But where they launch their careers is often not where they land. Below we highlight the stories of several CLS professionals who have found career success, all anchored in their passion for science and patient care and in an insatiable curiosity that keeps them on creative journeys.

### The Joy of Problem-solving

Erin Bartos, MT(ASCP)SC, a chemistry technical specialist at Children's Minnesota in St. Paul, knew from an early age that she wanted to work in healthcare. As a child she was diagnosed with aplastic anemia and received a bone marrow transplant at the University of Minnesota. "I became fascinated with what happened to my blood after it was taken," she explained.

After high school, Bartos was offered a scholarship to Mount Mercy College in Cedar Rapids, Iowa, and decided immediately to pursue medical technology. After completing her internship at St. Luke's Hospital in Cedar Rapids, Bartos worked at Trident Hospital in Charleston and eventually moved back to Minnesota.

For 14 years she worked for United Hospital in St. Paul, first as a generalist on the evening shift, then as chemistry lead on the day shift. In 2016 she took a job as chemistry technical specialist at Children's Minnesota. In her current position, Bartos performs competency assessments (including proficiency testing review for the College of American Pathologists) and ensures that the chemistry laboratory meets all federal and state regulations.

"What I like best about my job is that I do a lot of troubleshooting and problem-solving," said Bartos, who recently completed her MBA with a concentration in business analytics. "I like using data to drive informed decisions, and I'm very interested in quality control."

Bartos advises junior CLS to be open to new experiences and to get involved with professional organizations. Conferences are a great way to stay current, as are certificate programs such as those offered through AACC, she added. For example, Bartos is certified as a specialist in chemistry and also holds a graduate certificate from University of Minnesota in performance improvement.

### Facing Everyday Challenges

Amy Rockefeller, MLS(ASCP), switched her major from accounting to microbiology at the beginning of her college career and never looked back. She received a bachelor's degree in microbiology with a CLS option from California State University, Chico, and performed a 1-year internship at University of California, Irvine.

Rockefeller's first job was with Sharp Healthcare System in San Diego, where she worked as a generalist for 6 years. Eventually, she moved to University of California, San Diego, where she started as a senior specialist and was promoted to supervisor and then to clinical lab manager.

As a generalist, Rockefeller was exposed to various specialties, including hematology, coagulation, chemistry, and urinalysis. Working on the bench allowed her to be a key operator on different analyzers and to work on middleware information technology projects for

auto-verification. This ultimately led her off the bench where she crafted rules for auto-verification.

"I like that my job changes every day," she explained. "I like the fast pace, and I like the challenges I face. Analyzers are going down, the phone is ringing, there's always something going on. I also enjoy interacting with healthcare providers and collaborating. This allows me to use my critical thinking skills and to play detective. It's what makes this job so exciting."

Rockefeller advises new CLS professionals to volunteer when growth opportunities are offered within a laboratory to gain exposure



to different specialties. She also recommends taking advantage of online resources, such as online communities like AACC Artery (artery.aacc.org) and continuing education, as well as networking through attendance at conferences.

“There really are a lot of different paths you can take,” she said. “You can stay on the bench, you can go into administration. If you stay on the bench, there are many different departments you can work in depending on the size of your healthcare system. You can get into biotech. There are many options. If you have a CLS license, you won’t have a problem finding a job.”

### From CLS to Application Specialist

When his plans to attend medical school changed after getting his microbiology degree from the University of Idaho, Jeffrey Young, MLS(ASCP)<sup>CM</sup>, decided to pursue a career in clinical laboratory science at Idaho State University. The CLS program with a 90-day clinical rotation allowed him to graduate with a CLS degree at about 15 months. Young worked as a bench technologist for a short period before taking a position as a field application specialist for Beckman Coulter.

“It was kind of a hybrid role, part technical support and part customer service,” he explained. “I would help

labs with validation studies. I would make sure they understood how to use the analyzers and the software. I became a subject matter expert on five or six different clinical systems. I had a large territory, which meant that I traveled continuously.”

When his family grew and he needed a position that required less travel, Young took a job as a development technologist for Providence Health in Portland, Oregon. The role was similar to the one he performed for Beckman Coulter, but from the perspective of the customer, not the vendor.

“I perform validation studies, I write procedures, I help set up

**“I became a subject matter expert on five or six different clinical systems. I had a large territory, which meant that I traveled continuously.”**  
— JEFFREY YOUNG, MLS(ASCP)<sup>CM</sup>



instrument interfaces and verify that the vendor's equipment is communicating with our laboratory information system," he explained.

While he is in a somewhat unconventional role for a CLS professional, Young noted that there are many different career pathways for laboratory scientists, and that there are a lot of options outside of the traditional bench tech to lead tech to supervisor/manager career pathway.

"It's a stable career choice and has been dependable through times of economic turmoil," he said. Like the others interviewed for this article, Young advised that all CLS professionals get involved with professional organizations early in their career. "Go to conferences, network, and participate," he said.

### Broadening Horizons

After taking part in an allied health services camp while in high school, Pamela Banning, MLS(ASCP)<sup>CM</sup>, PMP(PMI), knew she wanted to study science in college. She obtained her bachelor's degree in biology at Boise State University in Idaho and then completed a 1-year medical technology program. Banning's internship was at St. Alphonsus Regional Medical Center in Boise.

Banning's first job was at Holy Rosary Hospital in Ontario, Oregon. After marrying a Marine, she moved around often, but always found there was a need for CLS professionals. "I never had a problem finding work," she said. "I worked at a doctor's lab, a trauma center, different sized hospitals. I had about eight different positions over 16 years, but that really helped me be a generalist. I got to do blood banking, microbiology, lots of different things."

By the late 1980s, as laboratory information systems first came into play, Banning found that she enjoyed working with information technology. She was hired by ARUP Laboratories to convert microbiology department workcards to computer-based templates. Eventually, she migrated to the IT department doing database administration.

After 7 years at ARUP, Banning joined 3M Health Information Systems (HIS) almost 19 years ago as a healthcare data analyst. In this job,



## Clinical Laboratory Scientist Career Resources

AACC's clinical laboratory scientists (CLS) community offers scientific, career, and networking opportunities for all members who work in laboratory management and operations. For career advice videos, mentoring, certification resources, and more, visit the AACC CLS community online, [www.aacc.org/community/clinical-laboratory-scientists-community](http://www.aacc.org/community/clinical-laboratory-scientists-community)

she advances promotion of vocabulary terminology, provides technical support in database management for various clients, and represents 3M HIS clients with standards development organizations, such as Regenstrief Institute's Logical Observation Identifier Names and Codes (LOINC) Committee.

"It's like the ultimate puzzle for me because I didn't build any of the information systems, but we apply LOINC for the assays and SNOMED CT for the non-numerical values to all of them," she explained. "All my earlier jobs prepared me for this. I use my medical terminology every day. It would be so much harder to do this job without medical technology certification."

Banning advises new CLS professionals to broaden their horizons, keep up with technology changes, and be involved online. "Seek out opportunities to be in cross-department teams, to see how other departments work," she said. "Learn to see things from a different point of view."

### From Bench to Research

Nadia Ayala-Lopez, PhD, MLS(ASCP), initially saw a clinical laboratory science degree as a stepping-stone to medical school, but after discussions with several

mentors, she decided to continue pursuing laboratory medicine. It took Ayala-Lopez 7 years to graduate from the program at University of Nevada, Las Vegas, because she was working full-time and going to school part-time. After graduating, she got a job at St. Rose Dominican Hospital in Las Vegas, where she was a generalist, rotating throughout the lab.

Ultimately, Ayala-Lopez decided to pursue research and moved to the University of Washington so that she could get academic medical laboratory experience. Following that, she attended Michigan State University, where she earned her graduate degree in pharmacology and toxicology.

"My research was on how adipose tissue affects blood vessels," she explained. "I graduated in 2016 and did a research post-doc fellowship at Yale University, where I was in lab medicine studying leukemia. My plan was to do a clinical chemistry fellowship after my research fellowship, and that's what I am doing now at Vanderbilt. I'm four months into a two-year fellowship to prepare fellows to be lab directors."

"I love being a CLS. Being a CLS requires that you have analytic skills, that you can interpret data and trends, that you can communicate those, both written and orally," she said. "As a CLS, you must be able to adjust to new procedures since science is always changing. There is a lot of room for growth, especially in molecular and informatics."

Ayala-Lopez recommends that CLS students find mentors in their programs who can guide them along their career paths. She also suggests reaching out to people on LinkedIn or through professional organizations to find out more about jobs they find interesting. "Just ask them if they would be willing to talk to you for 20 minutes. I've never had anybody turn me away," she said. "There are so many options for a CLS professional. You can work in a government lab, forensics, public health. Find what interests you and then pursue it!" ■



Erin Bartos



Amy Rockefeller



Jeffrey Young



Pamela Banning



Nadia Ayala-Lopez

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# New FDA Regulations, Hospital Glucose Meters

FDA Product Code PZI, 2019:

***Blood Glucose Meter for Near-Patient Testing***<sup>①</sup>

FDA Product Code NBW, 2019:

***Blood Glucose Test System, Over the Counter.***<sup>②</sup> *These device types are not intended for use in healthcare or assisted-use settings such as hospitals, physician offices, or long-term care facilities because they have not been evaluated for use in these professional healthcare settings.*<sup>③</sup>

**Use of a meter cleared by the FDA as Product Code NBW is considered “OFF-LABEL” when used anywhere in a hospital.**<sup>③④</sup>

**Is your hospital glucose meter cleared as FDA Product Code PZI for hospital use or NBW cleared and off label for hospital use?**

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② U.S. Food and Drug Administration. Product Classification NBW. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpdc/classification.cfm?id=633>

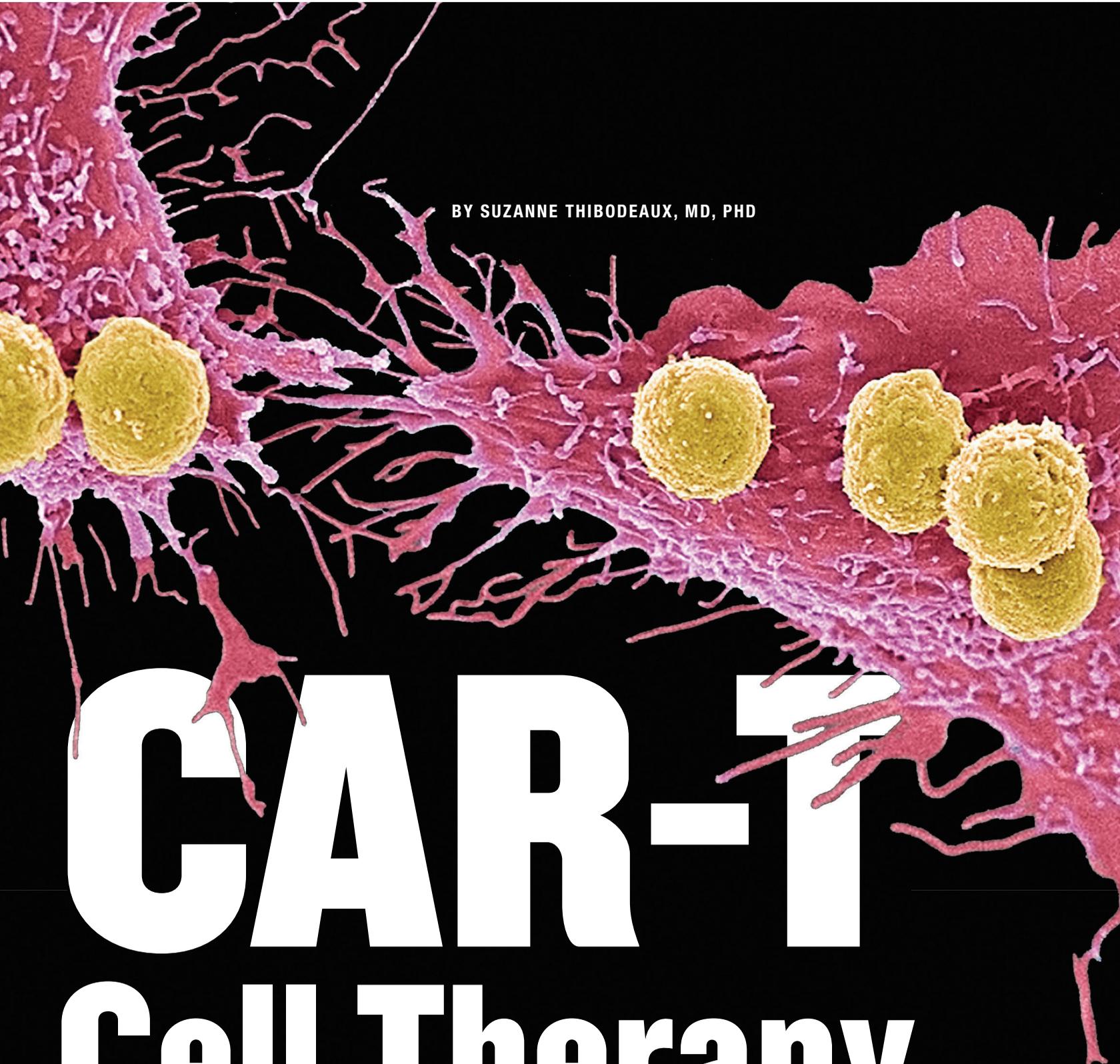
③ U.S. Food and Drug Administration. Self-monitoring blood glucose test systems for over-the-counter use. Guidance for industry and Food and Drug Administration staff. Silver Spring, MD: 2018. <https://www.fda.gov/media/87720/download>

④ Centers for Medicare & Medicaid Services. Reissuance of S&C 15-11. <https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Downloads/Survey-and-Cert-Letter-15-11.PDF>



Steve Gschmeissner / Science Source

BY SUZANNE THIBODEAUX, MD, PHD

A microscopic image showing a network of pink, fibrous structures, likely representing a cell culture or tissue. Several bright yellow, spherical structures are scattered throughout the network, possibly representing specific cells or components of interest.

# CAR-T Cell Therapy

**From a Clinical Laboratory Perspective**

## Careful monitoring before and after infusion is critical to successful treatment

**C**areful monitoring of patients throughout the duration of chimeric antigen receptor (CAR)-T cell therapy, including their laboratory profiles, helps guide and refine clinical management—from preparing and considering potential candidates to monitoring the long-term recovery of those who receive this powerful new therapy. Two CAR-T cell products, tisagenlecleucel and axicabtagene ciloleucel, have been approved by the Food and Drug Administration (FDA) and are quickly becoming mainstays in hematologic and oncologic treatment strategies (See page 24). This minireview considers CAR-T cell therapy from the perspective of clinical laboratories, with the goal of empowering clinical laboratorians with information so that patients receive optimal care regardless of clinical setting.

### The Role of Laboratories Before CAR-T Cell Infusion

Collecting source material is critical to the CAR-T cell manufacturing process. Since CAR-T cells are autologous, i.e. the donor is also the recipient, patients must be evaluated carefully before they become candidates for CAR-T cell therapy and cellular collection by apheresis. In the case of tisagenlecleucel, patients must stop certain treatments, including allogeneic therapies and immunosuppressants, for up to 12 weeks before apheresis collection. Monitoring hematologic parameters or immunosuppressant levels in the blood may be necessary to ensure patients are adequately prepared leading up to cellular collection and continued during treatment to adjust their therapy as needed to maintain their health status (7).

Although most cellular collections are successful, certain laboratory parameters are crucial to determine whether a patient can proceed with collection. There must be enough T cells in the peripheral blood to be collected, as measured by absolute lymphocyte count and/or peripheral blood CD3 counts. After collection, cells must be prepared and transported

for manufacturing, either in-house where the cells were collected and the patient will be infused, or at an external central manufacturing facility, the typical model for most sites (8).

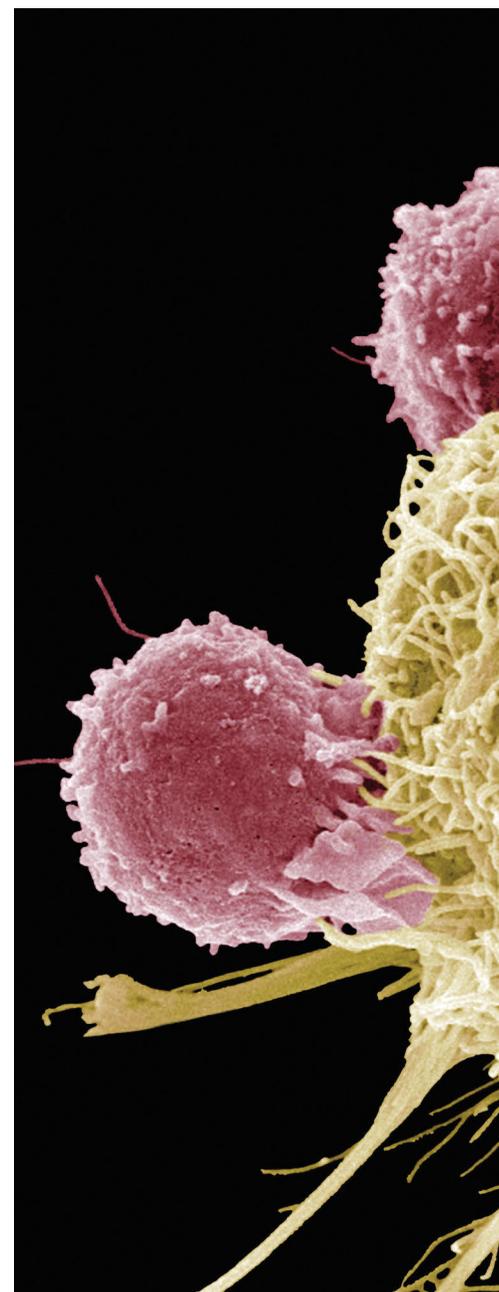
Many important considerations for product preparation and transport center on the safety of both patient and product. Labs must use special handling for any product that requires cryopreservation before the product gets packaged and shipped. This includes performing cell counts on a hematology analyzer, characterizing the cellular composition by flow cytometry, adding cryoprotectant and proper labeling, and checking both patient and product identification multiple times (8).

During manufacturing, which can take 2 weeks, patients need clinical monitoring to ensure that they remain stable until the CAR-T cells can be infused. The manufacturing process is typically monitored by release testing, which helps ensure product safety, purity, and potency. Laboratory assessment typically includes product composition by flow cytometric characterization of CAR-T cells; product sterility by microbial culture and testing for endotoxin and mycoplasma contamination; and functional assays to assess in vitro cytotoxic function and activation (9).

Once manufacturing is complete and testing has confirmed that the product can be released for use, the product is then frozen, shipped back to the infusion site, and stored in a cellular therapy laboratory until the patient is ready for product infusion.

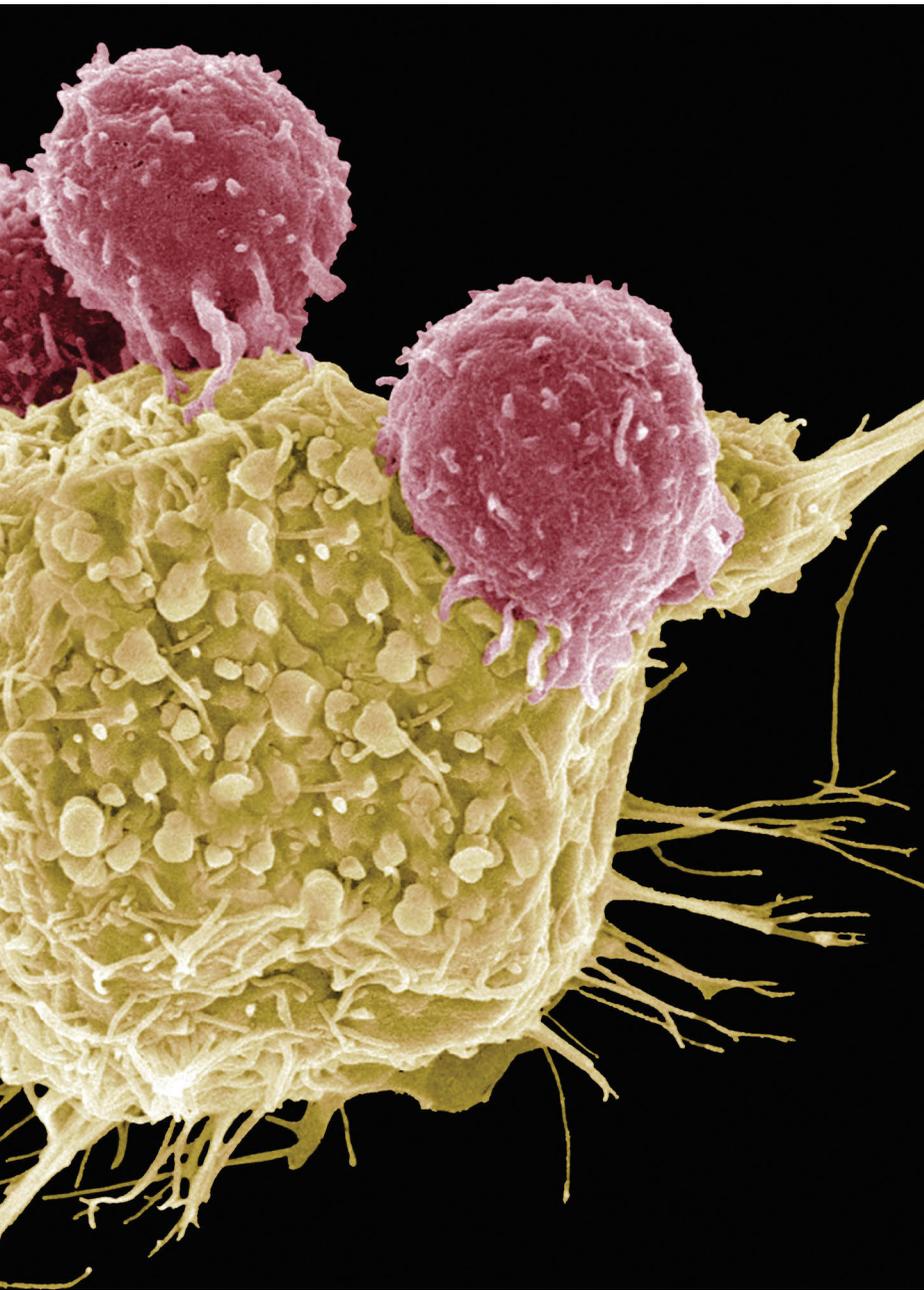
### After CAR-T Cell Infusion

After a patient has been infused with CAR-T cell product, the T cells ideally recognize their target antigen, activate, and begin to proliferate and exert antitumor effects. Response to therapy can be monitored by detecting malignant cells. The clinical lab examines peripheral blood or other potentially affected tissues by standard means such as examining peripheral blood smears for morphology and/or using flow cytometry to detect malignant cells by protein expression (7).



Detecting CAR-T cells themselves is not as straightforward. CAR-T cells can exhibit atypical morphologic features, and methods to detect the CAR protein itself are not commercially available. In addition, the potential customization of CAR proteins prohibits at this time development of any single assay to detect CAR-T cells (2).

Patients can exhibit expected and unexpected effects from CAR-T cell therapy infusion. A well-characterized and potentially serious adverse effect is cytokine release syndrome (CRS). Characterized by high fever, organ dysfunction, hypotension, and increasing



oxygen requirements, CRS ranges from mild to life-threatening and is attributed to extremely high levels of cytokines, specifically interleukin 6 (IL-6) (10, 11).

The American Society for Transplantation and Cellular Therapy (ASTCT) recently published guidelines for defining and grading CRS. While certain aspects of CRS are almost certainly determined by laboratory values, such as transaminitis and other signs of organ dysfunction, laboratory parameters are not included as factors to determine the presence or severity of CRS. Some tests, such as serum IL-6

quantitation, are not widely available, which translates into a long turnaround time since they must be sent out. The nonspecific nature of other lab parameters that might be altered during the course of CRS—such as ferritin and C-reactive protein—as well as the potential lag time between symptoms and altered lab values, support treating patients empirically based off their clinical presentation.

Neurotoxicity, also called immune effector cell-associated neurotoxicity syndrome, is another adverse effect of CAR-T cell infusion and can present with neurological symptoms such as

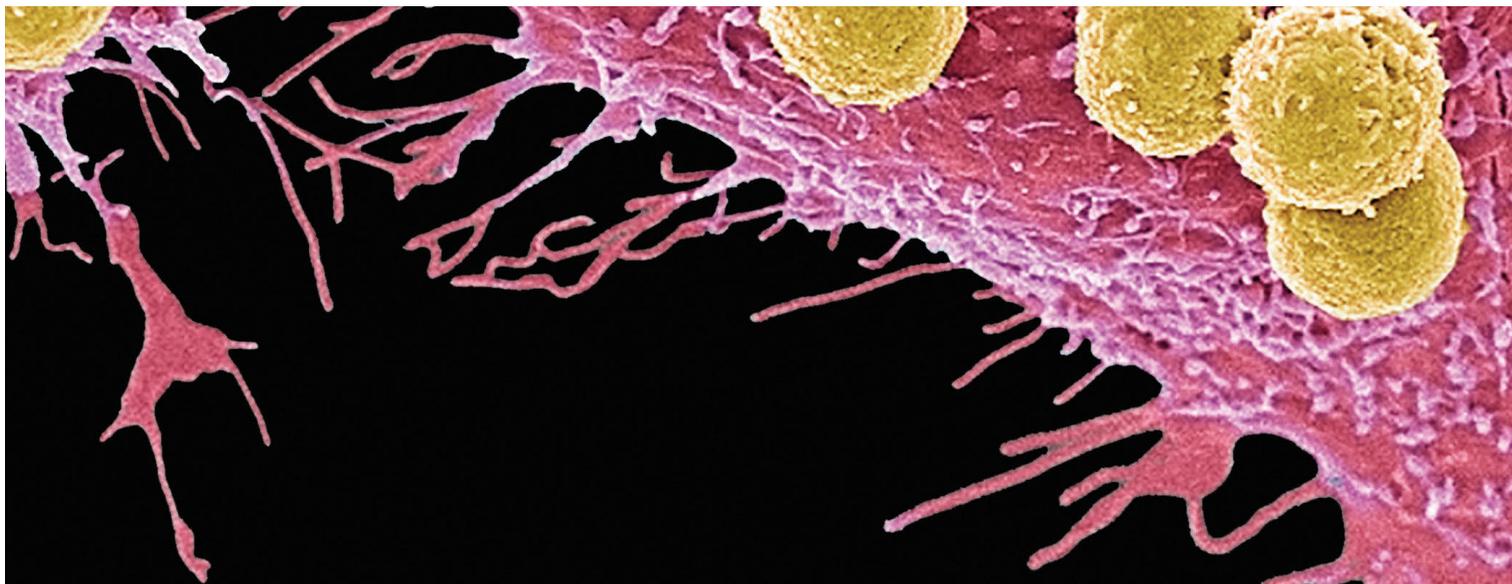
encephalopathy, agitation, delirium, and seizures (10). Laboratory evaluations currently do not aid in characterizing neurotoxicity. The ASTCT encouraged continued exploration of potentially useful laboratory characterization of patients who demonstrate clinical signs and symptoms of adverse events from CAR-T cell therapy (10). Additional laboratory characterization of patients who experience adverse effects from CAR-T cells could help inform the larger community about laboratory testing that has diagnostic, therapeutic, or prognostic potential for CRS and neurotoxicity.

Notably, CAR-T cells can effectively eliminate normal cells if they express the target antigen; this phenomenon is known as on-target/off-tumor toxicity. In the context of the FDA-approved therapies that target CD19, B cell aplasia is an anticipated effect, since normal B cells also express CD19 and are therefore subject to elimination by anti-CD19 CAR-T cells. This requires monitoring patients who receive CAR-T cells directed against CD19 to assess whether they develop B cell aplasia, mainly by measuring serum gammaglobulins (7). Hypoglobulinemia can be managed clinically with immunoglobulin replacement therapy.



**ALTHOUGH MOST CELLULAR COLLECTIONS ARE SUCCESSFUL, CERTAIN LABORATORY PARAMETERS ARE CRUCIAL TO DETERMINE WHETHER A PATIENT CAN PROCEED WITH COLLECTION.**

Clinical laboratorians should be aware of the potential laboratory abnormalities that accompany treatment with CAR-T cells. For example, patients might experience cytopenias in the period following infusion. In this instance, they might resemble a patient who has undergone a hematopoietic progenitor cell transplant, although they received entirely different cells. Prolonged B cell aplasia and hypogammaglobulinemia associated with CAR-T cells directed to CD19 could predispose them to develop infections. These patients might then be similar to other patients who are



## How CAR-T Cell Therapy Works

Chimeric antigen receptor (CAR)-T cells are autologous T cells that undergo genetic modification to express a receptor that contains four basic components: 1) extracellular single chain variable fragment (scfv) specific to a target antigen, 2) a transmembrane region, 3) intracellular T cell receptor (CD3 zeta chain), and 4) T cell co-receptor domain. The T cell receptor and co-receptor activates the T cell to exert its cytotoxic T cell functions upon the target cell (1).

These CAR-T cell components are customizable. For example, different scfvs can be used to recognize different targets, or different T cell coregulatory molecules can be added. CAR-T cells, via the scfv, recognize surface targets that are reproducibly expressed on malignant cells and not expressed on tissues that are known to cause irreparable damage to nonmalignant tissues that cannot be readily managed clinically.

CAR-T cells are manufactured from peripheral blood T cells. After collection of starting material by apheresis, the cells are transported to a processing facility where a vector, typically retroviral in nature, containing the genetic material for the CAR is introduced into the T cells. The T cells are then cultured and stimulated to proliferate. Once the desired number of cells for infusion has been obtained, the cells are transported back to the site of infusion. The patient then receives the cells, and is monitored for response in both acute and chronic settings (2).

The two Food and Drug Administration (FDA)-approved CAR-T cell products in clinical use—tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta)—both contain scfvs directed against CD19, a cell surface protein expressed on many B cell malignancies. The CAR constructs for the two commercial products differ mainly in the intracellular costimulatory component that renders the cytotoxic T cell function: CD28 in axicabtagene ciloleucel and CD137/4-1bb in tisagenlecleucel. They also differ in the vector used to deliver the genetic material into T lymphocytes: Tisagenlecleucel is manufactured using a lentiviral vector, and axicabtagene ciloleucel uses a gammaretroviral vector (2).

It is interesting to speculate that these noted differences between the commercial products might be due to the almost simultaneous and parallel progression of each through the FDA approval process. As data accrue over time, the different profiles of the two CAR-T cell products might become clearer. Tisagenlecleucel and axicabtagene ciloleucel have shown impressive results treating malignancies that, up until this point, have had extremely poor prognoses (3). Treatment with axicabtagene ciloleucel demonstrated a 58% complete response rate after 2 years in patients with relapsed refractory diffuse large B cell lymphoma (3, 4). Treatment with tisagenlecleucel yielded an overall survival rate of 73% at 1 year (4). Both products received FDA approval for large B cell lymphomas; tisagenlecleucel also has approval for relapsed and refractory B acute lymphoblastic leukemia (5, 6).

Notably, while CAR-T cell products have shown very promising results, they have only gained approval for certain hematologic malignancies and have less-than-100% response rates. In addition, efforts to use CAR-T cells in solid malignancies have not yet proven successful. So while at this point CAR-T cell therapy has not yet been proven to be a magic bullet, it does have the high potential to become a mainstay in oncologic therapy.

Most clinical and laboratory characterization in patients has taken place in the context of the two FDA-approved CAR-T cell products, and some laboratory profile components in patients are specific to the particular CAR T cell therapy. For instance, B cell aplasia is an expected side effect of CAR-T cells directed against CD19, since normal B cells also express CD19 and are therefore eliminated in the same manner as the malignant cells expressing CD19. However, this side effect would not be expected in a patient who received CAR-T cells directed against a different target antigen not expressed on B cells.

Familiarity with the different types of CAR-T cell products currently in clinical use as well as those in clinical development will be useful for anticipating potential scenarios that might arise during evaluation of these patients. Laboratory involvement is essential throughout the process of CAR-T cell treatment so that care can be delivered in a timely manner that optimizes patient outcomes.

predisposed to infections, and appropriate microbial testing is warranted to ensure prompt therapeutic intervention if necessary.

Serologic monitoring of antibody titers to previous vaccinations can also be prudent. Interestingly, although B cell aplasia can be profound, plasma cells have been shown to persist in patients after they've been treated with CAR-T cells (2). Plasma cells, which do not express CD19, are major antibody-producing cells of the immune system and help form memory to vaccines and antibody-mediated immune responses; plasma cell persistence could be protective for a patient. In addition, the lentiviral vector used to deliver the CAR genetic material into T cells in tisagenlecleucan, depending on the assay, result in false-positive HIV test results (2).

Laboratory testing and investigation reflects the variety of clinical scenarios of patients who receive CAR-T cells and requires an individualized approach. For instance, while B cell aplasia and hypogammaglobulinemia is specific to anti-CD19 CAR-T cell therapy, the potential for false-positive HIV test results might not be specific to the CAR-T cell target, but rather the viral vector used to introduce genetic material. Other side effects such as cytopenias and CRS might be generalized to treatment with CAR-T cell therapies regardless of a therapy's target.

Patients also must be monitored over time for development of unanticipated adverse effects of CAR-T cells, such as relapse of the primary malignancy, secondary malignancies, and mutagenic potential of the CAR-T cells themselves (2). Long-term monitoring involves careful consideration of the previous CAR-T cell therapy to ensure any potential effects of the treatment are identified. Awareness of the anticipated, unanticipated, specific, and general side effects can help guide clinical laboratories to investigate how testing can be improved upon as more becomes known about the different CAR-T cells—both those now in clinical use and the ones to come.

### New Therapies on the Horizon

CARs can differ in clinical targets, genetic structure, and even the cell in which the CAR resides. Even as the two FDA-approved CAR-T cell

therapies disseminate in practice, researchers are continuing to develop other CAR-T cells and other genetically modified cellular therapies.

CAR-T cells are very attractive as a potential therapy because they are fairly simple to construct, customizable, and have already shown the potential to alter the clinical course of diseases with otherwise very poor survival. The CAR construct can be modified to recognize different targets, such as B cell maturation antigen on multiple myeloma cells or mesothelin on certain solid tumors. Both these therapies are under clinical development and have undergone testing in humans.

Development of CAR-T cells expressing different target antigens requires thoroughly evaluating their side effect profiles in preclinical and clinical trials to identify any on-target/off-tumor effects, their potential clinical impact, and strategies to monitor and treat patients.

Laboratory evaluation of patients throughout the process of CAR-T cell therapy is critical to identify information that might be useful to monitor success or mitigate side effects of this therapy. Furthermore, knowledge and familiarity with the potential clinical and laboratory presentations of patients who undergo CAR-T cell therapy will encourage all providers to anticipate and adapt quickly to the changing CAR-T cell clinical landscape and will help to optimize care for patients who receive currently used CAR-T cells as well as those to come. ■

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

## Managing Proprietary, Esoteric Lab Tests Requested by Patients

Laboratory stewardship is not for the faint of heart. Performing this vital function demands considerable energy in fighting the constant, uphill battle against a small portion of the lab industry that enthusiastically markets new, proprietary tests with potentially exaggerated claims. This marketing is usually directed toward labs and sometimes to patients and families, either directly or through information on a website. While some of these tests are clinically useful, many lack clinical utility.

The difficulty in adjudicating these requests arises in that often they are marketed for clinical conditions which involve profound patient suffering. The psychosocial nature of wanting to understand more in the face of suffering is universal and understandable. This leads to tremendous pressures on care providers when patients directly request these tests.

In response to such test requests, laboratorians must perform challenging assessments about whether a test provides evidence-based clinical utility. This article will walk through a framework for handling these requests, using a composite teaching case that involves a commercial antibody panel. We have derived this de-identified case not only from our own experience but also that of several members of our Patient-Centered Laboratory Utilization Guidance Service (PLUGS).

### Case Study: A Questionable Commercial Antibody Panel

A single commercial laboratory has developed and marketed an antibody panel as a diagnostic test for pediatric

acute-onset neuropsychiatric syndrome (PANS) and pediatric autoimmune neuropsychiatric disorder associated with streptococcus (PANDAS). These disorders have similar proposed diagnostic criteria that include sudden onset of behavior changes, at least two qualifying behavior attributes, and lack of known medical or neurologic disorders. The main difference between the two conditions is that PANDAS includes tics as a possible primary symptom as well as a confirmed streptococcal infection before symptom onset.

The promise of new treatments targeted to autoimmune conditions, such as intravenous immunoglobulin therapy, makes diagnosis with biomarkers appealing. The panel from the commercial lab includes autoantibodies to dopamine receptors in which a positive result could justify treatment. In this case study, the lab receives a request from a psychiatrist to evaluate this testing at the request of a family who found the test online.

### The Laboratory's Response

The dilemma presented in this case study demands a threefold approach: Do homework, provide support to the care provider who received the request, and make a policy and procedure that helps deal with the next request for the same panel.

#### *Do the Homework*

In this case, as with all laboratory stewardship interventions, due diligence will carry the day in understanding the current state of the test in question. A thorough literature search can provide meaningful

information. Signs suggesting that a test might lack clinical utility include (from least to most concerning):

- The test does not appear in a diagnostic guideline offered from a reputable society or policymaking body.
- No peer-reviewed studies exist from independent sources indicating the test's clinical utility.
- The only peer-reviewed publication on the test's clinical utility comes from the commercial lab offering the test.
- No peer-reviewed publications exist on this test.
- Choosing Wisely ([www.choosingwisely.org](http://www.choosingwisely.org)) specifically notes that the test lacks clinical utility.
- The test appears on Quackwatch ([www.quackwatch.org](http://www.quackwatch.org)).

In addition to these signs, it is useful to determine whether other laboratories offer similar tests. While a clinically useful, cutting-edge test occasionally will be offered by only one laboratory, much more commonly a clinically useful test will be developed and offered by several major reference laboratories and elite academic medical centers.

In our example of the autoantibody panel for PANS/PANDAS, the literature painted an unusual and controversial landscape. Only one study independently evaluated the sensitivity and specificity of the autoantibody panel (1), and this study directly conflicted with a study authored by the inventors of the commercial panel (2). The independent study found that the control patients had a similar test positivity rate (86%) to the patients assessed for PANS/

PANDAS (92%). Thus, the authors concluded that since “none of the individual scores or any composite score corresponded with a diagnostic odds ratio  $>1$ ,” the commercial autoantibody panel was no better than chance in detecting PANS or PANDAS. Additionally, no other clinical lab could be found offering any of the autoantibodies in the panel.

#### *Provide Support*

Families often take the information they gather about proprietary tests to their care providers and direct the providers to order and coordinate testing. This is known as “patient-directed” testing, and nearly half of care providers encounter these requests in their practice. Providers are often unfamiliar with the test in question and feel pressured to complete the request to maintain a good patient-doctor relationship.

Laboratory stewardship programs can help these providers move from patient-directed testing to patient-centered testing. The latter involves testing that has a reasonable evidence base for clinical utility and is the right test for a patient.

In this case study, the psychiatrist reached out to the laboratory stewardship team to ask about the clinical utility of the autoantibody panel. The lab stewardship team shared with the practitioner the facts from their literature and guideline review and then strategized how to communicate with the family (See Figure 1).

The lab stewardship team also offered to step in and speak with the patient if the provider felt uncomfortable communicating this information. Often, laboratory stewardship involves replacing well-meaning, but inappropriate, test requests with appropriate testing. However, in this case no test was the best test.

#### *Make a Policy and Procedure for Future Requests*

Once a decision has been made not to use a certain laboratory or laboratory test, this decision should be put into practice through a policy and procedure that supports providers the next time a patient requests the test.

In our case study, the clinical lab incorporated a policy to ban the commercial autoantibody panel and added

### **F1** Items to communicate to a patient or family wanting to direct a care provider about what tests to order.

- **Share our values.** “Our hospital supports patient-centered evidence-based care.”
- **Address the distinction between analytical validity and clinical utility.** “Even though a test may have analytical validity (it can measure what it says), it is often harder to understand the test’s clinical utility: Will we do something different based on the results of the test? And, will that make you better?”
- **Refer to the hospitals’ lab stewardship program and review process.** “I am not sure if we can coordinate this request, and I will check with our laboratory stewardship team to learn more. This team reviews new labs/tests before they can be offered to our patients.”
- **Defer sample collection.**

the panel to the list of tests which have limited or no clinical utility. The lab links to this list in its online test catalog. As part of the lab’s procedures around banning a particular test, the lab stewardship team also will offer to explain to the patient-facing provider why the test is banned so that this provider will be better able to communicate to the patient or family. In addition to the list of tests with limited or no value—available to anyone who searches the lab’s test catalog—the policy and procedure links to test-specific pages that include instructions for phlebotomists or providers who may find themselves in front of a patient requesting the test.

After the lab published the information about our case study autoantibody panel in its online test catalog, the stewardship team heard from a different physician, not in psychiatry, that this information helped evaluate a request in their clinic, preventing patient-directed testing of no clinical utility. The patient in this case was grateful for the information and happy to not have testing.

#### **Conclusions**

The moral of this story is that due to skilled and sometimes aggressive test marketing, laboratorians who are serious about stewardship need to prepare for difficult discussions with providers and with patients about

tests that lack clinical utility. Having a well-considered plan for how to respond will help clinical laboratorians stay one step ahead of such requests and ensure that patients get only the right tests at the right time. ■

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**LABORATORY  
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BY BRIAN JACKSON, MD, MS

## Ethics of AI and Big Data in Laboratory Medicine

In the early 1900s a new epidemic began to spread through major American cities. It disproportionately targeted children; more than 100 died from it on the streets of Detroit in the year 1917 alone. Today, a century later, we still don't have a cure, but we've dramatically reduced the harms through a combination of technology and regulation. What was this epidemic? Influenza? Group A streptococcus? No, it was the automobile.

Today automobiles are an integral part of most of our lives. But if we could go back in a time machine, we would see just how unprepared cities were for this new technology. There were no licensing laws, no traffic lights, and no speed limits, let alone traffic police to enforce any of these. Motors may not have been powerful by today's standards, but brakes were even less so, especially when combined with narrow tires and gravel roads. And since modern playgrounds had yet to be invented, the streets were full of children.

In subsequent decades, society has developed a web of risk mitigation mechanisms for motor vehicles. Some advances have been regulatory, such as traffic laws and driver licensing. Others have been technologic, such as antilock brakes, airbags, and road design. These two categories complement and reinforce each other. Quite in contrast to being anti-innovative, auto regulation has spurred a wide range of social and technologic innovation that increases

public safety while expanding the usefulness of this form of transportation.

Today a new technology is changing the world in even more dramatic and far-reaching ways: artificial intelligence (AI). It has revolutionized advertising, entertainment, and education, and is invading many other areas of our lives. Some of the most obvious examples include self-driving cars, phones that understand our speech, and online search engines that answer virtually

single law or technology. Just as with automobiles, it will require a whole new ecosystem of norms, regulations, and technologies.

A major difference between automobiles and AI, though, is that the risks of AI are not directly physical in nature. They're subtler, involving core issues of privacy, social benefit, and fairness.

Medical ethics provides a useful framework for considering such AI



any question. Less obvious examples operate behind the scenes in retailing and service industries. And the medical world has high expectations for AI to improve healthcare.

### An Old Structure Fits a New Challenge

AI, like every other powerful technology, introduces new risks alongside new benefits. Managing these risks will not simply be a matter of a

risks. In the roughly 2,500 years since Hippocrates authored his famous oath, medical ethics has undergone significant updates. Modern representations include the World Medical Association code for medical practitioners as well as the Common Rule governing human subjects research within the U.S. Four principles underlie these codes: respect for persons, beneficence, nonmaleficence, and justice. AI presents risks to all four.

### Respect for Persons

Respect for persons includes patient autonomy and informed consent. Patients have the right to decide for themselves which medical procedures to accept or reject, and effective autonomy requires first understanding the risks and benefits of those procedures. Unlike traditional mathematic models such as logistic regressions, the details of deep learning and other modern AI techniques are not easily translated into human-understandable terms. In general, the more powerful the AI technique, the less explainable it becomes, and the higher the potential for hidden biases and unpredictable behavior. These techniques essentially become black boxes.

When dealing with medical applications of AI, then, it becomes incumbent on the developers of systems to make them freely available for academic study. Only when the behavior of AI models has been thoroughly and independently vetted will patients be able to make informed choices about being subject to them.

### Beneficence

Beneficence is perhaps the most obvious medical ethical principle. It says that everything in medicine needs to have a realistic prospect of benefiting a patient. This is potentially in conflict with the business models of technology companies such as Google, Facebook, Amazon, Apple, IBM, and Microsoft, which are far and away the leaders in AI technology in the Western world (China has several as well that are arguably as advanced, but they operate mainly in China).

The prevailing business model for AI at these companies involves acquiring massive volumes of personal data and then monetizing it primarily in the form of targeted advertising. This model is controversial enough in the case of nonmedical data, but potentially unethical in the case of medical data when there is no balancing benefit to the patients whose data is being collected.

### Nonmaleficence

The flip side of beneficence is nonmaleficence, sometimes known by the Latin phrase *primum non nocere*, or “first, do no harm.” One potential harm of AI has to do, not

## T1 Examples of Ethical Principles and Risks in AI

Ethical principle	Examples of risk	Examples of mitigation
Autonomy	Patients can't exercise informed consent if they don't understand the risks and benefits of the individual algorithms.	Ban black boxes: algorithms need to be made available for independent academic study.
Beneficence	Healthcare AI models might emerge that primarily serve nonmedical functions such as targeted advertising.	Prohibit sharing of personal health information with technology firms unless the downstream uses are explicitly for medical benefit.
Nonmaleficence	Massive data sets create potential for even de-identified health data sets to be used in ways that harm individuals.	Implement short time limits on retention of health data by tech companies. Prohibit both sharing with third parties and re-identification.
Justice	AI may exacerbate health disparities through exploitative pricing models.	Develop reasonable pricing clauses and adapt intellectual property law to reflect ownership rights by the public whose data were used to train the algorithm.

with the algorithms per se, but with acquiring and storing the large sets of personal data typically used for training and applying medical AI. In many cases these data sets have been de-identified in order to avoid HIPAA restrictions on data sharing and use. Given the widespread availability of nonmedical data sets of personal information, though, most de-identified data can be readily re-identified simply by cross-referencing with other data. A patient with a stigmatizing medical condition thus could be subject to higher life insurance rates or discriminated against by potential employers or landlords, all without anyone technically violating HIPAA.

At least until new legal privacy protections emerge in the U.S., it will be up to the healthcare industry, including hospitals and health systems, to vigorously protect their patients' data from potential abuses. And judging from news reports over the past year involving large health systems sharing data with large tech companies, it is not entirely clear how strong that line of defense is at present.

### Justice

The fourth foundational principle of medical ethics is justice, i.e. fairness. One measure of justice with respect to AI is the extent to which it increases or reduces health disparities. If AI developers pursue pharmaceutical-style pricing models, they could further widen the health delivery gaps

between haves and have-nots. One way to mitigate this risk might be for health systems and patient interest groups to insist on reasonable pricing and distribution clauses in exchange for sharing the patient data needed to develop AI systems.

### Clinical Laboratorians Must Stay Engaged

Medical AI applications will almost certainly grow in number and scope in the coming years. Many of these already are using clinical laboratory data, and in the future they might supplement or even replace certain laboratory tests. And there will almost certainly be large benefits. But the risks are real, and we would be foolish to not discuss and deal with them.

Just as automobile safety has co-evolved in parallel with advances in automotive capability and power, it should be possible to co-evolve AI safety even as its power and capabilities grow. This will almost certainly require new laws, but the pace of legislation almost invariably lags its target. In the meantime, medical and academic communities can do much to develop both technologic and policy-based solutions. ■

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## Regulatory Roundup

### Vela Diagnostics Gets FDA Authorization for NGS Test for HIV Drug Resistance

The Food and Drug Administration (FDA) has granted de novo authorization to Vela Diagnostics USA for its Sentosa SQ HIV Genotyping assay, making this the first FDA-authorized test that detects HIV type-1 drug resistance mutations using next-generation sequencing (NGS). Traditionally, healthcare providers have used viral load tests to monitor the efficacy of HIV antiviral drugs, with increasing viral loads indicating that the virus might have mutated and that a patient's current regimen is no longer effective at suppressing the virus. By identifying mutations in the HIV-1 virus that impact the efficacy of certain drugs, the Sentosa SQ assay is designed to provide additional information beyond viral load that could help healthcare providers better tailor drug treatment for patients who have developed resistance to HIV drugs, as well as for patients who are just beginning antiviral therapy.

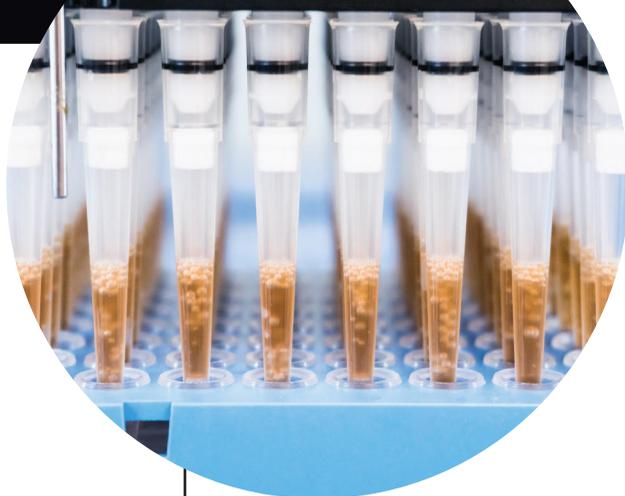
The Sentosa SQ assay is performed with plasma or serum samples, and detects 342 drug resistance mutations, including Group M subtypes A through K as well as drug resistance mutations in the virus's integrase, protease, and reverse transcriptase genes. Additionally, unlike traditional methods for HIV genotyping such as Sanger sequencing, this assay delivers results in days rather than weeks. To evaluate this test, FDA reviewed data from studies demonstrating that the test performs with a sensitivity and specificity greater than 95%.

adverse event reports about falsely low troponin results caused by biotin interference. In an effort to make sure that lab professionals, healthcare providers, and the public are aware of this issue, the agency has published a list at [www.fda.gov](http://www.fda.gov) of all the troponin diagnostic devices that are still subject to biotin interference. FDA also encourages lab professionals to inform healthcare providers if any tests used in their lab are subject to biotin interference, and to communicate with clinicians to identify patient samples that contain biotin.

#### T2 BIOSYSTEMS GETS CE MARK FOR DIRECT-FROM-BLOOD ANTIBIOTIC RESISTANCE TEST

The CE mark has been given to T2 Biosystems for the T2Resistance panel, which identifies 13 of the most serious antibiotic-resistance genes on the 2013

Centers for Disease Control and Prevention Urgent Threat list. These genes include the gram-negative markers *KPC*, *OXA-48*, *NDM/VIM/IMP*, *CTX-M 14/15*, and *AmpC (CMY/DHA)* and the gram-positive markers *vanA/B* and *mecA/C*, which indicate resistance to common empiric antibiotic therapies such as carbapenems, vancomycin, and penicillin. The test detects all of these resistance markers directly from whole blood in 3 to 5 hours, and features broad inclusivity of resistance variants, as well as  $\leq 10$  CFU/mL detection demonstrated for all targets. Studies have shown that the T2Resistance panel does not exhibit cross-reactivity with or inhibition due to common interfering substances. It was developed with funding from CARB-X, a global nonprofit partnership that works to accelerate technological development to combat the threat of drug-resistant bacteria.



#### FDA EMPHASIZES THAT BIOTIN INTERFERES WITH TROPONIN TEST RESULTS

The Food and Drug Administration (FDA) has updated its safety communication about biotin interference with laboratory tests to underscore the fact that biotin interference can cause falsely low results for troponin testing. Since FDA released its 2017 safety communication, some lab test manufacturers have successfully mitigated biotin interference with their assays, but others have not, according to FDA. FDA expresses concern over this in its updated communication, particularly because the agency continues to receive

### FDA OKS NANTHEALTH'S SEQUENCING TEST FOR OVERALL TUMOR MUTATIONAL BURDEN

**N**antHealth has earned Food and Drug Administration (FDA) clearance for the Omics Core, the first whole exome tumor-normal in vitro diagnostic that measures overall tumor mutational burden (TMB). The test is performed with formalin-fixed paraffin-embedded tumor tissue matched with normal specimens from patients with solid malignant neoplasms. It uses targeted next-generation sequencing to determine overall TMB by analyzing 19,396 protein-coding genes, as well as somatic alterations—such as point mutations and small insertions and deletions—in 468 cancer-relevant genes. TMB is then reported via two metrics: The first metric is the total number of somatic non-synonymous exonic variants within the protein-coding genes surveyed, and the second is an estimate of mutation rate calculated by counting all somatic, synonymous, and non-synonymous variants detected in gene coding regions and dividing by the approximate size of the whole exome. According to NantHealth, this information might be used to guide cancer treatment, as some studies have shown that patients with high TMB respond better to immunotherapy compared to those with low TMB (though at the moment FDA's clearance for the test does not cover any therapeutic indications).

### CE MARK GRANTED TO GENEDRIVE FOR GENETIC ANTIBIOTIC-INDUCED HEARING LOSS TEST

**T**he U.K.-based company Genedrive has received the CE mark for its rapid point-of-care test for antibiotic-induced hearing loss, the Genedrive MT-RNR1 ID kit. Performed with an inner cheek swab sample, the test screens infants in critical care settings for the m.1555A>G mutation in the *MT-RNR1* gene, which makes individuals susceptible to lifelong



deafness if they are given the frontline antibiotic gentamicin. The U.K.'s National Institute for Health and Care Excellence recommends that infants with suspected infection be treated with an antibiotic regimen including gentamicin within 1 hour of arrival in a neonatal intensive care unit. However, current genetic tests for the risk of gentamicin-associated hearing loss typically take 3-5 days to return results. To address this problem, Genedrive designed the MT-RNR1 ID kit to provide susceptibility results in less than 1 hour, so that infants with the m.1555A>G mutation can be prescribed a safer alternative to gentamicin.

### BIONEER EARNS CE MARK FOR HCV TEST

**T**he CE mark has been granted to the South Korea-based company Bioneer for its AccuPower

HCV Quantitative RT-PCR kit, which quantifies hepatitis C virus (HCV) RNA in human samples such as serum and EDTA-plasma. The test detects HCV genotypes 1-6 through real-time reverse transcription polymerase chain reaction (RT-PCR) and runs on Bioneer's semi-automated real-time quantitative PCR molecular diagnostic system ExiStation. The test also uses Bioneer's proprietary AccuPower Dual-HotStart RT-PCR premix, which includes Dual-HotStart reverse transcriptase. This reverse transcriptase can achieve RT reaction in unusually high temperatures (up to 70°C), making it possible to adopt template RNAs even if they have a complex secondary structure. Additionally, the AccuPower HCV Quantitative RT-PCR kit is designed for use with ExiStation Manager software, which automatically analyzes the test results from this kit based upon the threshold cycle value.

## Industry Playbook

# Illumina, PacBio Contest U.K. Regulator's Proposal to Prohibit Their Impending Merger

Illumina and Pacific Biosciences (PacBio) are disputing a U.K. regulatory body's determination that the anticipated merger between these two companies could weaken competition in the U.K. market for next-generation sequencing (NGS) systems. Illumina inked an agreement to acquire PacBio for approximately \$1.2 billion in November 2018, and at the time, the companies expected the transaction to close sometime in 2019. However, in October of that year, the U.K. Competition and Markets Authority (CMA) came to the preliminary conclusion that the merger could result in adverse effects for the country's NGS market, such as "reduced choice, an increase in prices, deterioration in quality, deterioration in service, and/or loss of innovation." To prevent this, CMA proposed blocking the companies' merger.

In response, Illumina and PacBio challenged CMA's proposal in a November 2019 document alleging that there is no evidence supporting CMA's supposition that Illumina's short read systems and PacBio's native long read systems currently compete. In particular, the document states that the regulator's proposal fails to account for the majority of the customers CMA interviewed who said that Illumina and PacBio's systems are not interchangeable, which suggests that they do not fall into the same product market.

Separately, Illumina and PacBio also proposed remedying any potential anticompetitive effects of their merger by providing competitors with perpetual,

royalty-free licenses to any of the two companies' pre-closing patents and patent applications. To date, though, their U.K.-based competitor Oxford Nanopore Technology has rejected this proposal.

### INFLAMMATIX GETS BARDA FUNDING TO DEVELOP RAPID POCT FOR ACUTE INFECTIONS

The winner of the 2019 AACC Disruptive Technology Award, Inflammatrix, has entered an agreement to further develop and commercialize its point-of-care HostDx tests with funding from the Biomedical Advanced Research and Development Authority (BARDA), which is part of the U.S. Department of Health and Human Services' Office of the Assistant Secretary for Preparedness and Response. Under the terms of the deal, Inflammatrix will receive \$6 million in the first phase of a cost-sharing contract that is worth up to \$72 million based on

achieving certain milestones. The first phase of work will focus on the HostDx Fever test, which analyzes gene expression patterns in the immune system to identify in under 30 minutes whether a suspected infection is bacterial or viral. This could enable physicians to quickly determine whether or not to prescribe antibiotics. The HostDx Fever test uses fingerstick blood samples and is designed for use in primary care, urgent care, and other outpatient clinical settings.

Additionally, the contract may optionally support the development of two additional Inflammatrix tests, HostDx Sepsis and HostDx FeverFlu. HostDx Sepsis will be a blood-based test that rapidly determines the

likelihood that a patient has or will develop sepsis and will be designed for use in emergency department or other hospital settings. HostDx FeverFlu will be performed using nasal swab samples and will combine traditional influenza testing with host-response biomarkers.

### WAVE LIFE SCIENCES TAPS ASURAGEN FOR HUNTINGTON'S DISEASE COMPANION DIAGNOSTICS

Asuragen and Wave Life Sciences are collaborating to develop and commercialize companion diagnostics for Wave's allele-selective silencing therapeutics for Huntington's disease (HD). Wave is currently conducting Phase 1b/2a clinical trials to evaluate



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two HD therapeutics, the stereopure oligonucleotides WVE-120101 and WVE-120102. HD is caused by an expansion of CAG repeats in the *HTT* gene, and these drugs are designed to lower the mutant *HTT* mRNA transcript by targeting one of two single-nucleotide polymorphisms (SNPs) uniquely linked to the CAG-expanded *HTT* allele while leaving the wild-type transcript relatively intact. The two SNPs targeted by Wave's therapeutics are represented alone or together in up to 70% of the HD population. Under the terms of this partnership, Asuragen will use its AmpliX polymerase chain reaction technology to develop companion diagnostics that size and phase *HTT* CAG repeats with the two SNP targets of Wave's drugs. These tests could help clinicians to identify HD patients who are likely to respond to Wave's therapeutics.



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### ■ SYSMEX, BIOLIDICS TEAM ON LIQUID BIOPSY TESTS

**T**he Singapore-based medical technology company Biolidics is partnering with Japan's Sysmex Corporation to develop circulating tumor cell (CTC) assays. The new tests will use Biolidics' ClearCell FX1 system, which is a fully automated instrument that separates and enriches cancer cells from small amounts of blood. The ClearCell FX1 takes blood samples from which the red blood cells have been removed and passes them through Biolidics' CTChip FR1, a single-use microfluidic biochip that isolates CTCs from leukocytes. In addition to this technology, Biolidics' and Sysmex's new CTC assays will use Sysmex's molecular imaging flow cytometer (MI-FCM). The MI-FCM features a special camera that produces highly detailed images of in-flow cells, as well as software that automatically analyzes these images. With this technology, the instrument is able to detect protein locations and chromosomal aberrations within a cell, enabling the precise identification of minute numbers of circulating tumor cells in the blood.

### ■ SPEEDX, QUANTUMDX, AND FIND PARTNER ON LOW-COST STI TESTS

**S**peeDx and QuantuMDx have joined forces with the Foundation for Innovative New Diagnostics, a global nonprofit organization that aims to drive development and delivery of diagnostics to combat major diseases in resource-limited areas. The trio's collaboration will assess the feasibility of developing low-cost point-of-care (POC) tests for common sexually transmitted infections (STIs). Under the terms of the partnership, SpeeDx will also use its PlexPCR technology to develop multiplex tests for common STIs, including gonorrhea and *Mycoplasma genitalium*, that will run on the QuantuMDx Q-POC device. "We are excited by this collaboration ... and the potential to expand access to high-quality testing options to the areas of the world that really need it," said Elisa Mokany, PhD, SpeeDx founder and chief technology officer. "Patients around the globe are already benefiting from the clinically relevant information provided by SpeeDx tests, but we are cognizant that the current platforms and processes in use to run these tests do not readily translate to all regions of the world."



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## Ask The Expert

# What Labs Should Know About Pediatric Thrombosis



### EXPERT

**Jumoke Oladipo**  
MD, DABCC, FAACC

#### What are the most common causes of thrombosis in children?

**A:** The incidence of hospital-associated pediatric thrombosis has risen over the last 2 decades. This is due to improved survival of children with chronic conditions and a concomitant increase in the use of central venous catheters—the most common

cause of thrombosis in children—and other lifesaving technology.

The presence of inherited thrombophilia in children is more of a risk factor for than a cause of thromboembolism and is usually of greater importance in adolescent children who develop venous thromboembolism without any triggers or who develop an exaggerated response compared to the trigger. Hereditary thrombophilia are classified mainly into the high or low risk for thrombosis groups. The high-risk group includes: deficiencies of the coagulation inhibitors anti-thrombin, protein C, and protein S, while the low-risk group includes factor V Leiden and prothrombin gene mutation.

#### What does testing for hereditary thrombophilia involve?

The most common tests performed in cases of hereditary thrombophilia include those for anti-thrombin, protein C, and protein S activity, as well as factor V Leiden and prothrombin mutation analysis done via polymerase chain reaction. All of these tests together constitute the hypercoagulable panel at my institution. We might also test for plasma homocysteine concentrations, especially if a patient has arterial thrombosis.

Hereditary thrombophilia testing does not influence the immediate care of patients with thrombosis and should be deferred for approximately 3–6 months after an acute episode and after anticoagulant therapy has ceased. This is because both the thrombotic consumptive process and anticoagulants affect tests for coagulation inhibitor activity. However, labs can run molecular testing for factor V Leiden and prothrombin gene mutation at any time.

While labs should perform this testing on a case-by-case basis, it is generally reserved for children with unprovoked thrombotic episodes and a family history of thrombosis. Hereditary thrombophilia testing is usually not recommended if a thrombotic episode is provoked by strong risk factors like major surgery, catheter use, immobility, major trauma, or malignancy. Additionally, comprehensive testing based on a positive family history alone is controversial but might be necessary when prescribing oral contraceptives. In all scenarios,

communication between the laboratory and clinicians is essential for deciding when, whom, and what to test.

Labs should always remember that the purpose of these tests is primarily for risk assessment, not for identifying a cause of thrombosis. This means that a patient with a positive result might never actually have a thrombotic episode.

#### What is the biggest challenge with hemostasis testing in children?

The coagulation system of neonates and children evolves with age, which means that pediatric concentrations for a majority of coagulation factors and inhibitors differ markedly from adult concentrations. For example, protein C levels at birth could be anywhere from 17% to 53% of adult levels. These levels usually rise to >50% of adult levels by 6 months, with some reports indicating that full adult levels may not be reached until around 16 years of age.

Differences like this between children and adults have significant biological and clinical implications. In an ideal world, diagnostic laboratories processing pediatric samples would therefore use age, analyzer, and reagent-appropriate reference ranges—but currently this is not always possible. Many hemostatic reference values for preterm infants are lacking, and the ones that researchers have already reported rely on small study groups. Because of this knowledge gap, adult-based reference ranges are often used for the diagnosis of pediatric patients.

#### Are direct oral anticoagulants (DOACs) approved for use in children?

None of the newer DOACs have been approved for use in children. Several clinical trials are still ongoing that will hopefully soon result in guidelines for pediatric DOAC use. These drugs would particularly benefit children on long-term therapy since new DOACs do not need to be monitored and also have fewer food and drug interactions.

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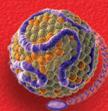


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