ASSESSING SIGMA METRICS

68.7%

Percentage of 115 assays assessed by a single algorithm that achieved 6 Sigma or better

PRECISION DRAWS:
Mastering
phlebotomy basics

Guidance on respiratory virus testing

Proficiency testing changes

ADLM Association for Diagnostics & Laboratory Medicine™
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CLN
Clinical Laboratory News

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DEPARTMENTS

"The commonly reported lithium therapeutic ranges (0.6–1.2 mmol/L) are too high for older adults and may lead to missed lithium toxicity." p40

Federal Insider

Laboratory developed tests regulation survey highlights concerns for pediatric health

The Association for Diagnostics & Laboratory Medicine (ADLM, formerly AACC) conducted a survey of clinical laboratories to assess the potential impact of proposed Food and Drug Administration (FDA) regulations on laboratory developed tests (LDTs). The findings underscored significant concerns that these regulations could hinder patient care, particularly in pediatric settings.

LDTs play a pivotal role in timely diagnoses and treatment decisions in hospitals. However, an FDA rule aims to regulate LDTs in addition to existing oversight by the Centers for Medicare and Medicaid Services (CMS). ADLM opposes this dual regulatory framework, which the association believes may be beyond the FDA's statutory authority.

The survey, which garnered responses from 140 U.S. laboratories, revealed several key insights, including onerous burdens on hospital labs and significant challenges to continuing quality patient care. Children's hospitals in particular expressed apprehension. If the FDA imposes regulations on LDTs, many of these hospitals would face difficult choices — either outsourcing tests to commercial labs or transitioning tests to alternative FDA-approved kits that may be less accurate. Both scenarios could lead to life-altering delays in diagnosis and treatment for sick children, according to ADLM.

With the FDA final rule still pending, the survey shows labs face profound uncertainty. Some 87% of facilities that currently perform LDTs have not developed contingency plans to deal with potential FDA oversight. Reasons cited include the financial burden associated with FDA regulation and the relative unfamiliarity of FDA rules compared to existing CMS regulations.

"If laboratory developed tests become FDA-regulated, children's hospitals could be forced to make exceedingly difficult tradeoffs at the expense of patient care," said ADLM President Octavia Peck Palmer, PhD, in a statement. "While ADLM shares FDA's goal of ensuring that laboratory developed tests are safe and effective, we need to balance that with preserving the accessibility of these tests — especially for the most vulnerable patient populations. ADLM's survey findings underscore the fact that placing these tests under additional FDA oversight would undermine care for children across the U.S."

● ADLM-LED COALITION URGES ADDITIONAL FUNDING FOR CDC HARMONIZATION INITIATIVE

In a letter to Congressional leaders, an ADLM-led coalition has called for increased funding for the U.S. Centers for Disease Control and Prevention (CDC) to support the harmonization of clinical laboratory test results. Harmonization ensures that laboratory data can be shared and meaningfully utilized, benefiting both clinicians and patients, the letter noted.

As the healthcare delivery system moves toward greater integration, laboratory data becomes a key piece of health information shared among providers, patients, and payers, the letter emphasized. However, for most laboratory tests, a gold standard either does not exist or is not readily applied. This lack of harmonization means that different clinical test methods may yield varying numeric values for the same patient sample, even though each result is accurate within its own context.

Congress has supported ADLM's advocacy for more CDC funding over several years, leading to significant achievements, the letter noted. Increased funding has allowed the CDC Clinical Standardization Programs to produce and distribute reference/harmonization materials for clinical standardization programs worldwide. The CDC also has substantially increased the number of harmonized biomarkers — from 10 in 2014 to 26 in 2022.

● REPORT: CMS SHOULD BE MORE FLEXIBLE IN PAYING FOR TESTS DURING PUBLIC HEALTH EMERGENCIES

In response to the COVID-19 pandemic, the Centers for Medicare and Medicaid Services (CMS) had to quickly determine how much it would pay for clinical laboratory tests for SARS-CoV-2. Now a new report from the Department of Health and Human Services Office of Inspector General (OIG) has found that CMS did not pay enough for testing even as it pushed clinical laboratories to rapidly expand capacity. The report recommended that CMS establish a new procedure to ensure it adequately reimburses labs for tests during a public health emergency.

OIG noted that neither the CMS clinical laboratory fee schedule statute nor its implementing regulations deal with how officials can quickly set rates for new laboratory tests before the lengthy public consultation rate-setting process. In March 2020, CMS contractors (MACs) set rates for new SARS-CoV-2 viral tests through CMS's interim rate-setting policy, but the agency had to take additional action beyond its standard rate-setting procedures to set and adjust rates.

For example, in March 2020, MACs set the payment rate for a SARS-CoV-2 test at $51, based on the assays being similar to preexisting tests for Zika virus. Just one month later, CMS decided to increase the rate to $100 with new codes, with the expectation that laboratories would have to acquire high-throughput instruments, train staff, and perform additional quality assurance procedures.

CMS changed payment again in January 2021, reducing payment to $75 but adding a special new $25 add-on code. Labs could only bill for the $25 code if they returned results within 2 days — and could show they completed most SARS-CoV-2 tests for all patients within 2 days during the prior month.

This plan didn't allow contractors to set rates that fully covered the cost of SARS-CoV-2 tests for all laboratories. OIG also noted that "CMS may have missed opportunities to obtain important information that could have improved its response to the COVID-19 pandemic from laboratory associations and the MACs' pricing coordinators when it made decisions about the new clinical diagnostic laboratory test rates."

In the report, the OIG recommends that CMS work on communication among all stakeholders who are involved in setting new laboratory test rates during a public health emergency and potentially seek new regulatory authority to ensure it can act quickly and appropriately.

Agencies must respond to OIG reports. In written comments, "CMS did not explicitly state its concurrence or nonconcurrence with our recommendations but stated that it will take our findings and recommendations into consideration for future public health emergencies," the OIG report said.

Bench Matters

Navigating method evaluation in clinical laboratories

Kornelia Galior, PhD, DABCC

David Koch, PhD, DABCC, FADLM

Jill Palmer, MT(ASCP)

It's a familiar scenario in clinical laboratories: An instrument is aging and needs replacement, a physician is requesting a new test in-house, or a more advanced methodology has become available, and the laboratory is tasked with deploying it. In any case, before implementing a new instrument or test, laboratories need to evaluate each method carefully. This practice not only follows regulatory and accreditation requirements but also assesses how much error and what type of error is present in the test method when compared to the comparative or gold standard method.

Two terms are used often when it comes to method evaluation — analytical validation and analytical verification. These terms refer to evaluating Food and Drug Administration (FDA)-modified/laboratory developed tests (LDTs) and FDA-approved tests, respectively. Method evaluation requirements vary depending on the complexity of the test — non-FDA-approved tests (LDTs) require more studies to evaluate them than FDA-approved tests. Method evaluation for FDA-approved waived tests is not required but often is performed as good laboratory practice. Regardless of the type of test, most often the evaluation starts with outlining the plan and predetermining performance goals for each analyte, followed by evaluation experiments to allow data collection. At the end of the evaluation, the lab determines the acceptability of each method for use in patient care is determined.

WHY IS PREDEFINING PERFORMANCE GOALS IMPORTANT?

Developing a detailed method evaluation plan with predetermined acceptability criteria is an important step in method verification or validation as it ensures that the specific test meets the quality goals needed for patient care. Performance goals are generally defined in terms of allowable total error (ATE), and they dictate the performance characteristics required to pass the method evaluation. ATE goals can be expressed in percentages or concentration units and are specific for an analyte and their intended use. There are several resources and guidelines that can be used when defining ATE for a clinical test: clinical outcome studies, biological variation databases, professional organizations, regulatory agencies, proficiency testing organizers, and state-of-the-art models for the specific method. These sources differ in the magnitude of total error allowed for each analyte, laboratories should choose ATE objectively and appropriately to match their analytical system.

WHAT STUDIES ARE REQUIRED IN THE METHOD EVALUATION?

After defining performance goals, a plan for the individual studies describing the number of samples, timeline for data collection, and acceptability criteria for each study should be outlined. For FDA-approved tests, verification of performance specification includes precision, accuracy, and reportable range studies. Reference range verification also should be part of the evaluation process and can be done by confirming the manufacturer's reference interval, or by evaluating the appropriateness of the currently used reference range if the test is already offered in the clinical laboratory.

LDTs need the same basic studies as FDA-approved tests, but they also require an analytical sensitivity study (how low can a method accurately and precisely detect an analyte of interest) and analytical

specificity experiments (to learn what possible entities can interfere with the measurement). As best practice, any changes made to an FDA-approved test also should be addressed in the validation. For example, if the approved patient population for an assay is adults 18 years or older, and a lab wants to perform the test on pediatric patients, comparison samples from the pediatric population should be included in the evaluation.

Interestingly, if the method is FDA-approved on a specific analyzer, but the laboratory is using an analyzer that the method was not FDA-approved for, then the test falls into the non-FDA-approved/FDA-modified category. The same applies to specimen types such as body fluids. If the test was FDA approved on blood, but the laboratory wants to use the test on a body fluid that has not been FDA approved, then the laboratory needs to show analytical sensitivity and specificity in addition to other studies. There are many other evaluation studies that the laboratory can consider performing, such as carryover stability of the analyte over time, or a dilution study to extend the analytical measuring range.

A table outline of each study and criteria for acceptable performance can be found in the online version of this article at www.MyADLM.org/CLN. These acceptable criteria are based on those set at the University of Wisconsin Health and Emory University at Grady Hospital Systems in Atlanta and are based on professional experience. There are several Clinical and Laboratory Standards Institute guidelines that are helpful in outlining studies for method evaluation. Manufacturer claims offer another approach to decide whether the method being

Developing a detailed method evaluation plan with predetermined acceptability criteria ensures that the specific test meets the quality goals needed for patient care.

evaluated is performing as expected. Accuracy and precision studies can be evaluated separately but ultimately should be evaluated together by estimating total analytical error (combining precision and accuracy) at various medical decision levels and comparing the result to ATE.

WHAT ARE SOLUTIONS TO ISSUES THAT OCCUR DURING METHOD EVALUATION?

Laboratories often run into the issue of not meeting the performance goals during a method evaluation. Below are some helpful solutions to this issue.

Precision day to day: Look for outliers, repeat the precision study, select different quality control (QC) materials, or compare the coefficient of variation (CV) from the precision study to the current QC performance (if applicable).

Accuracy study: Look for outliers on a Bland Altman plot, recalibrate both assays (if applicable), or change the reagent lots. If high concentration specimens are unable to be obtained to reach the high end of the analytical measurement range (AMR), create samples by spiking with known materials or use historical proficiency testing samples. The correlation coefficient (r) does not provide information about the accuracy of the new method but does help in deciding which linear regression approach should be used to obtain slope and y-intercept. An r > 0.975 permits one to use the common least squares regression, whereas an r < 0.975 dictates that one should use Deming or Passing-Bablok regression instead.

Reportable range study: Use saline or other diluent to lower the observed range if you are unable to meet the measurement within 10%, use a different kit of the linearity material or a different calibrator lot, or use a patient sample with a high concentration and then serially dilute the specimen to obtain multiple concentrations over the range. If none of the above alternatives are available, truncating the AMR is also an option. It is important to note that truncating or shrinking the AMR within the approved range is not considered a modification to an FDA-approved test.

Evaluation of new methods is a necessary and important process for clinical laboratories to perform so that the testing used by the laboratory meets quality goals and can be safely used to support patient care. Knowing when to verify versus validate these new methods will keep your lab on the right track as it supports patients and providers.

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New insight into laboratory sigma metrics

A recent study demonstrates a new method for condensing Sigma metrics from hundreds of analyzers into a single metric of assay quality (J Appl Lab Med 2024; doi: 10.1093/jalm/jfad125).

The method produces a broad snapshot that may serve as a baseline for understanding assay performance in the presence of variability in instruments, materials handling, environmental conditions, and reagent lots in labs running Vitros analyzers.

Commercial lab companies use Sigma metrics to highlight the quality of their assays and incorporate observed accuracy, precision, and total allowed error. The higher a process Sigma level, the better its performance. But studies assessing Sigma metrics are limited by a dearth of well-controlled systems. The metric typically runs on a scale of 0–6 but is sometimes higher.

In response, researchers developed an algorithm to extract quality control data and derive the Sigma metric for 115 analytes from sites connected to the Quidel/Ortho E-Connectivity database. The researchers then used results of this process to derive the Sigma metric for each assay.

Of the 115 assays, 68.7%, or 79 assays, achieved a metric of 6 Sigma or better, and 85.2%, or 98 assays, achieved Sigma 5 or better. Troponin, creatinine, high-sensitivity C-reactive protein, procalcitonin, and potassium were among tests key in managing critically ill patients that achieved Sigma metrics of 5 or better. Another important assay, pro B-natriuretic peptide, achieved a Sigma metric of 4.1.

Scores of assay metrics included in the comprehensive metabolic panel were glucose, 5.8; calcium, above 6; sodium, 3.8; potassium above 6; carbon dioxide, 5.2; chloride, 4.4; urea nitrogen, 6; albumin, 4.6; total protein, 5.5, alkaline phosphatase, above 6; alanine aminotransferase, above 6; aspartate aminotransferase, above 6; and bilirubin, above 6.

Because study analyzers are running in working laboratories from around the world, the study can serve as a baseline for understanding the assay performance achieved in the presence of lab-to-lab, instrument-to-instrument, material handling, environmental conditions, and reagent lot variability. The significant number of assays demonstrating high Sigma levels did so despite this variation, the researchers wrote.

● THREE BIOMARKERS IMPROVE WORKUP FOR APPENDICEAL ADENOCARCINOMA

Elevated levels of carcinoembryonicantigen (CEA), carbohydrateantigen19-9 (CA19-9), and cancer antigen 125 (CA125) are associated with overall survival in appendiceal adenocarcinoma, according to a recent paper (JAMA Network Open 2024; doi:10.1001/jamanetworkopen.2024.0260).

The three serum tumor biomarkers have been useful for managing gastrointestinal and

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gynecological cancers. However, information regarding their utility in appendiceal adenocarcinoma is limited.

In response, the researchers conducted a retrospective cohort study on 1,338 patients with a median age of 56.5 years at diagnosis at a single tertiary comprehensive care facility. Just over 80% of patients had metastatic disease. CEA was elevated in 56% of patients, while CA19-9 and CA125 were elevated in 34% and 27% of patients, respectively. Individually, elevation of CEA, CA19-9, or CA125 was associated with worse 5-year survival. Elevated versus normal survival was 81% versus 95% for CEA (hazard ratio [HR], 4.0; 95% CI, 2.9–5.6), 84% versus 92% for CA19-9 (HR, 2.2; 95% CI, 1.4–3.4), and 69% versus 93% for CA125 (HR, 4.6; 95% CI, 2.7–7.8).

Although metastatic tumors had higher levels of all tumor markers, when the researchers restricted their survival analysis to 1,080 patients with metastatic disease, elevated CEA, CA19-9, or CA125 were still associated with worse survival (HR for CEA, 3.4; 95% CI, 2.5–4.8; P < .001; HR for CA19-9, 1.8; 95% CI, 1.2–2.7; P = .002; and HR for CA125, 3.9; 95% CI, 2.4–6.4; P < .001). Tumor grade was not associated with CEA or CA19-9 level, while CA125 was slightly higher in high-grade tumors relative to low-grade tumors (mean value, 18.3 versus 15.0).

Troponin, creatinine, high-sensitivity C-reactive protein, procalcitonin, and potassium were among tests key in managing critically ill patients that achieved Sigma metrics of 5 or better.

Study limitations include its retrospective design, the low number of patients (30% of the cohort) undergoing next-generation sequencing, selective tumor marker test ordering by different physicians, and lack of consideration for patients' chemotherapy and cytoreductive surgery history.

Despite these limitations, the study highlights the importance of including all three biomarkers in initial workups of patients with the disease, the researchers noted.

● STUDY IDENTIFIES NEW GENETIC MARKERS OF TYPE 2 DIABETES

A large study identified new genetic factors associated with type 2 diabetes (T2D) and pointed to the value of integrating multi-ancestry genome-wide association study (GWAS) data with single-cell epigenomics to untangle variation in factors that drive the development and progression of the disease (Nature, 2024; doi: 10.1038/s41586-024-07019-6).

T2D is a heterogeneous disease that develops through diverse disease processes and molecular mechanisms that are often specific to cell type.

To characterize the genetic contribution to these processes across ancestry groups, the researchers aggregated GWAS data from 2,535,601 individuals. Of these, 39.7% did not have European ancestry and represented 428,452 T2D cases.

The researchers identified 1,289 independent association signals at genome-wide significance that map to 611 loci. Of these, 145 loci had been previously unreported. The researchers also defined eight nonoverlapping clusters of T2D signals characterized by distinct profiles of cardiometabolic trait associations. These clusters are differentially enriched for cell-type-specific regions of open chromatin, including pancreatic islets, adipocytes, endothelial cells, and enteroendocrine cells.

After building cluster-specific partitioned polygenic scores in an additional 279,552 individuals of diverse ancestry, including 30,288 cases of T2D, the researchers tested their association with T2D-related vascular outcomes. Cluster-specific partitioned polygenic scores are associated with coronary artery disease, peripheral artery disease, and end-stage diabetic nephropathy across ancestry groups, all of which highlight the importance of obesity-related processes in the development of vascular outcomes.

These findings may help diabetes care throughout the world, the researchers concluded.

ADLM experts tackle the flood of test methods, sample types, and viruses to inform patient-centered care in laboratory medicine.

Authoritative guidance on respiratory virus testing

BY KAREN BLUM

Coming off a tough winter for respiratory viruses, with high rates of flu, SARS-CoV-2, and respiratory syncytial virus (RSV), it might seem particularly timely that the Association for Diagnostics & Laboratory Medicine (ADLM, formerly AACC) released its first guidance document on laboratory diagnosis of respiratory viruses (J Appl Lab Med 2024; doi: 10.1093/jalm/jfae010).

But the idea for the work dates back a couple of years, the authors said. Respiratory testing "was a particularly hot topic after the COVID-19 pandemic," said coauthor Heba Mostafa, MBBCh, PhD, director of the molecular virology laboratory at The Johns Hopkins Hospital in Baltimore. Additionally, she said, there is increasing diversity in testing modalities and types of samples used, along with some confusion about the clinical utility of testing for a broader range of molecular targets. "It was time to take a dive into the literature and what is known … and form a guideline."

Testing had been evolving even before the pandemic, said coauthor Esther Babady, PhD, D(ABMM), FIDSA, FAAM, chief of the clinical microbiology service at Memorial Sloan Kettering Cancer Center in New York City. "But as you can imagine, with COVID, that really was accelerated" to include at-home testing for the first time, she said.

As the methodology became more simple and some tests became CLIA-waived, point-of-care tests for viruses such as SARS-CoV-2 could be offered in expanded settings like physician offices and emergency rooms. "There are so many more people that not only have access to the tests but are in charge of selecting which tests to use for different indications," Babady said. "We thought this was a great opportunity … to share our clinical microbiology expertise."

The guidance, compiled by clinical microbiologists and infectious disease clinicians, covers everything from which tests should be used to detect respiratory viruses, to the sample types and methods used for detection of these viruses, to how test results should be interpreted and who should be tested in the first place. Extensive tables list common viral pathogens and their associated clinical syndromes, testing methods for routine detection of respiratory viruses, and examples of molecular respiratory viral testing by level of complexity.

A suggested testing algorithm for respiratory viruses can help clinicians determine when and how to test patients for these viruses.

The document should be helpful as a guide "on what people need to order, for which population, and in which clinical settings," Mostafa said. "However, I'm sure that each practice and each provider will modify their testing based on the population of patients they have, along with other factors like insurance and billing."

WHAT'S IN THE GUIDANCE

The document starts with an overview of the most common viruses causing respiratory illness, their signs and symptoms, and complications that can occur. Although healthy, immunocompetent individuals usually recover from acute respiratory infections without the need for laboratory diagnosis or treatment, laboratory testing generally is necessary for immunosuppressed patients and those with underlying conditions in order to implement appropriate, targeted therapy when available, or isolate the patient if necessary, the authors said. The accuracy of clinical diagnosis alone may be limited.

In the testing section, the authors note that nasopharyngeal swabs are the preferred specimen type for upper respiratory infections. When this is not practical, alternatives include nasal or throat swabs, saliva, or bronchoalveolar lavage fluids (for lower respiratory tract infections). Nucleic acid amplification tests (NAATs) are the gold standard for viruses, but when that is not readily available, antigen tests provide a less sensitive alternative. Direct fluorescent antibody assays, serology, and viral

A suggested testing algorithm for respiratory viruses can help clinicians determine when and how to test.

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culture are not recommended for routine diagnosis.

Specimen collections should match the particular test used for diagnosis, Mostafa emphasized: "We consider nasopharyngeal swabs as the gold standard, but we also started to see nasal specimens collected, and saliva. It's really important for providers to understand the test requirements and assemble the proper specimen, because this is the key for accurate results."

In the interpretation section, authors note that viral load test results should be interpreted in light of clinical symptoms. For example, a positive molecular or antigen test result in someone without symptoms may reflect asymptomatic carriage, presymptomatic infection, or shedding following a resolved infection. Conversely, negative test results in symptomatic patients may be

> "We consider nasopharyngeal swabs as the gold standard, but we also started to see nasal specimens collected, and saliva." — Heba Mostafa

false-negative, and repeat testing is recommended.

The high sensitivity of NAATs "provides a great opportunity to detect infection when it's there," Babady said. "However, we also know that you can have a positive molecular NAAT once you've resolved the infection, because it's so sensitive it's picking up minute amounts of RNA or DNA left by a virus that's already gone and not replicating. How you interpret that is important. You have to take into consideration when the patient presented and how long they've had the infection."

Laboratory medicine professionals can provide interpretation using data including seasonality, positivity rates, and a patient's clinical presentation, Mostafa added.

Testing should be performed only if there is a high pretest probability of respiratory viral infection based on clinical presentation and local prevalence, the authors said, and in cases where results will change clinical management. Testing should be limited to children who are hospitalized or who have underlying conditions, as well as aging, ill, and immunocompromised patients. Immunocompetent adults should be tested only if results will impact management, primarily for influenza and SARS-CoV-2.

DIAGNOSTIC STEWARDSHIP IS ESSENTIAL

One section is dedicated to diagnostic stewardship. Much like antimicrobial stewardship efforts that advocate for judicious prescribing of antibiotics, diagnostic stewardship aims to select the right test at the right time for the right patient, thereby generating accurate, relevant results to guide clinical management. In this area, the guidance recommends educational material be made available for clinicians to guide respiratory test selection, that electronic health record algorithms help drive appropriate test selection, and that clinicians generally opt for small, multiplexed panels or targeted NAATs unless patients are immunocompromised.

"Better utilization of tests in the correct scenarios is very important, particularly when it comes to a molecular test that can detect multiple targets," Mostafa says. Individual labs should work with hospital infection control departments to define stewardship and the best clinical utility of tests. "If you're ordering a test and you're not planning to use the result for clinical management, you shouldn't consider ordering the test." Practices may differ based on location and type, "but the overall rule is the test has to generate a result that will be acted on," she said.

With a plethora of testing options, it can be tempting "to just test everybody all the time for everything," Babady added, but patient-centric care is important, as is recognizing there is a limit to payor reimbursement for testing. "The importance here is really to think about what the ultimate goal of the test is going to be."

LESSONS FROM COVID-19

Since the pandemic, clinicians have learned that testing can be possible in many more types of samples — including at home — and how whole genome sequencing can provide information on different types of viruses present in a clinical sample, Babady said.

"I don't want to say that there was a good side of the pandemic, because there's no good side to the pandemic, but the explosion of testing options has been incredible," she said. "We've learned a lot." Tenets that used to be dogma, such as not using saliva for respiratory virus testing, were dismissed in some SARS-CoV-2 tests, and now laboratorians are considering how it could be used for other types of testing, she said.

Scientific developments, such as CRISPR-based diagnostics and next-generation sequencing, also continue, Mostafa said. "It's interesting to see the CRISPR modalities making it into diagnostic methods and reaching point-of-care testing and testing modalities," she said.

What might the future portend? Things will continue to evolve, Babady said. When the authors began writing the document, for example, the RSV vaccine Abrysvo had not yet been FDA-approved. "As things like that become a reality — not just vaccines but treatments for the viruses that we can detect right now — all of that information is really going to guide how, who, when, and why we should be testing," Babady said. "It will be interesting to see how all of that evolves and connects with respiratory testing."

Many testing platforms used for SARS-CoV-2 might eventually expand to other viruses such as influenza and RSV, the authors said. As such, "laboratorians should remain alert and involved to provide guidance on managing testing and the information obtained from a wider range of testing settings." 🩸

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BY JEN A. MILLER

Get ready for proficiency testing changes

This essential part of CLIA gets its first major update since 1992, with new analytes and new grading measures.

A new rule from the Centers for Medicare & Medicaid Services (CMS) that overhauls proficiency testing (PT) for clinical laboratories goes into effect on July 11, 2024. According to CMS, these changes bring CLIA regulations in line with current laboratory medicine practices. The updates are necessary because much has changed in terms of accuracy, precision, and commonly used tests since CLIA became law in 1988, with PT rules implemented in 1992.

The rules add more PT challenges and require more samples per challenges, change limits, and require PT for CLIA-licensed labs that may not be accredited by another approved agency. The rule takes effect in July 2024, and it will be implemented for labs and PT providers in January 2025 with the next PT survey cycle.

James Nichols, PhD, DABCC, FADLM, professor of pathology, microbiology, and immunology and medical director of clinical chemistry and POCT at the Vanderbilt University Medical Center, believes that meeting these regulations won't be an uphill climb for most laboratories, as conversations about these changes have been ongoing for some time.

"Many of us have been concerned about troponins being a nonregulated analyte for some time." – James Nichols

Laboratories have had "plenty of warning about this, and laboratories that are doing this are subscribing to proficiency surveys anyway," he said. "They're not going to be blind sided."

Here's what laboratories need to know to make sure they're not.

UPDATE ON PT WITH NEW ANALYTES

For nonmicrobiology specialties and subspecialties such as chemistry and toxicology, CMS is adding 29 analytes, and removing five identified as unnecessary, obsolete, or excessively burdensome for laboratories.

These changes are "getting rid of old analytes that are rarely used anymore, and bringing on new analytes that are important in terms of modern medicine," Nichols said. For example, tests for cardiac troponin and HbA1c were not routinely performed in 1992.

None of these changes are a surprise, experts agreed. "Many of us have been concerned about troponins being a nonregulated analyte for some time, and only getting two challenges a year, when it's one of the most important tests out there," Nichols said. He also noted that HbA1c tests are routine and necessary for many patients' care.

CMS went through a "very consensus driven process," said Brad S. Karon, MD, PhD, FCAP, chair of the College of American Pathologists Council on Scientific Affairs and professor of laboratory medicine and pathology at the Mayo Clinic in Rochester, Minnesota. "I don't think there were any great surprises in the addition of regulated analytes," he said.

For microbiology specialties and subspecialities including bacteriology and virology, CMS is finalizing requirements to specify broad categories of tests for which proficiency testing is required. This will also allow flexibility for new technologies currently in use, and those that may be developed and used in the future, according to CMS.

CHANGES IN PT CHALLENGES AND GRADING

The rule also requires three challenges per year, with five samples in each challenge, where before only two challenges may have been required. "In those laboratories that were not accredited and operated under a CLIA certificate, they often would only enroll in PT for regulated analytes," said Karon. "They now have these additional 29 analytes they'll have to enroll in."
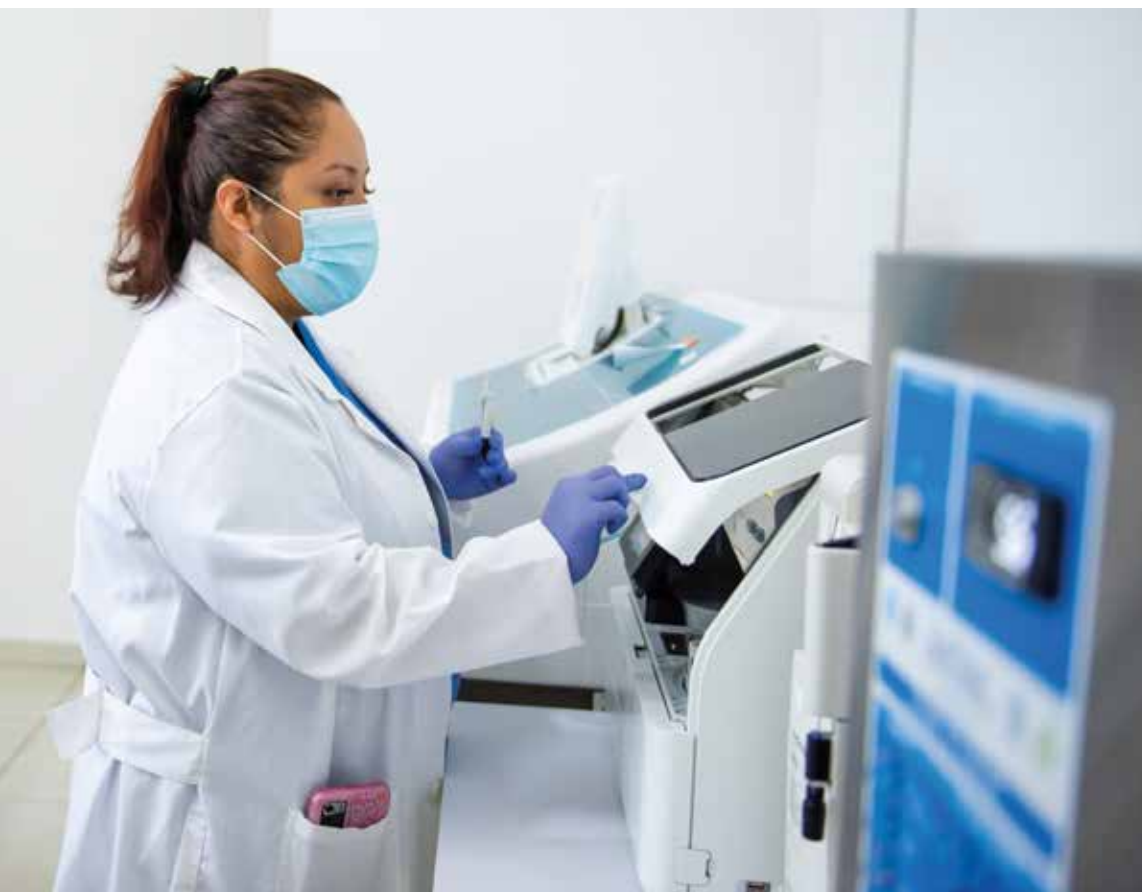
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Most limits are also changed from standard deviations to percentage-based limits. Fixed concentration units are also added to fixed percentage units to address lower concentrations, with scores based on whichever is more tolerant. For example, for bilirubin, acceptable performance will be ±20% or ±0.4 mg/dL. For thyroid stimulating hormone, it will be ±20% or ±0.2 mIU/L, and for lithium, ±15% or ±0.3 mmol/L.

For microbiology PT challenges, PT programs must attempt to grade using both participant and referee laboratories before determining that the sample is ungradable. Mixed culture requirements have also been lowered from 50% to 25% for bacteriology, mycobacteriology, and mycology. Types of services listed for each micrology subspeciality were removed, and a more general list of organism groups categories were added.

Grading will be standardized among PT providers. All told, these changes are "going to improve patient safety by demanding that labs show greater accuracy for those tests," Karon said.

Under CLIA, moderate and high-complexity laboratories that also performed waived tests are not required to enroll in PT for waived tests but are held to requirements for testing of PT samples if voluntarily enrolled for waived tests. Waived tests are also not excluded from PT referral prohibitions.

The rules have potential to improve the quality of laboratory testing overall, as CLIA-licensed laboratories will now undergo more strict challenges, Karon said. "For accredited labs, they may have been doing most or all of this additional PT. Now they will be doing more challenges and using grading criteria fixed by regulations," he said. Nonaccredited labs will have to enroll, too.

"This is going to improve patient care because some laboratories are going to get additional specimens for some tests," Nichols said. For laboratories that have already been doing proficiency surveys, this rule may help them in terms of improving peer group performance for some tests.

In the rule, however, CMS emphasized that labs should not use acceptance limits as the criteria to establish performance goals. "Proficiency testing is intended to identify laboratories that are not performing with acceptable analytic accuracy; it is not intended, nor suited, to provide goals for analytical accuracy or clinical performance."

HOW LABORATORIES CAN PREPARE

Laboratories accredited from a deemed accrediting agency have already most likely heard from that agency, said Karon, and have been told "here's what you have to enroll in based on what you're telling us." Laboratories should still check "just to make sure they do have a survey for each of the regulated analytes," he added.

Nonaccredited labs will have to do this work themselves by looking at the list of regulated analytes and enroll in a PT product.

The main challenge, said Karon, will not necessarily be to laboratories, but to PT providers. The new rule "discourages them from offering low challenges unless the criteria were set with both absolute and fixed percent targets," he said. "Most were, but a few weren't."

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> **"You don't have to repeat all the validation necessarily, but you should review them to see if there are some discrepancies." – Osa-Andrews**

In a webinar on preparing laboratories for CLIA 2024 on behalf of ADLM, Bremansu Osa-Andrews, PhD, DABCC, NRCC, medical director of clinical chemistry and clinical assistant professor at the University of Florida College of Medicine, recommended that, to prepare for the first inspection under the final rule, laboratories should be ready for more stringent inspection, review previous PT data for impacted analytes, and re-asses with current acceptance limit. They should also review all validation records for these analytes.

"You don't have to repeat all the validation necessarily, but you should review them to see if there are some discrepancies," Osa-Andrews said.

Laboratories should confirm that they are assigned to the correct peer group, mark the shipping dates for proficiency test samples on the calendar, review the checklist, avoid specimen handling and clinical errors, and submit results by the due date. Laboratories should also review the standard deviation index (SDI) data on the evaluation supplied by the proficiency test provider, Osa-Andrews said.

These inspections are "going to be a part of inspections just like you already have been having," Osa-Andrews said. "The difference is that the first inspection in the year 2025 will take into consideration the CLIA final rule and all the requirements of the rule including the new analytes and new acceptable limits, the updates that have made for microbiology and non-microbiology disciplines."

If laboratories have not heard from their accrediting agencies or PT providers, they should reach out as soon as possible, he said, in order to be ready for the rule change in July, and then implementation of the rule change in January.

The final rule can be downloaded from the Federal Register, document citation 87 FR 41194, at www.federalregister.gov. 🩸

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New analytes for proficiency testing

CLIA Regulation Area	Analyte
General Immunology	Anti-HBs Anti-HCV C-reactive protein (high sensitivity)
Routine Chemistry	B-natriuretic peptide (BNP) Pro-BNP Cancer antigen (CA) 125 Carbon dioxide Carcinoembryonic antigen (CEA) Cholesterol, LDL, direct measurement Ferritin Gamma glutamyl transferase (GGT) Hemoglobin A1C Phosphorus Prostate specific antigen, total (PSA) Total iron binding capacity (TIBC), direct measurement Troponin I Troponin T
Endocrinology	Estradiol Folate, serum Follicle stimulating hormone (FSH) Luteinizing hormone (LH) Progesterone Parathyroid hormone (PTH) Testosterone Vitamin B12
Toxicology	Acetaminophen, serum Salicylate Vancomycin

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Best practices in phlebotomy:

Sticking to the basics

BY CHRISTOPHER W. FARNSWORTH, PHD, DABCC, FADLM

As a key preanalytical factor, phlebotomy done right ultimately means better patient care.

Most laboratory errors occur in the preanalytical phase. Studies have demonstrated that 60–70% of errors occur prior to specimens being received in the laboratory (*1*). Most of these errors are often be attributed to the practice of phlebotomy. Phlebotomy, defined simply as the act of withdrawing blood from a patient using a needle, is a critical first step in the process of laboratory testing.

Despite its importance for quality laboratory testing, the significance of correct phlebotomy is often overlooked. A survey by the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) found that phlebotomy training was required curriculum for only 21% of nursing programs and 32% of technologist programs (*1*). In the U.S., requirements for performing phlebotomy vary widely. For example, some states, such as California, require licensing to perform phlebotomy. In contrast, states such as Missouri require only on-the-job training and no formal certification.

In many U.S. hospitals, nursing staff is permitted to draw blood with minimal training and no formal certification in phlebotomy. Although there is little recent data, a CAP Q Probes survey from 1991 found that only 17% of the 393 intuitions surveyed required a phlebotomy training course (*2*).

Although considering the impact of improper phlebotomy, many laboratorians jump to hemolysis as the primary negative outcome. Indeed, hemolysis is an important clinical problem and one of the most frequent preanalytical errors. However, a narrow focus on hemolysis overlooks the potential for errors at any step in the process, and the potential affect on the patient.

The entire process of phlebotomy and best practice are discussed in detail in the Clinical & Laboratory Standards Institute (CLSI) document GP47 (*3*). Each step has important processes and safeguards built in place that protect the patient and the phlebotomist while procuring an acceptable specimen for clinical testing.
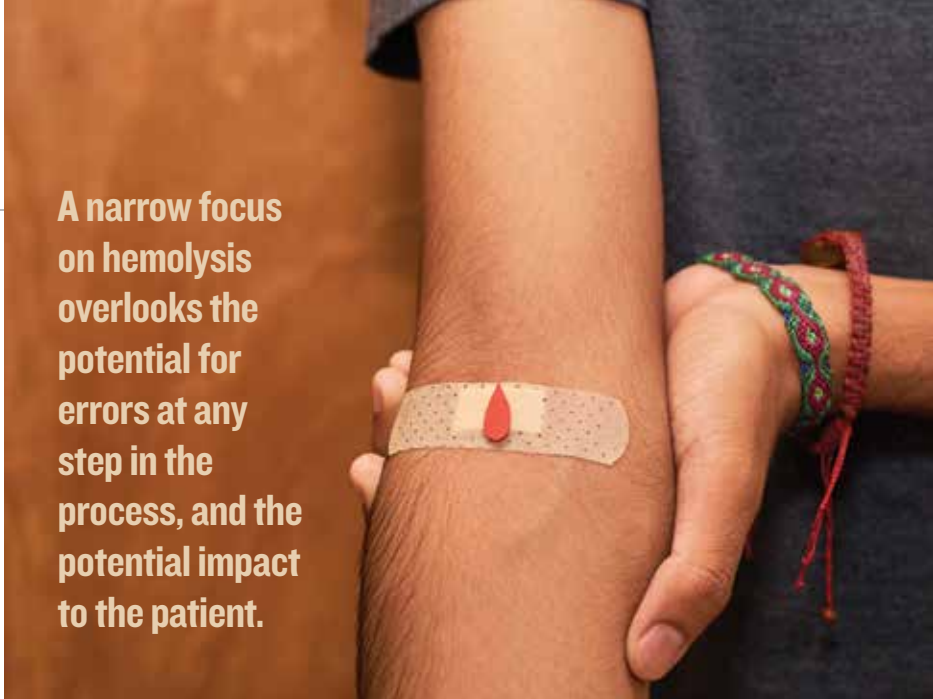
PATIENT AND SPECIMEN IDENTIFICATION

Correct patient identification is crucial. This is typically completed by asking the patient their full name and date of birth and then confirming these details with their arm band (when hospitalized) or photo ID (if not hospitalized). These sources are then compared to the test request and/or sample labels. Errors in this phase of phlebotomy lead to wrong blood in tube errors; patient specimens are drawn into tubes meant for other patients and the results from testing attributed to the wrong patient.

A narrow focus on hemolysis overlooks the potential for errors at any step in the process, and the potential impact to the patient.

The frequency of wrong blood in tube errors has decreased considerably with the implementation of positive patient identification (PPID), which is used to label the specimen containers at the bedside. However, this technology is infrequently used in outpatient settings and has not been universally adopted. Labs have also attempted to mitigate wrong-blood-in-tube errors by implementing delta checks. A delta check uses the lab information system to compare results from a previous sample to the current sample for an individual patient. A set of rules are applied with the goal of finding changes in an analyte that is unlikely to occur physiologically. While once state of the art, delta checks are often thought of as unnecessary in the PPID era.

PHLEBOTOMY TECHNIQUE

Once the correct patient has been identified, the phlebotomist must prioritize site selection. Most often, median cubital veins in the forearm are used with the lateral, outer veins considered peripherally to avoid nerves that are closer to these veins. The appropriate needle must be selected, generally a 21G or 23G needle, with smaller needles (higher gauge) increasing the likelihood of hemolysis. The site must be appropriately cleaned with 70% alcohol, according to the World Health Organization (WHO), and allowed to dry to reduce likelihood of infection or contamination of blood culture bottles with skin flora. A tourniquet must then be applied only for one minute to avoid pooling of analytes and patient discomfort/harm, and the patient told not to pump their fist, which can increase the release of potassium locally, causing an artificially high result.

For hospitalized patients, it is common for specimens to be collected from indwelling venous or arterial catheters. While convenient for the hospital staff and often preferred by patients (as opposed to fresh venipuncture), this practice is associated with increased blood culture contamination rates and hemolysis.

Hospitals and laboratories should consider the potential benefits to patients with the potential hazards when drawing from indwelling lines. If a previous indwelling line for vascular access is used, all intravenous (IV) fluids must be stopped, the line flushed with 0.9% sodium chloride, and a proportion (typically 1 mL) of blood should be discarded (usually in a red top serum tube) prior to collecting blood into specimen containers designated for laboratory testing.

IV fluid contamination is a relatively common problem when blood is collected from an indwelling line that is not appropriately flushed. Delta checks are commonly used by laboratories to assess for IV fluid contamination but are nonspecific and lack sensitivity for this purpose. Recently, there has been a rise in publications assessing novel tools for distinguishing IV fluid contamination.

A recent manuscript from Yale demonstrated multianalyte delta checks were able to increase the sensitivity for IV fluid contamination (4). Briefly, the authors used wet-bench experiments to define rules in which 10% contamination with IV fluid would be detected. For example, a rule implemented in which chloride increased by 7.7 mmol/L, potassium decreased by 0.7 mmol/L, and calcium decreased by 1.7 mg/dL was able to accurately detect patients with presumed normal saline contamination.

Another recent manuscript in Clinical Chemistry used unsupervised machine learning and a dimension reduction technique to increase the sensitivity for detection of IV fluid contamination (5). Using this approach, the authors demonstrated an estimated positive predictive value of 78% relative to manual chart review by trained laboratory directors and the model was able to accurately detect almost three times more contaminated specimens than technologists during their routine workflows. Optimistically, these studies will soon lead to novel tools for laboratories to detect contamination in real-time.

TUBE TYPES

A common error labs encounter is specimens collected into tubes with the wrong anticoagulant, or tubes that

have been drawn in the wrong order. It is crucial that specimens are not contaminated with anticoagulants that can impact testing. The typical order of draw is: 1. blood culture bottles, 2. serum tubes (red top), 3. sodium citrate tubes (blue top, coagulation testing is very sensitive to other anticoagulants), 4. lithium heparin tubes (green top, often switched with K2 EDTA, resulting in falsely increased potassium and decreased calcium), 5. K2 EDTA tubes (purple or pink top), and 6. others, including gray top tubes for glucose and lactate testing.

When tubes are drawn out of order, a small amount of anticoagulant can be transferred to the subsequent tube, potentially affecting testing. For example, it is not uncommon for hospitalized patients to have prolonged protime (PT) and partial thromboplastin time (PTT) due to anticoagulant therapy. If a blue top citrated tube is drawn immediately after a green top tube, both PT and PTT likely will be artificially prolonged by lithium heparin contamination. Deciphering these contaminants from a patient on anticoagulant therapy is incredibly difficult for a laboratory technologist and potentially for a physician.

SPECIMEN TRANSPORT
A final consideration for specimen collection is transportation of the specimen to the laboratory. Within hospitals, pneumatic tube systems are commonly used to transport specimens. While effective and rapid, they also exert considerable forces on the specimen resulting in hemolysis and potentially other pre-analytical errors.

Laboratories should consider validating the pneumatic tube system and the potential impact on patient specimens, as manufacturers do not commonly do this. While external laboratory transport is likely less susceptible to traumatic hemolysis, temperature and time from collection may impact testing and is not commonly considered. Because each hospital may have different processes for transport, laboratories should consider all aspects of transport postcollection and attempt to mitigate any potential impact to testing.

Despite its perceived simplicity, phlebotomy is a complicated component of the laboratory testing process that requires considerable training and competency. There are many things that can go wrong during blood collection that can impact test results and ultimately patient care. Where possible, laboratories should consider ways to monitor phlebotomists' technique (6). There are limited tools at our disposal to capture error once specimens have been collected. However, where these have been implemented, such as in the case of PPID, error can be reduced greatly. Future efforts are needed to generate new tools for detecting error in the preanalytical phase of testing.

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AN INTERVIEW WITH SHAWN FAHL, PHD

The role of MSI and *KRAS* in advancing cancer research

By Jen A. Miller

With the advancement of diagnostic technology and the pursuit of precision therapies, the use of microsatellite instability (MSI) and *KRAS* mutational profiling continues to grow in clinical practice. These tests identify genetic alterations in tumors and play a crucial role in diagnosis, prognosis, and treatment guidance for several cancers.

To broaden our understanding of the role that MSI and *KRAS* gene mutations play in cancer, and potentiate new applications for these biomarkers, robust testing of diverse sample types from various cancers is needed. Discovery Life Sciences (Discovery), a leading biospecimens expert and specialty services provider, is playing a pivotal role in this endeavor. Discovery owns the world's largest commercial biobank and procurement network and provides a diverse portfolio of multiomics services. Discovery can test thousands of biospecimens simultaneously and is harnessing this sheer volume with unmatched technological prowess to help researchers better understand the underlying drivers of cancer.

CLN spoke with Dr. Shawn Fahl, vice president of Lab Operations, Cell Services & R&D, Biospecimens at Discovery Life Sciences about the company's work.

Can you discuss why you implemented fragment analysis-based MSI testing and Sanger sequencing-based testing for genetic biomarkers, such as *KRAS*, in formalin-fixed paraffin-embedded tissues (FFPE)?
We have a large repository, and we wanted a highly targeted analysis on clinically relevant biomarkers. Many technologies in our industry tend to provide extensive data. But in this case, we wanted something very specific and user-friendly. We also wanted to put together a well-defined, end-to-end workflow that simplifies the need for complex pipeline builds and provides seamless processing and analysis from specimen intake to data delivery.

Sanger sequencing isn't exactly out of style, but it's not the only method used anymore. Why did you decide to go this route?
There has been a significant shift towards next-gen sequencing, offering an excellent way for obtaining comprehensive genomics data. Discovery's own Genomics Services lab right down the hall performs NGS studies for thousands of samples a day. That said, we've been noticing an increase of Sanger sequencing projects, largely because of its more targeted nature. The analysis is easier, and the footprint for running Sanger sequencing from start to finish is minimal.

A case in point: We have labs here in the U.S., where I'm located, as well as in Bulgaria, where a lot of Discovery's clinical sites are located. Implementing Sanger sequencing in our Bulgarian labs allow us to be more efficient operationally.

What is the rationale behind retrospective annotation of a biorepository?
This is where much of our focus has been because we started as a biobank with a reliable biospecimen procurement network. We have millions and millions of specimens.

But having an extensive repository does not necessarily mean the specimens have annotations of the most current clinically relevant biomarkers. Leveraging our integrated multiomics service capabilities, we are able to go back and test our inventory retrospectively, accelerating research and clinical projects.

What advantages does a characterized biorepository have over uncharacterized samples?
An enduring lesson from my time in graduate school resonates: We have solved cancer in mice hundreds of times, but we have not done it in humans. The intricate nature of human biology, marked by a higher level of complexity, makes cancer research significantly more challenging.

At Discovery, we aim to minimize data noise by meticulously controlling as many

confounding factors as possible. That's why precharacterizing our biorepository gives us many advantages, and this proactive approach allows us to gain clearer insights and enhance the reliability of our findings.

In the biorepository, do you have a single sample type per patient, or do you have matched specimens across multiple sample types?
One of our priorities involves the strategic acquisition of new matched specimens from the same consented patients. We actively look for matched FFPE and fresh tissue samples, with the latter providing fresh viable cells, giving us the ability to conduct additional studies that may not be feasible with FFPE tissue samples. Moreover, we have started to collect tissue and blood from the same patients simultaneously.

The idea is that patients can undergo a blood draw, enabling us to monitor disease progression and evaluate the success of treatments based on circulating tumor cell-free DNA (ctDNA) at the same time.

In addition to FFPE, are there other biospecimen types you have tested for MSI or Sanger sequencing?
One we are most excited about is that we have started to run MSI and Sanger sequencing testing on tumor DNA circulating in blood. By analyzing ctDNA, we have successfully detected MSI high patients and *KRAS* mutations. This marks a transition from the traditional reliance on tissue testing to the promising potential of blood-based diagnostics or liquid biopsies.

Can you discuss any multiomics evaluation you have performed using MSI/*KRAS*-characterized biospecimens?
Our unique advantage lies in our comprehensive approach to multiomics. Extensive work has been dedicated to studying MSI and *KRAS* across different platforms. We've evaluated common immuno-oncology markers through flow cytometry.

Initially exploring PD-L1, PD-L2, and PD-1 proteins, we observed a lot of correlations with these markers. Then, we shifted our focus to more novel markers such as the inhibitory receptor TIGIT, along with CD226, CD112, and PVR proteins. These less-explored markers provide fresh perspectives compared to the extensively studied PD-L1/2. We have also moved into single cell transcriptomics, where — rather than limiting our scope to 20 genes or markers — we're examining thousands. This approach allows us to discover new biomarkers and tap into the vast landscape of human genomes.

Have you utilized MSI/*KRAS*-characterized biospecimens to develop new tumor models?
This is an area we are looking forward to. Leveraging our abundant collection of viable frozen tumor tissue, we have the ability to cultivate and test new compounds. Adapting human tumor specimens to grow in a cell culture dish is a challenging process. However, we've found success using long cell tumoroid models within a gel-like extracellular matrix.

The prospect of creating new drugs for specific *KRAS* mutations is generating considerable interest. We're exploring the possibility of generating tumor models from dissociated colorectal tumor cells to establish a comprehensive bank of targeted tumors. These models can then be swiftly tested in vitro against various drug compounds, given that we already have the parent materials. This approach allows us to quickly and precisely address targeted questions based on the characterized samples in our possession.

What do you hope for in the future with this technology?
I would love to see this technology utilized more broadly, especially with Sanger sequencing. Despite its decline in popularity with the rise of next-gen sequencing, Sanger sequencing has the advantage of speed, providing faster turnaround times when focusing on a defined set of targets with a more straightforward and consistent approach.

I think Sanger Sequencing holds the potential to play a more significant role in clinical settings. The ability to swiftly examine genes, particularly with the increasing prevalence of liquid biopsies, could make this technology exceptionally valuable in clinical applications.

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FOCUS ON

MOLECULAR DIAGNOSTICS

Elevating oncology by understanding HRD cytogenetics

By Jen A. Miller

According to the National Cancer Institute, ovarian cancer has only a 50.8% five-year survival rate, and one of the leading causes of cancer death in women. One reason for these high rates is that the cancer's symptoms, which can include bloating and lower back pain, often can be chalked up to something else, so the cancer is not discovered until it's in later stages.

Researchers have identified homologous recombination deficiency (HRD) as a biomarker that can guide treatment in high grade cancer. Yann Christinat, PhD, a clinical bioinformatician at the Geneva University Hospitals, Switzerland spoke to *CLN* about the significance of cytogenetic analysis for HRD scoring and how he uses the OncoScan platform for research.

What is HRD and why is it relevant for human cancers?
HRD represents a deficiency in one of the pathways that repair DNA in the cell. This defect affects the cells' capability to repair double strand breaks in DNA. That means HRD-positive ovarian cancer cells also have a harder time repairing themselves. We can target them with PARP inhibitors, drugs that, through synthetic lethality, target only HRD-positive tumor cells. These inhibitors block the cancer cells' repair mechanism further, leading to more of them dying.

The cancer that benefits the most from detection of this biomarker is high grade ovarian cancer. Many ovarian cancers are discovered very late, so they often are lethal. Determining the HRD scoring can also be helpful in breast cancer and prostate cancer.

How do you research HRD?
In general, we use only one technology, the OncoScan platform, a whole-genome microarray research solution. On top of that, we developed our own score, which we also validated on retrospective data from a large clinical trial.

OncoScan does not call BRCA mutations, does this hinder your analysis?
We don't really look at the *BRCA* genes for our HRD analysis. That's because when you have *BRCA* mutations, you also will have HRD. When there is not a *BRCA* mutation, a patient still could have HRD due to something else happening in the cells.

We can also find *BRCA* mutations when we use our NGS panel. The *BRCA* mutation is really the confirmation.

What are the main advantages of microarray-based technology to understand the HRD cytogenetic signature?
What makes this technology really cool is that the lab doesn't need to amplify or treat FFPE DNA before running the assay. This technology

works because it has a probe that links to DNA. You fill in the gap, and then you amplify the probe. If there is low-quality DNA, and it's amplified, you get low-quality results. With OncoScan, even with low quality FFPE DNA, if you can bind to the probe's small footprint, then it's clean DNA with a clean result.

Quite often when next-generation sequencing was not working for mutation detection, we could get a result with OncoScan, but almost never the other way around. Now we have better representative results with low quality DNA, and it's also more reliable and better for low tumor content.

You used OncoScan within the scope of a clinical trial. What did you find?

We participated in a European HRD tests evaluation trial where we verified the Geneva HRD method. On a funny note, the validation project was run by sending samples to several laboratories in Europe, and each test got nicknamed after its city of origin.

We found, and published last year, that the Geneva method is similar to reference NGS methods in terms of positivity, but the Geneva method has a lower error rate, which allows a 10% increase in samples that receive a conclusive laboratory result.

We have a new paper we're currently writing with respect to the results we saw in our clinical study on overall survival. In this paper, we report results where the Geneva method has a greater impact on overall survival in treatment of high-grade ovarian cancer patients.

What is your hope for this technology in the future?

We are going to continue developing this assay and making our method even better. We have collaborations with researchers in Switzerland to develop version 2.0 that will integrate *BRCA* mutations and drug resistance mechanisms.

For more information on Oncoscan CNV Assays for Research, please visit www.thermofisher.com/oncoscan

Note to readers:
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BY VAHID AZIMI, MD

Leveraging laboratory and geospatial data for population health

Laboratory medicine has the data, skills, and mindset to improve health outcomes, and geospatial analysis is emerging as a critical tool.

There is growing recognition that health is determined largely by factors outside of the healthcare system. These social determinants of health (SDoH) include factors such as a person's neighborhood and built environment, socioeconomic status, educational attainment, and access to healthcare (*1*).

Given the impact of SDoH, as well as current trends in healthcare payment models toward a value-based system, healthcare systems and payors are working to identify and help tackle the SDoH-related factors that lead to higher costs and poor patient outcomes (*2*).

One resource in this effort is geospatial analysis, a powerful tool at the intersection of geography and data science. Healthcare systems can use geospatial analysis to collect, interpret, and visualize geographic data to identify geospatial trends and relationships. Geospatial analysis can help enhance resource allocation, disease surveillance, and public health planning (*3*). Geospatial data also can be used to link patient health metrics to population-level socioeconomic and demographic data in order to analyze the effect of SDoH on health outcomes (*4*).

The clinical laboratory generates a trove of high-quality, often quantifiable, patient health data across a large spectrum of medical conditions. This makes laboratory data an invaluable resource for assessing population health, SDoH, and health equity. Moreover, given their subject-matter expertise, quality improvement mindset, data analytics capabilities, and position to affect healthcare delivery, clinical laboratorians are especially well-positioned to leverage geospatial data to identify opportunities for closing care gaps (*5*).

This article will introduce and describe considerations in the experimental design of a geospatial analysis with a focus on laboratory data.

Key components of experimental design

Formulate a research question

In any scientific endeavor, it is important to define research goals and hypotheses to guide the experiment and derive meaningful conclusions. Within laboratory medicine, potential use cases for geospatial analysis may include disease surveillance, identifying disease hotspots or laboratory testing deserts, or analyzing the impact of SDoH on laboratory testing and results (*6, 7*).

Determine scale and geographic units

A geospatial analysis can be local, regional, or global in scope. This decision will be driven by the specific research question and will also inform the geographic units used in the analysis.

For example, if the question involves an entire country, the analysis might be performed at the regional, provincial, or state level. Analysis of a state may involve smaller geographic units, such as census tracts or block groups.

Note that although zip codes may be the first geographic unit that comes to mind, aggregating data at the zip code level is discouraged, as they do not encompass socioeconomically and demographically similar populations (*4*). As a result, they may obfuscate trends between health and SDoH-related factors.

Conversely, census tracts or block groups are designed to be homogenous in their demographic and socioeconomic makeup and are the preferred geographic units for small-scale analyses.

Identify data sources and analysis tools

Many laboratorians are familiar with accessing patient laboratory

FOCUS ON DATA SCIENCE

or health-related data from their institution's laboratory information system (LIS) or electronic medical record (EMR). They may be less familiar with connecting a patient's lab results to a geographic location. The key to making this connection is to retrieve data on patients' residential addresses or the addresses of testing locations (depending on the research question), information that should be available in a modern LIS or EMR.. Of course, a person's address can change, so it is important to use the address at the time of testing rather than a patient's most recent address.

Once address data is retrieved, the next step is to map it to its latitudinal and longitudinal coordinates via a process called "geocoding." While many different geocoding tools are available, many are not Health Insurance Portability and Accountability Act (HIPAA) compliant, as they may require sending patient addresses over the Internet (8). Thus, one must use a geocoding tool that performs geocoding locally.

One option for local geocoding is ArcGIS Pro, a graphical-user-interface (GUI)-based software that is robust and widely used within the geospatial analysis community (9). A disadvantage to this software is that it requires a fee-based software license. For users who want to get their feet wet with geospatial analysis without paying a fee, a validated geocoding software tool called DeGAUSS is freely available for download, although it does require basic knowledge of command line tools (10).

Once a dataset has been geocoded, it can be linked to population-level socioeconomic and demographic data for analyzing SDoH-related factors. A wide range of population-level data on SDoH-related factors are freely available from the U.S. Census Bureau (11). Validated composite metrics of social vulnerability at the census tract or block group level, such as the Social Vulnerability Index (SVI) (12) or Area Deprivation Index (13), are also publicly available.

Once a lab has retrieved, cleaned, and geocoded, the work of geospatial analysis can begin. This may include geospatial visualization and modeling, which also require specialized software. Software tools for visualization and modeling can be categorized as GUI- and non-GUI-based.

GUI-based tools include ArcGIS Pro, which, as mentioned above, is robust, widely used, has excellent documentation and support, and comes with a fee. Alternatively, QGIS is a free GUI-based program (14) that provides much of the core functionality of ArcGIS Pro. Users with programming experience may prefer the customizability enabled by non-GUI-based tools such as R and Python, which each offer robust and well-documented packages for conducting geospatial analyses (15, 16).

Choosing a geospatial analysis or modeling approach

There is a wide variety of geospatial analysis and modeling techniques, and they range in their level of complexity. Deciding which to use depends on the specific question or use case. One of the most used analytical approaches is choropleth mapping, which involves classifying and visualizing geographic units using color-coded palettes. This approach is useful for observing overall trends in the geospatial data, as well as for performing exploratory data analysis.

Spatial autocorrelation is another useful technique. It takes advantage of statistical methods to identify geographic "hot spots" and "cold spots" for a given metric of interest.
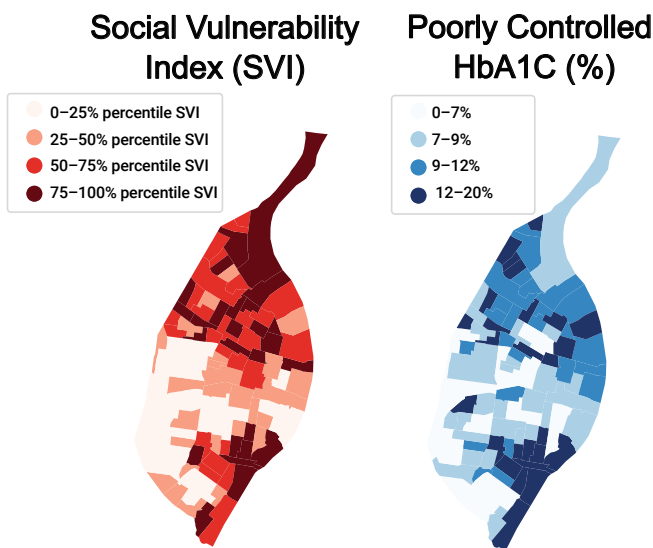
Finally, spatial data can also be used in conjunction with traditional supervised or unsupervised machine learning algorithms, such as clustering or regression. For example, unsupervised clustering can group socioeconomically and demographically similar regions, enabling analysis of SDoH and potentially informing resource allocation. A more detailed explanation of analytical methods is outside the scope of this article, but further reading is available (17).

A critical tool for labs to bridge healthcare gaps

Geospatial analysis is a powerful and well-established discipline that researchers have used with great success in a variety of fields, but whose use in healthcare, and especially laboratory medicine, is still maturing. With the growing recognition of the impact of SDoH, using geospatial analysis to identify care gaps and plan appropriate interventions can be a tremendous value-add to a healthcare organization. Given our unique access to high-quality health data and

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Figure 1. Poor glycemic control is associated with social vulnerability

Left: St. Louis census tracts colored by social vulnerability index (SVI) (12). Darker red colors indicate a higher level of social vulnerability. Right: HbA1c results were retrieved from the LIS along with the patient's address of residence. Addresses were geocoded and assigned to census tracts, and the percentage of patients whose most recent HbA1c was in the uncontrolled range (9%) was calculated per census tract.

Social Vulnerability Index (SVI)

- 0−25% percentile SVI
- 25−50% percentile SVI
- 50−75% percentile SVI
- 75−100% percentile SVI

Poorly Controlled HbA1C (%)

- 0−7%
- 7−9%
- 9−12%
- 12−20%

subject matter expertise, laboratory medicine professionals are uniquely suited to fill this role.

Using laboratory data in combination with geospatial and socioeconomic data allows us to observe a disparity, namely, the census tracts in the north and southeastern regions of the city, which tend to be more socioeconomically vulnerable, have higher rates of poorly controlled diabetes.

These data should be used to mobilize interventions to reduce these disparities, and prospective analyses can be used to monitor the effectiveness of those interventions.

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Regulatory Roundup

FDA clears first POC high-sensitivity cardiac troponin I assay

Polymedco has received Food and Drug Administration 510(k) clearance for its Pathfast high-sensitivity cardiac troponin I (hs-cTnI-II) assay, making this the first hs-cTn test cleared for point-of-care use in the U.S., according to the company. Developed for Polymedco's Pathfast Biomarker Analyzer, the test aims to facilitate the accurate, rapid diagnosis of myocardial infarction in near patient settings.

The timing of troponin test results is critical for patient diagnosis and care. Prior to this clearance, hs-cTn was available only in the hospital central laboratory, and results could take an hour or more to reach the physician, Polymedco said in a statement. In contrast, the Pathfast platform delivers results in 17 minutes at the point of care.

With this clearance, the test may be sold in the U.S. for use on the Pathfast analyzer with whole blood and plasma patient specimens. Results should be used in conjunction with other diagnostic information, such as electrocardiogram, clinical findings, and patient symptoms.

● EXPANDED FDA CLEARANCE WITH CLIA WAIVER FOR VAGINAL PANEL

The Food and Drug Administration has granted expanded clearance and a CLIA waiver to Cepheid's Xpert Xpress MVP, a multiplex vaginal panel. The test can be performed now in near-patient settings, enabling results within 60 minutes from a single specimen for bacterial vaginosis, vulvovaginal candidiasis, and trichomoniasis. The test runs on Cepheid's GeneXpert Xpress instruments and has been approved for testing for women 14 years of age and older.

Diagnosis of vaginitis is often made through a clinical examination. Sometimes clinicians prescribe treatment regimens that may not be appropriate for a patient's specific infection. Because the causative agents are from three distinct pathogen classes, but present with similar symptoms, a precise diagnosis afforded by multiplexed PCR testing can enable more targeted and timely treatments.

Cepheid officials hope that the addition of the CLIA waiver will allow physicians to quickly and accurately identify their patient's infection and prescribe the correct treatment regimen, with the goal of avoiding multiple office visits associated with therapeutic failure.

● DIGITAL CYTOLOGY SYSTEM GETS FDA CLEARANCE

Hologic's new Genius Digital Diagnostics System with the Genius Cervical AI algorithm has received Food and Drug Administration clearance. The company said the digital cytology system combines deep-learning-based artificial intelligence (AI) with advanced volumetric imaging technology to help identify precancerous lesions and cervical cancer cells.

FG Trade / iStock

The digital cytology system combines deep-learning-based AI with advanced volumetric imaging technology.

Currently, cytologists and pathologists typically review glass slides with patients' cervical cells under a microscope. In contrast, the Genius Digital Diagnostics System allows digital imaging of the slides and cells. An AI algorithm then identifies the cells that cytologists and pathologists should review.

According to Hologic, the new process and technology demonstrated an overall improvement in sensitivity without a corresponding decrease in specificity.

● IMMUNEXPRESS GETS FDA OK FOR EDTA BLOOD COMPATIBLE CARTRIDGES FOR SEPTICYTE RAPID

The Food and Drug Administration has cleared Immunexpress' EDTA blood compatible cartridges for use with SeptiCyte Rapid, a host response molecular test for sepsis. Clinical labs in the U.S. can now use the updated SeptiCyte Rapid cartridges with undiluted EDTA blood in place of proprietary PAXgene blood RNA tubes, an option that has been available in Europe since August 2022.

Immunexpress' EDTA cartridges were validated in a multisite study conducted at University Hospitals in Cleveland, Case Western Reserve University, and other healthcare systems. The research was partly funded by a contract from the Biomedical Advanced Research and Development Authority (BARDA), which is part of the Office of the Assistant Secretary for Preparedness and Response at the Department of Health and Human Services. BARDA awarded this grant to Immunexpress in 2020 as part of the Drive Solving Sepsis program.

● FDA CLEARANCE ADDS BACTERIAL SPECIES TO SEPSIS PATHOGEN PANEL

The Food and Drug Administration has granted clearance to T2 Biosystems for its expanded T2Bacteria Panel, which now detects the bacterial species *Acinetobacter baumannii* (*A. baumannii*). *A. baumannii* causes bloodstream infections, which can range from benign transient bacteremia to septic shock. These infections pose risk to seriously ill patients in intensive care units, on ventilators, with catheters or open surgical wounds, or who have prolonged hospital stays.

The T2Bacteria Panel also detects *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli*.

● FDA CLEARS PLATFORM THAT ENABLES PANEL CUSTOMIZATION PLUS RESPIRATORY PATHOGEN ASSAY

Diasorin has earned Food and Drug Administration 510(k) clearance for its new Liaison Plex platform as well as for the platform's first panel, the Liaison Plex Respiratory Flex Assay.

The Liaison Plex is designed to allow customization of syndromic panels. The fully automated sample-to-answer system has a streamlined workflow with room-temperature stable consumables. The operational hands-on time is only 2 minutes per sample and results are produced in less than 2 hours, according to Diasorin.

The Liaison Plex Respiratory Flex Assay tests for 19 pathogens commonly associated with respiratory infections, including 14 viral and 5 bacterial targets detected from nasopharyngeal swabs. Unlike most panel tests, which give users results for all targets at once, Flex testing allows users to generate and pay for a subset of specific results based on a patient's clinical picture.

● JAPANESE AGENCY APPROVES COMPANION DIAGNOSTIC FOR RET GENES

Chugai Pharmaceutical Company has received approval from Japan's Ministry of Health, Labour, and Welfare to offer Foundation Medicine's FoundationOne CDx Cancer Genomic Profile test. The test is approved to be used as a companion diagnostic with Eli Lilly Japan's rearranged during transfection (RET) receptor tyrosine kinase inhibitor, Retevmo capsules (selpercatinib), a therapeutic for RET fusion-positive solid tumors. With this approval, clinical labs in Japan can now use this test to detect RET fusion genes in order to determine whether a patient could benefit from selpercatinib. Chugai officials said that the test is useful for determining a treatment plan for patients because, in addition to detecting a rare RET fusion gene, it also detects other extremely rare genetic mutations that are expressed across cancer types.

Ginkgo Bioworks announces acquisitions

Ginkgo Bioworks, which has a platform for cell programming and biosecurity, recently announced the acquisition of Patch Biosciences, Proof Diagnostics, and key assets of Reverie Labs.

Patch Biosciences has built an artificial intelligence (AI) platform for sequence design that enables more effective, specific, and durable genetic medicines. The acquisition is intended to strengthen Ginkgo's gene therapy, cell therapy, and RNA therapeutics services. Ginkgo will incorporate Patch's machine learning models and downstream assays into its existing platform, making new capabilities in synthetic promoter and untranslated region engineering available to partners.

Proof Diagnostics is a life sciences tools, diagnostics, and computational discovery company that is developing genome engineering tools for both therapeutics and diagnostics applications. The company has built a portable system for the detection of infectious and other diseases. Proof was founded to develop a low-cost, rapid, easy-to-use, and sensitive diagnostic system for SARS-CoV-2, Flu A/B, respiratory syncytial virus, and other diseases. Proof's libraries of programmable OMEGA RNA, non-Cas enzymes, and associated intellectual property are the key focus of Ginkgo's acquisition.

Reverie Labs built and used AI and machine learning (ML) tools to accelerate drug discovery. Ginkgo has acquired Reverie's infrastructure and software for training large-scale AI foundation models. The acquisition is intended to strengthen Ginkgo's AI/ML-driven discovery services offerings and to accelerate Ginkgo's work to build next-generation biological foundation models.

● FREENOME RAISES FUNDS FOR EARLY CANCER DETECTION PLATFORM

The biotechnology company Freenome recently announced that it received $254 million from new and existing investors to advance the pipeline of single-cancer and tailored multicancer early detection tests built on its multiomics platform.

The platform uses computational biology, machine learning, and other technologies to develop screening tools to detect cancer in its earliest, most treatable stages. The platform, augmented with biological insights derived from the multiomics platform, is being evaluated for its ability to detect minimal residual disease noninvasively.

Freenome said that Roche Diagnostics led the financing, joined by several other investors.

Freenome is also conducting additional studies to evaluate a blood-based screening test among adults at average risk for colorectal cancer, to validate a lung screening test in certain current and former smokers, and to compare blood samples from patients with and without cancer.

● HC1 LAUNCHES WORKFORCE OPTIMIZATION

hc1 Insights recently announced the launch of hc1 Workforce Optimization, a new solution that uses trained artificial intelligence models to project future volume trends and provide actionable recommendations for optimizing laboratory staffing levels.

In partnership with the American Oncology Network (AON), a network of community-based oncology practices, the new solution was developed and tested throughout 2023. Launched in 2018, the AON network represents 106 physicians and 86 nurse practitioners and physician assistants practicing across 18 U.S. states.

The U.S. federal government has projected a 22% increase in demand for medical and clinical laboratory technologists and technicians by 2025. Coupled with reported understaffing in most labs, this situation places a continuing burden on lab professionals to do

more with less. By predicting demand for lab services department-by-department across an organization, hc1 Workforce Optimization enables proactive identification of potential shortages or overages, staffing assignment adjustments, and monitoring the impact of staffing changes over time, hc1 officials said.

AON officials stated that the solution can streamline staffing models and make suggestions using machine learning predictive analytics.

● BIOMÉRIEUX AND JMI LABS PARTNER AGAINST ANTIMICROBIAL RESISTANCE

bioMérieux and JMI Laboratories have announced a 6-year partnership to evaluate the performance and potential of rapid and innovative microbiology diagnostics as tools against antimicrobial resistance (AMR).

JMI specializes in the advancement of antimicrobial therapies, surveillance, and post-market observations and insights in the antimicrobial susceptibility testing (AST) field. In 1997, JMI established the Sentry Antimicrobial Surveillance Program. To help monitor the prevalence of AMR, Sentry has collected 40,000 clinical isolates of bacteria and fungi annually from a network of more than 150 medical centers worldwide.

bioMérieux is recognized globally for its advancements in rapid and actionable diagnostics, such as faster pathogen identification and AST to support antimicrobial stewardship efforts.

Through this partnership with JMI, bioMérieux will be able to continually assess antimicrobial susceptibility testing results and validate against evolving global

The U.S. federal government has projected a 22% increase in demand for medical and clinical laboratory technologists and technicians by 2025.

antimicrobial susceptibility data collected through the JMI-led Sentry program, bioMérieux said.

● DIACARTA AND ONCOASSURE COLLABORATE ON PROSTATE CANCER TEST

DiaCarta recently announced a strategic collaboration with OncoAssure to commercialize OncoAssure's prostate cancer test for patients with a lower risk of prostate cancer recurrence.

The prognostic test is a 6-gene expression assay that assesses the risk of aggressive disease post-diagnosis and the risk of biochemical recurrence over a 5-year period post-surgery.

The collaboration aims to leverage DiaCarta's expertise in customizable clinical diagnostic services to facilitate the completion of the laboratory developed test validation for the OncoAssure Prostate test. The collaboration also includes an application to the Centers for Medicare & Medicaid Services for coding, billing, and reimbursement, the companies said.

● AGILENT ANNOUNCES AND INCYTE TO DEVELOP ADVANCED COMPANION DIAGNOSTICS

Agilent Technologies recently announced an agreement with Incyte to develop companion diagnostics (CDx) to support development and commercialization of Incyte's hematology and oncology portfolio.

The agreement enables Agilent to continue to expand its companion diagnostics portfolio with novel biomarkers. The agreement helps

Incyte leverage Agilent's expertise in in vitro diagnostics development, global regulatory approvals, and commercialization to support clinical trials and potential registration and commercialization of CDx in the U.S. and Europe.

Agilent officials said the deal paves the way for strategic transformation of the treatment paradigm for a broad spectrum of cancers. By working together, Agilent and Incyte hope to expedite the development of innovative precision products that will potentially allow for enhanced patient health outcomes, they added.

Ask The Expert

Lower lithium therapeutic ranges for older adults with bipolar disorder

By Lei Fu, PhD, DABCC (CC, TC, MD), FADLM, FCACB

Lithium is prescribed as a first-line mood stabilizer for the management of bipolar disorder. It is effective during both the depression and mania/hypomania phases of this condition and may offer neuroprotection in addition to reducing the risk of suicide. However, due to its narrow therapeutic index, lithium toxicity is a concern, particularly in older adults who are ≥60 years of age. A recent study by Fung, et al. (EJIFCC 2023; 34:153–166) reported their experience implementing clinically appropriate, age-stratified lithium therapeutic ranges in the hopes of raising awareness and promoting the safe and effective use of lithium in older adults globally.

What is an appropriate lithium therapeutic range in older adults?

A: The International Society for Bipolar Disorder (ISBD) established an Older Adults Task Force aiming to provide specific directions for lithium therapy in older adults with bipolar disorder (OABD). In 2019, this group published recommendations for lithium therapeutic ranges in OABD, which are in the range of 0.4-0.8 mmol/L for ages 60-79 and in the range of 0.4-0.7 mmol/L for ages 80 and above (Bipolar Disord 2019; doi: 10.1111/bdi.12714).

In 2017, a Delphi consensus survey conducted by the ISBD Older Adults Task Force and a pattern-of-practice survey administered by the Institute for Quality Management in Healthcare (IQMH) in Toronto both found that the most common therapeutic range for lithium reported by laboratories was in the range of 0.6-1.2 mmol/L without age-dependent stratification.

Thus, requests were made to the clinical laboratory community to update and provide lower and narrower therapeutic ranges for lithium in older adults to improve the safety of lithium therapy in this vulnerable population.

Why are lower and narrower lithium therapeutic ranges important in older adults?

In older adults, the risk of lithium toxicity is increased due to decreased renal function, co-morbidities, and polypharmacy-associated drug-drug interactions with commonly used drugs, such as diuretics, angiotensin-converting enzyme inhibitors, and nonsteroidal anti-inflammatory medications. Moreover, lithium toxicity is often unrecognized and misdiagnosed as other conditions, resulting in inappropriate additional prescriptions. The commonly reported lithium therapeutic ranges (0.6-1.2 mmol/L) are too high for older adults and may lead to missed lithium toxicity because some potentially toxic levels can be misinterpreted as "within the therapeutic range." Providing lower and narrower therapeutic ranges for older patients would help to prevent adverse side effects, particularly neurotoxicity.

Is it feasible to adopt standardized therapeutic ranges for lithium therapeutic drug monitoring?

Review of proficiency testing survey reports between September 2020 and September 2022 from IQMH and the Royal College of Pathologists of Australasia Quality Assurance Programs (RCPAQAP) in St. Leonards, Australia, demonstrated acceptable agreement between commonly used lithium measurement methods with minimal variations. Specifically, the all-methods' standard deviation showed a range of 0.04-0.06 mmol/L for concentrations ≤1.5 mmol/L and <0.12 mmol/L for concentrations >1.5 mmol/L amongst eight different instrument groups of lithium colorimetric assays from five major manufacturers and reported data from 311 RCPAQAP and 86 IQMH clinical laboratory participants.

However, proficiency testing survey reports from the College of American Pathologists showed that some rarer methods, such as direct ion selective electrode, can have a bias of up to +0.3 mmol/L when compared to the all-methods' means, even though most of the common methods are generally agreeable. Thus, a review of site-specific laboratory and clinical data is still needed prior to the implementation of the recommended ISBD OABD therapeutic ranges.

In summary, it is feasible to use standardized lower lithium therapeutic ranges in older adults and they may improve the safety of lithium therapy for this patient population.

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