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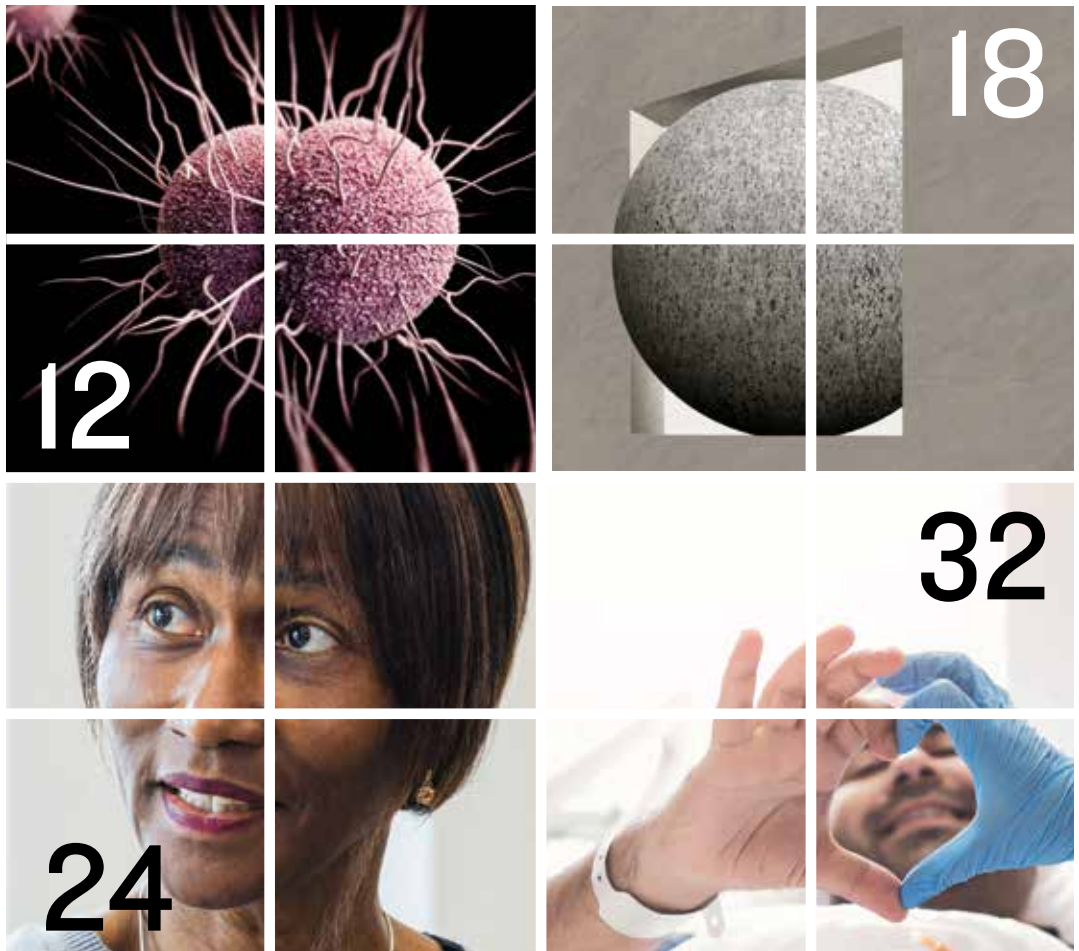


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Newborns with a positive result on the direct antiglobulin test will be tested more frequently, in accordance with 2022 guidelines.

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Federal Insider

FDA Launches Pilot Program for Lab-Developed Tests Used in Cancer

The Food and Drug Administration (FDA) introduced a voluntary, 1-year pilot program targeting laboratory developed tests (LDTs) used in cancer treatment selection. FDA says the program will give clinicians guidance and “transparent performance recommendations” for diagnostic tests, helping them identify appropriate cancer treatments.

“The agency has become increasingly concerned that some tests made by laboratories and not authorized by the FDA may not provide accurate and reliable test results or perform as well as FDA authorized tests,” the agency wrote in a news release. Adding that the agency “will continue to work on a broader approach for LDTs, including moving forward with rulemaking.”

During the pilot program, FDA will gather performance information on tests used in clinical trials supporting drug approval from drug manufacturers. Based on this assessment, FDA will release minimum recommended performance characteristics for similar tests used to select patients for treatment with approved drugs.

FDA believes this will help labs develop LDTs that accurately identify biomarkers for treatment selection.

After AACC and other organizations advocated against FDA regulating LDTs as proposed in the VALID Act in 2021, the bill failed to advance in Congress.

AACC remains focused on modernization of CLIA regulations as the best and most effective way to ensure patient access to high-quality laboratory testing, including LDTs.

HEALTH SPENDING TO SWALLOW 20% OF GDP BY 2031

The Centers for Medicare & Medicaid Services (CMS) Office of the Actuary released its projections for National Health Expenditures (NHE) and health insurance enrollment for 2022-2031.

According to the report, the average annual growth in NHE over the next decade will be 5.4%, surpassing the average annual expected growth of 4.6% in gross domestic product (GDP). As a result, the share of health spending as a proportion of GDP would rise from 18.3% in 2021 to 19.6% in 2031.

For Medicare specifically, CMS projects average growth of 7.5% over 2022-2031. In 2022, the combination of fee-for-service beneficiaries using emergent hospital care at lower rates and the reinstatement of payment rate cuts associated with the Medicare Sequester Relief Act of 2022 resulted in slower Medicare spending growth of

4.8%—down from 8.4% in 2021, the report notes.

In 2025, Medicare spending is projected to grow 8.9%, then slow to 6.8% in 2030 and 2031. The anticipated slowdown is due to the Inflation Reduction Act’s provisions on drug price negotiation and inflation rebates, as well as slower enrollment growth as the last of the baby boomer generation, those born between 1946-1964, enroll in 2029.

WINNERS OF \$9.2 MILLION ARTIFICIAL KIDNEY PRIZE UNVEILED AT KIDNEYX SUMMIT

The Department of Health and Human Services (HHS) and the American Society of Nephrology announced the eight winners of the Artificial Kidney Prize Phase 2, a competition toward creating a bioartificial kidney. The Kidney Innovation Accelerator (KidneyX) is

a collaboration between HHS and the American Society of Nephrology.

The competition divided teams into two tracks, with Track 1 participants each receiving \$1,600,000 and Track 2 participants each receiving \$1,000,000. The winners were selected for their approaches in developing a fully functional bioartificial kidney, using new methods in xenotransplantation and regenerative medicine.

Designing a bioartificial kidney is very difficult due to the organ’s complexity and different cell types, according to HHS. The agency is focused on fostering collaboration among scientists in regenerative medicine, cellular engineering, tissue engineering, systems biology, and synthetic biology.

The technologies awarded include an immunoprotective bioreactor for kidney cell encapsulation, combining kidney organoids and peritoneal dialysis, and a 3D vascularized biomimetic renal construct platform.



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What Can Go Wrong With Point-of-Care Testing?



By Jessica
Jenkins, MSA,
MLS (ASCP)^{CM}

Point-of-Care testing (POCT) provides rapid test results with the potential to improve treatment. Additional advantages of POCT include small sample volumes, a wide variety of tests available, little to no processing required to run the tests, and ease of use within the clinical patient flow. However, when incorrectly performed or inappropriately utilized, POCT can generate misleading results that require additional follow-up testing at increased cost and risk to the patient.

Just as in traditional laboratory testing, the majority of POCT errors occur in the pre-analytical phase. These are processes that occur before the specimen is analyzed. Unfortunately, the instrument, operator, or clinician interpreting the results cannot readily identify most pre-analytical errors. Some pre-analytical variables specific to POCT are patient misidentification, improper specimen collection, air bubbles, hemolysis, improper site selection, and interfering substances.

Common Errors in POCT

Patient misidentification is a major source of error in POCT. Many POC devices use manual entry for

patient identification, which leads to typos and incorrect information being entered. If a POC device is equipped with a barcode scanner, it is recommended to utilize the scanner to prevent such errors. For samples that must be collected from the patient and transported to the POC device, the small size of the sample container can make properly labeling the specimens a challenge. However, it is imperative that two patient identifiers are verified prior to performing testing.

Another common error is clinicians scanning loose labels in a patient's room. It is not unusual to find other patient labels in a room that may have been left by a previous patient or accidentally carried into the room by the clinician. It is important to always scan the

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patient's armband that is worn by the patient to assure accurate identification prior to testing.

Specimen collection is also a source of error when performing capillary collections for POCT. These errors can include poor lancing technique, using a previously punctured site, milking the puncture site, not producing an adequate volume of blood prior to adding to the test strip or cuvette, and air bubbles in the sample. Another problem: performing a finger stick on the same side as a peripheral IV infusing a substance that may interfere with the assays, such as dextrose or insulin.

When incorrectly performed or inappropriately utilized, POCT can generate misleading results that require additional follow-up testing at increased cost and risk to the patient.

Milking refers to excessive squeezing or massaging and is generally done when not enough blood volume is being produced. Milking is often the result of poor lancing technique and can cause decreased concentrations of some analytes due to dilution of the blood sample with tissue fluid. To avoid milking a puncture site, it can be helpful to use a lancet of adequate size and to warm the collection site to increase blood flow prior to puncture.



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Air bubbles may cause erroneous results, particularly in blood gas measurements for pCO₂ and pO₂. Air bubbles present in cuvettes for hemoglobin tests that use optical readings can also cause erroneous results. It is vital that blood gas samples and cuvettes are collected free of air bubbles to obtain accurate results. Air bubbles in blood gas samples can be prevented by collecting the first drop of blood in one fluid motion. If a second drop is needed, the capillary tube should remain at an upward angle while the second drop is being formed to prevent air from entering the tube.

Samples with hemolysis can also impact results for certain analytes. Hemolysis can be caused by different factors, but a large contributor is milking of the puncture site. Analytes that are affected by hemolysis include potassium, aspartate aminotransferase, and lactate dehydrogenase. The results of these analytes will increase as the degree of hemolysis increases. Ways to prevent hemolysis are to avoid milking the puncture site, ensuring the puncture site is completely dry if using alcohol to clean, and selecting the appropriate size of lancet for the volume of blood needed. Unfortunately, there are no current methods to detect hemolysis in the POCT setting, and it is likely to be missed.

Selecting the proper location to perform a capillary puncture is important. Clinicians should avoid sites that have been previously punctured and perform proper cleaning. Our pediatric institution only allows capillary collections to be performed on a patient's heel, middle finger, or ring finger, though ear lobes and other sites are also used for capillary punctures at other institutions.

Lastly, interferences are another source of pre-analytical errors that can impact POCT. For example, glucose is one of the most highly utilized POC tests, and it is very important for patient monitoring along with insulin management. However, POC glucose can be affected by interference of ascorbic acid (vitamin C) and body lotions containing hydroquinone. Ascorbic acid interferes with glucose measurements on some meters due to the method the meter uses. Depending on the type of meter and concentration of ascorbic acid in circulation, the results can be falsely increased or falsely decreased.

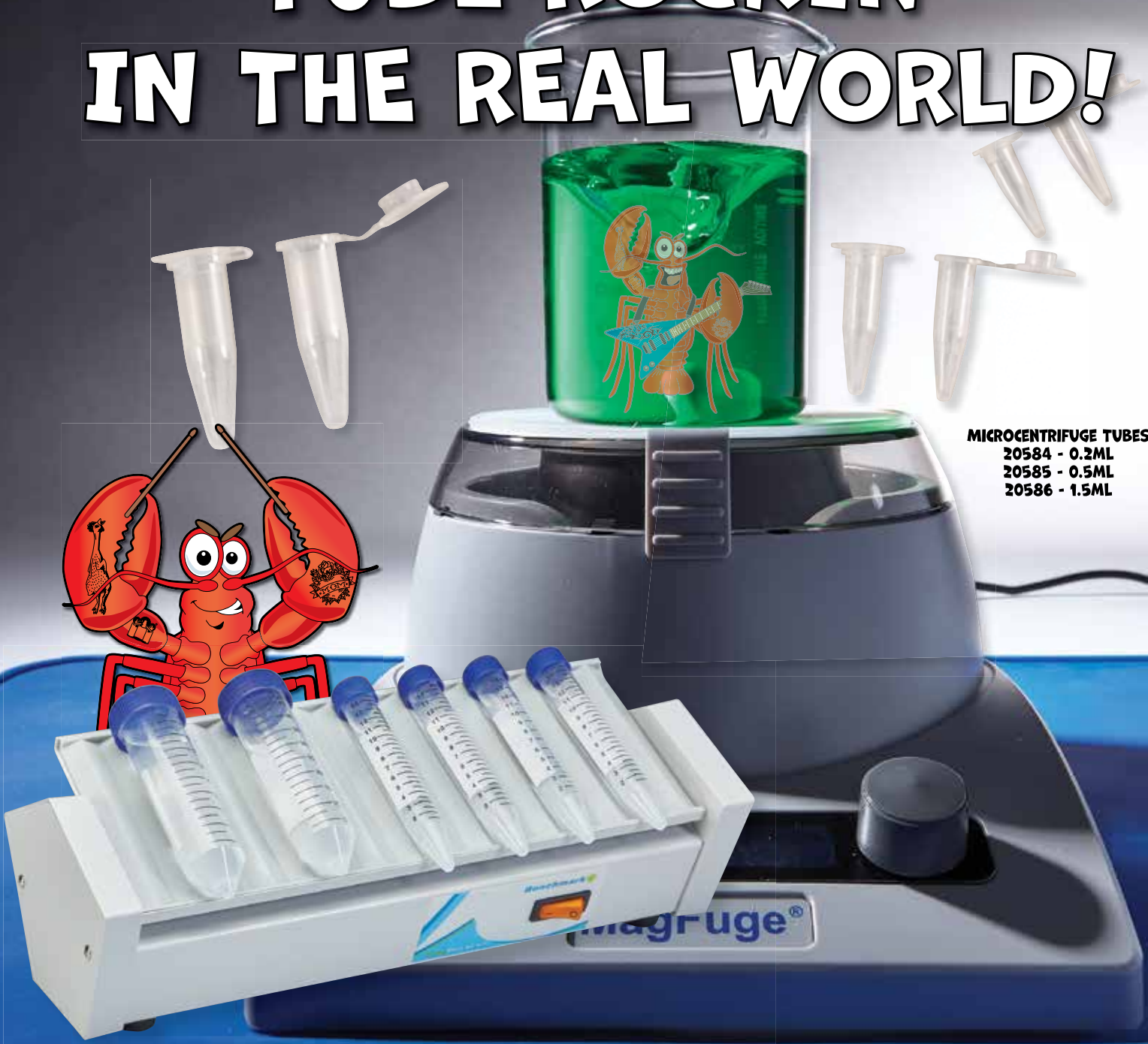
Hydroquinone-containing body lotions can falsely increase glucose measurements. These lotions are commonly used to reduce age spots and lighten dark spots on the skin. It is important that both the practitioner and patient be educated about possible interferences so proper testing technique is used to ensure reliable results.

The request for POCT continues to grow. POCT has unique challenges because it is not typically performed by lab personnel. Training and continuous education for clinicians is important to help reduce errors. A quick result does not always mean an accurate result.

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Glycated Albumin Not Ready as a Diagnostic Tool

Glycated albumin (GA) is highly specific but may not be sensitive enough to screen for diabetes in adults with obesity, according to researchers (J Appl Lab Med 2023; doi: 10.1093/jalm/jfad004).

Most American adults who develop diabetes are obese. Several studies have shown an inverse association between body mass index and GA, suggesting GA may have a role as a biomarker of hyperglycemia, or high blood sugar, as GA is a short-term measure of glycemic control. In 2017, the Food and Drug Administration approved GA for clinical use in managing diabetes. However, no guidelines provide advice on using GA to diagnose prediabetes and diabetes. And no related diagnostic cut points have been established.

To assess GA as a potential biomarker of glycemia, the researchers measured GA in adults who participated in the 1999–2004 National Health and Nutrition Examination Survey. In separate groups of adults with and without diabetes, the researchers assessed the association between GA and adiposity measures in sex-stratified multivariable regression models. The adiposity measures included body mass index (BMI), waist circumference, trunk fat, total body fat, and fat mass index. The researchers compared GA sensitivity and specificity to identify elevated hemoglobin A1C (HbA1C) by obesity status.

Of the 10,835 participants with samples, 1,085 self-reported a diabetes diagnosis, and 9,750 did not. In covariate-adjusted regression models, all adiposity measures were inversely associated with GA in adults with and without diabetes. Among GA in adults with diabetes, β equaled -1.73 to -0.92% -point GA per 1 standard deviation (SD). Among GA in adults without diabetes, β equaled -0.48 to -0.22% -point GA per 1 SD adiposity measure.

Among participants with diabetes, GA identified above-target glycemia (HbA1c $\geq 7\%$) with specificity of more than 80% overall. GA had sensitivity of 81% in adults with obesity, versus 93% in those without obesity. Comparing adults with versus without obesity, GA had lower sensitivity (43% vs 54%) to detect undiagnosed diabetes (HbA1c $\geq 6.5\%$).

The researchers called for future studies of how albumin turnover, circulation, and glycation kinetics are altered in the context of obesity to clarify the mechanism by which adiposity affects GA.



POSSIBLE ALZHEIMER'S DISEASE BIOMARKER IDENTIFIED

Bisecting N-acetylglucosamine in combination with tau is a valuable blood biomarker for predicting Alzheimer's disease (AD),

recent research concludes (Alzheimers Dement 2023; doi: 10.1002/alz.13024).

A previous study by the same researchers showed that levels of the bisecting N-acetylglucosamine glycan

epitope was elevated in cerebrospinal fluid in AD. However, its diagnostic value in blood is unknown.

To determine its value as an AD blood biomarker, the researchers analyzed blood levels of bisecting

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N-acetylglucosamine and total tau in a retrospective cohort of 233 individuals. They compared progression to AD between the groups using Cox regression and determined the biomarker's predictive power by logistic regression.

The researchers observed a more than twofold increased risk of developing AD in the group with intermediate tau/bisecting GlcNAc ratio, compared with the groups with high or low tau/bisecting GlcNAc ratio. Individuals in the high or low tau/bisecting GlcNAc ratio groups had either lower bisecting GlcNAc levels or lower t-tau levels than average. Because

both bisecting GlcNAc levels and t-tau are elevated in AD patients' cerebrospinal fluid, the researchers believe that lower bisecting GlcNAc or lower t-tau levels in blood have protective effects on AD development.

Although neither tau nor bisecting GlcNAc on its own predicted AD, the tau/bisecting GlcNAc ratio significantly predicted progress to AD in individuals with intermediate tau/GlcNAc ratio. Combining tau/bisecting GlcNAc ratio with APOE $\epsilon 4$ allele status further improved the prediction of AD. Combining tau/bisecting N-acetylglucosamine ratio, apolipoprotein E (APOE) $\epsilon 4$ status, and Mini-Mental State Examination score produced a strong predictive model, the researchers wrote (area under the curve=0.81, 95% CI: 0.68–0.93).

They suggested further research on the tau/bisecting GlcNAc with an eye toward validating it as a blood biomarker for early prediction of AD.

A PREDICTION MODEL FOR KIDNEY FUNCTION DECLINE IN DIABETES

Researchers have developed a reliable prediction model for kidney function decline and estimated glomerular filtration rate (eGFR) in adults with type 2 diabetes and for early-to-moderate chronic kidney disease (CKD) (JAMA Network Open 2023; doi:10.1001/jamanetworkopen.2023.1870).

Type 2 diabetes increases the risk of progressive diabetic kidney disease, but reliable prediction tools for clinical practice are lacking. In response, researchers aimed to externally validate a model to predict future trajectories in eGFR among adults with type 2 diabetes and CKD using data from three multinational, European cohorts.

The current study included a total of 4,637 adult participants age 18–75 years with type 2 diabetes and mildly to moderately impaired kidney function, defined

as a baseline eGFR of at least 30 mL/min/1.73 m². Of these subjects, 3,323 from the German Chronic Kidney Disease (GCKD) and Prospective Cohort Study in Patients with Type 2 Diabetes Mellitus for Validation of Biomarkers (PROVALID) were in the model development cohort. The current study's validation cohort included 1,314 subjects from the Diabetes Cohort (DIACORE).

The researchers examined variables from routine clinical care visits. They included age; taking blood pressure, glucose-lowering, or lipid-lowering medications; body mass index; hemoglobin; HbA1C; mean arterial pressure; serum cholesterol levels; sex; smoking status; and urinary albumin-creatinine ratio. Investigators used a linear mixed-effect model for eGFR measurements at baseline and multiple visits up to 5 years after the baseline.

Updating the random coefficient estimates with baseline eGFR values yielded improved predictive performance. Improved predictive performance was particularly evident in the visual inspection of the calibration curve (calibration slope at 5 years: 1.09; 95% CI, 1.04–1.15). The prediction model had good discrimination in the validation cohort, with the lowest C statistic at 5 years after baseline (0.79; 95% CI, 0.77–0.80). The model also had predictive accuracy, with an R² ranging from 0.70 (95% CI, 0.63–0.76) at year 1 to 0.58 (95% CI, 0.53–0.63) at year 5.

These findings reveal the potential of a publicly available online tool that can be used by patients, caregivers, and primary health care professionals to predict individual eGFR trajectories and disease progression up to 5 years after baseline, the researchers wrote.

An accompanying commentary noted that some of the required 13 variables may not be routinely measured, such as total cholesterol in some patients on statins. The editorial called for validation in non-white populations.



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Are Sexually Transmitted Infections Becoming More Dangerous?

Home testing and other strategies have not yet slowed the growing burden of STIs.

Drive on highways in Philadelphia, and you'll see typical billboards advertising products and services ranging from snack foods to health insurance, to personal injury attorneys. And then there's a new, more jarring one: "DRUG RESISTANT GONORRHEA ALERT," it cries in all capital letters, accompanied by an illustration of a boat hitting an iceberg, where most of the floating mass is below water.

The billboard from the AHF Wellness Center, which has locations across the U.S., is disturbing, but drug-resistant gonorrhea is one of a handful of sexually transmitted infections (STIs) that are becoming more dangerous and common, experts say.

According to the CDC, more than 2.5 million cases of chlamydia, gonorrhea and syphilis were reported in the U.S. in 2021, about 6% more than in 2020. Reported syphilis cases hit 176,000 in 2021, up from about 134,000 in 2020—as high as numbers have been since the 1950s. Congenital syphilis rose 32%, leading to 220 infant deaths and stillbirths.

The STI landscape is changing for many reasons, including reduced funding for STI testing that would catch cases before they spread, changes in behavior caused by the pandemic, and growing drug resistance from specific kinds of infections. Here's what clinical laboratorians should look out for.

BY JEN A. MILLER



DRUG-RESISTANT GONORRHEA

Gonorrhea is the most commonly diagnosed STI, with 710,000 cases reported in 2021. That's an increase of 4.6% from 2020, according to CDC. Cases have been rising over time, with the number of cases up 118% since 2009.

CDC estimates that half of gonorrhea infections show resistance to at least one antibiotic. And while that may sound alarming—and look distressing on a billboard—it may not yet be as dire a situation as it seems, said Barbara Van Der Pol, PhD, MPH, professor of medicine and public health at the University of Alabama at Birmingham and president of the International Society for STD Research.

Resistance to one antibiotic does not mean the infection is untreatable. Only 0.2% of cases required four or more antimicrobials to treat, according to 2021 CDC Sexually Transmitted Diseases Surveillance. And while a novel strain of drug-resistant gonorrhea was found in Massachusetts, that was only in two patients, and were both successfully treated with ceftriaxone, the current standard gonorrhea treatment, according to the Massachusetts Department of Public Health.

Clinical laboratories are essential to identifying the right treatment to

use first. “Many of those [with drug-resistant gonorrhea] could use older treatments if we had better diagnostic technology that would detect markers,” Van Der Pol said. “But we don't know that, so we automatically go to the next-tier drug.”

With current technology, detecting drug-resistant gonorrhea would require testing from culture isolates, and eventually better molecular tools, noted Allison Eberly, PhD, assistant professor at the Washington University School of Medicine, and associate medical director microbiology and of the Molecular Infectious Disease Laboratory at the Barnes Jewish Hospital. “We have to try to culture the isolate, then at most labs it would be sent to a reference laboratory for antibiotic susceptibility testing,” Eberly said. “It can be performed at some places in-house. For us, the volume doesn't warrant us bringing it in-house. It just takes time to get those results back.”

Furthermore, designing assays that would get FDA approval is not so easy. “If you want to develop a new test, you have to do a clinical study and are not allowed to use isolates out of a freezer,” Van Der Pol said. “How many people do you have to enroll to A, catch gonorrhea; B, catch drug resistant ones; and C, follow them up for clinical outcomes?” She doesn't see a clinical diagnostic

company willing to pay for such a trial. “That's why we're stuck.”

MYCOPLASMA GENITALIUM

Also on clinical laboratorians' radars is *Mycoplasma genitalium*, which a 2022 study from the journal *Sexually Transmitted Infections* showed might be associated with an increased risk of pre-term birth (doi: 10.1136/sextrans-2021-055352). It can also lead to infertility in women. In men, it causes symptomatic and asymptomatic urethritis.

It's still not considered a common STI, though: It's been reported in 1.7% of people age 14–59 in the U.S, according to one report, with infection rates higher in people who have another STI (Sex Transm Dis 2021; doi: 10.1097/OLQ.0000000000001394).

Clinical laboratories can test for it. “It wouldn't change much in terms of methodology or sample collection. Often the same specimens for chlamydia and gonorrhea can also be used,” Eberly said. “But what next?” So far, research into what *Mycoplasma genitalium* does, especially in asymptomatic patients, isn't mature enough to answer that question. “What happens with that test result? If clinicians aren't certain what to do with a positive result,

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how do they know when to treat?” she said.

The CDC does not recommend screening for asymptomatic patients. Van Der Pol agrees, because doing so may lead to treatment and make *Mycoplasma genitalium* more drug resistant. “We don’t always want to treat it. We’re not sure if it has long-term downstream health outcomes, and asymptomatic infections may self-clear and then cause no problems,” she said. “It develops resistance so quickly, that if you try to treat it and don’t know the resistance profile you’re likely to lead to more resistance.”

POINT-OF-CARE TESTING ENTERS THE FRAY

The COVID-19 pandemic forced the accelerated development of all kinds of at-home testing. One lasting effect of that is the acceptance or even expectation of such tests from patients. “The pandemic really opened the doors to the possibility of self-collection,” said Eberly. “We need better access to all kinds of testing and a strategy to bring testing access to folks.”

She also doesn’t think home tests will entirely replace laboratory-based

molecular testing, as molecular tests are often used to confirm a point-of-care test diagnosis — as it was before COVID-19. Laboratories confirm many other home tests the same way.

In March, Visby Medical received FDA clearance and a CLIA waiver for their second-generation Sexual Health Test for Women point-of-care test, a PCR diagnostic test for chlamydia, gonorrhea, and trichomoniasis. The company reports that the tests have 97% accuracy, and that their device returns results in 30 minutes.

It’s a rare achievement in at-home testing kits for STIs, said Van Der Pol, because the FDA wants 95% accuracy, which can be difficult to achieve. She added that, in a lot of cases, “even 80% accuracy would be better than no test at all.”

Because the FDA barrier is so high, though, many direct-to-consumer tests (also called online tests and self-tests) offer only laboratory-developed tests and are marketed as a more convenient and less stigmatized option to STI testing. In a position statement, the American Sexually Transmitted Disease Association (ASTDA) acknowledged

that these tests are appealing to some consumers because they can be initiated at home and allow people to avoid potential embarrassment or discomfort around a discussion of sexual history (Sex Transm Dis 2021; doi: 10.1097/OLQ.0000000000001475). They added that the tests also may reduce the burden on health care providers.

But the organization also cautioned about several problems within the home-testing landscape. At-home tests can be hard to access for those who are experiencing housing insecurity and therefore don’t have a fixed mailing address. The costs, which ASTDA found typically range from \$49 to \$189 or higher, may be prohibitive, and are often not reimbursable by insurance because they’re not ordered by a healthcare provider. Using these tests also requires internet access, which 8% Americans don’t have at home.

Another concern was that ASTDA found that bundled direct-to-consumer tests may include unnecessary assays, like for *Ureaplasma* species or *Mycoplasma hominis*, for which there are no screening or treatment recommendations. They also found that the methodology to determine validity

“It develops resistance so quickly, that if you try to treat it and don’t know the resistance profile you’re likely to lead to more resistance.”

-Barbara Van Der Pol



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of the collection, transport, and testing process is often not made public. The ASTDA recommends these laboratories offer follow-up care as well, which only some do.

Promises that these direct-to-consumer tests for STIs would usher in access to more people, and more kinds of people, have not yet panned out, said Van Der Pol. "We thought they would be really great in expanding access. But they can be expensive, and that's not helping with health equity."

As for billboards like the one in Philadelphia, she acknowledges that drug-resistant gonorrhea is a problem that is increasing worldwide. However, it's a small sliver of the infectious disease picture, especially when the percentage of drug-resistant cases does not mean they are untreatable, she said.

Currently, only one treatment remains for resistant infections: cephalosporins. However, the CDC has not verified any clinical treatment failures using cephalosporin in the United States. ■

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The new AACC Academy/National Kidney Foundation guidance document highlights the clinical laboratory's role in achieving kidney disease health equity.

In the United States, more than 37 million adults—or 1 in 7 people—are affected by kidney disease. In its earliest stages, kidney disease is silent, and approximately 90% of people who have chronic kidney disease (CKD) are unaware. Many remain undiagnosed until they have kidney failure. Kidney disease is associated with complications in every organ system, and more deaths from kidney disease are caused by cardiovascular disease than by kidney failure. Early detection of kidney disease is critical, because clinical and lifestyle interventions can slow disease progression and reduce complications.

Now, new guidance from AACC Academy and the National Kidney Foundation (NKF) will enable laboratory medicine experts and clinicians to work together to implement the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 equations. The guidance emphasizes improved detection in high-risk populations and marks a significant leap forward in emphasizing an inclusive approach for all populations.

This landmark guidance calls for collaborative efforts among clinical laboratories and providers to drive meaningful change. Multidisciplinary teams are urged to unite to achieve improved disease detection, particularly in high-risk populations.

THE EVOLUTION OF LABORATORY TESTING FOR CKD

Kidney disease diagnosis and staging primarily relies on laboratory testing. Glomerular filtration rate (GFR) currently serves as the best overall index of kidney function, and

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albuminuria as the most widely studied marker of kidney damage. Direct measurement of GFR requires measuring the clearance of an exogenous filtration marker and is impractical in routine clinical practice. However, GFR can be estimated (eGFR) by combining endogenous filtration markers, such as creatinine or cystatin C, with surrogates for non-GFR determinants that influence filtration marker concentrations independent of GFR. Including these surrogates in calculation of the eGFR improves its accuracy relative to measured GFR (mGFR). Because clinical laboratories routinely measure creatinine as part of the basic or comprehensive metabolic panel, the routine reporting of eGFR from creatinine (eGFR_{cr}) has transformed medical practice. Notably, the introduction of eGFR into clinical practice has resulted in significant advances in kidney disease care, including federal investments in kidney disease surveillance programs and standardization of laboratory assays for creatinine.

Over the past few years, eGFR equations have been scrutinized increasingly because of their inclusion of a race variable (African American vs. non-African American) in eGFR_{cr} calculation. The most widely used eGFR_{cr} equations—the 4-variable Modification of Diet in Renal Disease (MDRD) and CKD-EPI 2009 equations—incorporate the variables age, sex, and race in addition to creatinine concentration (1,2). Use of age, sex, and race as surrogates for the non-GFR determinants of creatinine increase the accuracy of eGFR_{cr} computed by the MDRD and CKD-EPI 2009 equations.

During the derivation of these equations, investigators observed that the average creatinine concentration in the study participants who self-identified as African American (12% in the MDRD study and 31% in the CKD-EPI development and internal validation populations) was higher compared to non-Black participants of the same age, sex, and mGFR (1,2). Inclusion of a race variable in these equations provides a higher eGFR_{cr} in African American persons compared to non-African American persons of the same age, sex, and creatinine concentration. At

the time, researchers hypothesized that all three variables—age, sex, and race—were related to creatinine generation by muscle mass or diet. Of interest, blood cystatin C concentrations differ less with age, sex, and race, and race was not included in the CKD-EPI 2012 equation using cystatin C (eGFR_{cys}). Race, however, was included in the CKD-EPI 2012 equation using both creatinine and cystatin C (eGFR_{cr-cys}) which is more accurate than either eGFR_{cr} or eGFR_{cys} (3). eGFR_{cys} and eGFR_{cr-cys} were recommended as confirmatory tests (4).

We now recognize that race is a social construct rather than a biological variable. Including race as a distinct variable in eGFR and other clinical algorithms incorrectly reinforces race as a biological construct, and it overlooks the social costs of systemic racism. Race is a particularly problematic surrogate because it was historically co-opted for the purpose of oppression, and should not be confused with genetic similarity, which is measurable and can be used to infer ancestry (5). While population-level racial differences are observed in creatinine, the individuals that comprise these socially constructed racial groups are both genetically and economically diverse. Race can serve as a proxy for the unequal access to and allocation of healthcare resources, poorer quality of healthcare, and worse social determinants of health experienced by racialized people. Current guidelines recommend that the socioeconomic and environmental stressors that influence human health and disease should be directly measured (5). Race should not be used as a proxy.

Racial disparities are evident at every stage in the detection, evaluation, and management of kidney disease. Black and Hispanic people are less likely to receive patient-centric dialysis treatment, and they are more likely to develop end stage kidney disease. Black and Hispanic people are overrepresented in neighborhoods with high levels of socioeconomic deprivation, which is associated with poorer kidney health, less access to medications that delay kidney disease progression, and delayed nephrology referral (6,7). For this reason, it was especially appropriate to reconsider the use of race in eGFR equations. At

the time of writing, there is no conclusive evidence that inclusion of race in eGFR equations contributed to these disparities; however, a unifying approach with potential consequences that do not disproportionately affect any one group of individuals was needed. In addition, an approach that avoided typological thinking that assumes that people can be grouped into distinct, homogeneous categories by race was desirable.

In November of 2020, NKF and the American Society of Nephrology (ASN) formed a task force to reassess the inclusion of race in diagnosing kidney diseases. The task force subsequently recommended immediate implementation of the CKD-EPI 2021 eGFR_{cr} equation that does not include a race variable (8,9). This recommendation was supported by the AACC eGFR and Race Equity Task Force, which conducted a systematic review of the use of race in the eGFR equations and found no evidence to support this practice (10). The CKD-EPI 2021 eGFR_{cr} equation was developed using the same data sources in the derivation of the 2009 CKD-EPI eGFR_{cr} equation (9). The refit equation achieves the goal of removing race, and while it is less accurate in both Black and non-Black subgroups, it is sufficiently accurate for clinical use for both Black and non-Black people. Similar findings were observed for the CKD-EPI 2021 eGFR_{cr-cys} without race that was developed by refitting the coefficients in the 2012 development and internal validation population without race.

HOW THE NEW GUIDANCE WILL LEAD TO HEALTH EQUITY

In the July 2023 issue of the Journal of Applied Laboratory Medicine, the AACC/NKF Guidance Document on Improving Equity in Chronic Kidney Disease Care was published; it's a new to implement the Task Force recommendations. The guidance document provides recommendations on the implementation of cystatin C testing, since the NKF-ASN Task Force called for increased use of cystatin C, and describes clinical situations in which the CKD-EPI 2021 eGFR_{cr-cys} or 2012 eGFR_{cys} may provide more accurate estimates than the CKD-EPI 2021 eGFR_{cr} equation.



As clinical laboratorians, we are intimately familiar with the multiple potential sources of error that can bias our quantitative measurements.

The implementation of race-agnostic eGFR equations by clinical laboratories represents important progress towards racial equity in kidney disease, and the field of nephrology is the first to course-correct the harmful practice of including race in clinical calculators. The guidance document highlights multiple other considerations for clinical laboratorians as we collaborate with our nephrology colleagues in the quest to achieve kidney disease equity.

As clinical laboratorians, we are intimately familiar with the multiple potential sources of error that can bias our quantitative measurements. Although eGFR represents a reasonably accurate estimate of “population average mGFR,” it is not a precise estimate of an individual’s mGFR (11). There are numerous sources of error in eGFR_{cr} (12). In addition to errors in the creatinine assay (more pronounced with the Jaffe than the enzymatic methods), there are errors due to excessive variation in non-GFR determinants of creatinine (extremes of muscle mass or diet and inhibition

of tubular secretion of creatinine), as well as errors in mGFR, which inflate the magnitude of error observed when eGFR is compared to mGFR.

While nephrologists use eGFR_{cr} with nuance, non-nephrology providers often consider the reported eGFR_{cr} to be an exact value with respect to true GFR. Furthermore, reliance on eGFR_{cr} as the sole measure of kidney disease—without confirmation by eGFR_{cys} or eGFR_{cr-cys} and without assessment of albuminuria—can delay kidney disease detection, evaluation, and management. The clinical laboratory has a lot to offer in this regard, including using enzymatic creatinine assays instead of Jaffe methods, cystatin C testing, urine albumin-to-creatinine ratio (ACR), and combining ACR testing with eGFR into a single test order: the Kidney Profile.

It also is appropriate to consider the use of sex in eGFR equations. Unlike race, sex is a biological factor. However, the associations of sex with blood creatinine and cystatin C concentrations are variable, and in

some circumstances, the harms from using a binary sex variable may not be worth the added accuracy in GFR estimation.

For example, applying a sex variable for transgender persons is inherently problematic since gender-affirming hormones shift muscle mass and fat distribution. Changes in creatinine concentration after initiation of gender-affirming hormones vary between sexes, and individuals and can be influenced by gender-affirming hormone dose and duration of use (13).

This is further complicated by conflicting data describing the impact of gender affirming hormones on creatinine concentrations. For example, some studies show that people on masculinizing or feminizing hormones experience modest increases or decreases in creatinine concentration over time, respectively, while others report that use of either exogenous hormone confers no change in creatinine measurements. The sex-identifier used to compute eGFR is institution-specific and can be based on the

capability of the electronic health record in use. Sex used to compute eGFR may be sex assigned at birth, legal sex, or gender identity. None of these, however, take into account the effects of gender-affirming hormone therapies and their short and long-term impact on endogenous filtration markers and other physiological variables that are relevant to kidney disease measures.

Thus, interpreting eGFR in transgender people requires a holistic approach that takes into consideration the individual's muscle mass (for estimates that incorporate creatinine) and hormonal therapy. Most importantly, their gender identity must be respected. Of interest, eGFR_{cys} equations are available that were developed without including sex as a variable and do not require specification of sex for calculation of eGFR (14,15), but there is little experience in the U.S. with these equations.

A CALL FOR COLLABORATION

Calculating eGFR has transformed the interdisciplinary relationship of nephrology and laboratory medicine—a collaboration that has undoubtedly improved care across populations. However, fundamental to this laboratory result is the little “e” in eGFR. This value is an estimate for all people but is only one of several available laboratory measures of kidney disease. Collaboration among laboratory medicine and nephrology specialists can improve the use of these measures for detection, evaluation, and management of kidney disease.

Finally, there is a broader lesson to be learned from resolving the controversy about using race in eGFR equations: Biological variability and socioeconomic and environmental stressors must be considered in clinical research and practice to achieve more equitable care. ■

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Making the Most of Bone Turnover Marker Testing

BY MATTHEW B. GREENBLATT, MD, PHD, AND KYLE W. MORSE, MD

Used carefully, these markers can inform clinical decision-making and help individualize patient care.

Osteoporosis and other disorders of low bone mass are common, and osteoporotic fractures can incur substantial morbidity and mortality. However, determining a patient's level of risk for fracture and monitoring the effectiveness of treatment can be challenging for clinicians. One reason is that osteoporosis is essentially clinically silent until a fracture occurs.

Another is that the impact of the most common forms of osteoporosis on the skeleton and the response to therapies to treat osteoporosis are both very slow. Thus, a change in therapy or clinical risk factors can take months to translate into changes in bone parameters as measured by dual energy X-ray absorptiometry (DXA), a standard radiographic method to estimate bone mass and fracture risk.

This slow response of the skeleton can make optimizing medical management difficult, as it greatly delays empiric assessment of therapy response and switching to another agent if necessary. This issue is further exacerbated as clinicians increasingly consider sequential or combination therapies for osteoporosis management, escalating the overall complexity of management options.

In this context, bone turnover markers (BTMs) can help clinicians refine treatments to individual patients, and there is substantial interest in using BTMs to either assess fracture risk or to assess the response to therapy. However, preanalytical factors and proper utilization are key for effective BTM testing.

RESORPTIVE AND ANABOLIC BONE TURNOVER MARKERS

BTMs are categorized into either resorptive markers or anabolic markers that correlate with the rate of bone matrix removal by osteoclasts or deposition by osteoblasts. Many BTMs are fragments of collagen or other bone matrix proteins liberated during bone matrix synthesis or resorption. The best validated BTMs for bone resorption by osteoclasts are the Collagen type I C-terminal and Collagen type I N-terminal telopeptides (CTX and NTX, respectively) that are released during osteoclast-mediated removal of bone matrix.

In practice, CTX is often run on serum, and NTX is run on urine, as serum NTX is less responsive to treatment with drugs that block osteoclast activity, such as bisphosphonates. Both CTX and NTX generally show similar performance.

A separate group of markers, most notably including the N-terminal propeptide of type I collagen (PINP) and bone-specific ALP, correlate with bone formation by osteoblasts. The collagen propeptides are cut when bone matrix is produced and therefore correlate with rates of bone formation. PINP

is initially present as a bundled trimer of three propeptides that is then converted to single monomer units in circulation. Clinical assays can measure either a combination of the monomer and dimer, termed total PINP, or just the trimeric form termed intact PINP. Trimeric PINP is cleared via uptake in the liver, while monomeric PINP is mostly cleared renally. In patients with renal disease, testing of intact PINP is preferred to avoid biologic interference from impaired renal clearance of the PINP monomer.

Although alkaline phosphatase (ALP) is made at high levels by bone-forming osteoblasts and is an almost universally available clinical assay, total alkaline phosphatase activity in serum reflects the combined activity of 4 genes (*ALPI*, *ALPL*, *ALPP*, *ALPP2*). As a result, the ALP activity produced by bone-forming osteoblasts is only a small fraction of the total ALP present. Accordingly, only diseases with truly remarkable elevations in bone formation, such as Paget's disease of bone, typically display elevations in total ALP levels.

To counter this issue, a number of methods have been developed to measure only bone-derived ALP, with

immunoassays currently being the method of choice. Importantly, current bone ALP immunoassays have some degree of cross-reactivity with forms of ALP produced by the liver and must therefore be interpreted with caution in patients with liver disease.

However, despite this potential usefulness of BTMs, bone turnover marker testing poses a particular challenge for laboratory professionals. BTMs can display substantial analytic and biologic variation that often masks their ability to predict rates of bone turnover. Careful consideration of preanalytic testing conditions and clinical context of utilization can minimize these issues.

UTILITY OF BONE TURNOVER TESTING

Total bone mass reflects the balance between the activity of osteoblasts to build bone and osteoclasts to resorb bone. As a result, there has been great interest in using BTMs to predict both bone loss and responsiveness to osteoporosis treatment.

However, while there is a clear association between perimenopausal BTM levels and subsequent bone loss, the correlation between BTM levels and bone loss in elderly Caucasian women is modest. Although there may be utility in measuring BTM levels, currently the cost-effectiveness and efficacy of BTM monitoring have yet to be demonstrated in prospective randomized clinical trials. Therefore, while BTM monitoring may have utility in addressing the risk of bone loss in individual patients when these caveats are kept in mind, the use of BTMs is not currently recommended as a systematic public health measure to identify patients at risk of rapid bone loss.

The use of BTMs to assess fracture risk should be considered separately from their ability to predict bone loss, as many other factors besides the total amount of bone—including bone architecture and materials properties—also contribute to fracture risk. Increased resorptive BTM levels do appear to correlate with subsequent fracture risk for up to 5 years after measurement. However, anabolic BTM levels do not appear to show this same ability to predict fracture, perhaps reflecting that



Bone turnover markers can display substantial analytic and biologic variation that masks their ability to predict rates of bone turnover.

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postmenopausal osteoporosis is often a resorption-driven process.

The risk associated with elevated BTM levels can be further modified by other conditions, and BTMs are known to notably underestimate fracture risk in patients with diabetes.

Osteoporosis is a known risk factor for orthopaedic fixation failure; therefore, optimizing bone quality prior to surgery is imperative. The preoperative assessment is an opportune time to screen for osteopenia and osteoporosis and subsequently provide the appropriate intervention. BTMs can be assessed preoperatively to initiate osteoporosis therapy if needed to improve postsurgical outcomes. Patients can be monitored for bone health improvement and optimized prior to undergoing surgery. Postoperatively, recent evidence suggests that BTMs may be useful for monitoring successful fusion.

In summary, while BTM levels can be linked to both future bone loss and fracture risk, these associations may not be clear or strong enough to recommend that all patients get BTM measurement to predict future bone loss or fracture risk. However, BTMs may still be highly useful for this purpose in individual patients, especially in patients with other secondary diseases driving bone loss, including hyperparathyroidism, hyperthyroidism, vitamin D deficiency, and certain blood cancers.

Interestingly, beyond just predicting future bone health, increases in bone turnover markers are associated with all-cause and cancer mortality in older men, recent studies suggest. The underlying mechanism responsible for this link is unclear and must be uncovered before this observation can be used in clinical practice.

USE OF BTMS TO MONITOR OSTEOPOROSIS THERAPY

A clearer case can be made for the

use of BTMs to monitor osteoporosis therapy, than for using them to monitor bone loss or fracture risk. Both baseline BTM levels and BTM levels shortly after initiating therapy generally predict changes in bone mass.

For example, PINP levels at baseline or after therapy initiation predict responses to the bone anabolic agent teriparatide. Similarly, suppression of bone resorption markers seen after treatment with antiresorptive drugs such as bisphosphonates or denosumab correlates with later changes in bone mass. Moreover, BTM levels correlate with the degree of reduction in fracture risk in response to these therapies. Therefore, assessing BTMs may aid clinical decision-making in patients for whom there is particular concern regarding the response to osteoporosis treatment.

STRATEGIES TO MINIMIZE VARIATION IN BONE TURNOVER MARKER TESTING

Nearly all BTMs display marked diurnal variation, peaking between midnight and 8 a.m. and reaching a trough in the early afternoon. BTMs also drop after meals due to the direct effect of gastrointestinal hormones on bone resorption. There is also seasonal variation of BTMs, with BTMs typically peaking in the early winter months, especially in premenopausal women. For this reason, BTMs are strongly recommended to be measured in a morning fasting draw. BTMs can also vary with menstrual cycle, being highest in the mid- to late-follicular phase and lowest during the mid-luteal phase, leading to a preference to sample during the follicular phase in premenopausal women when feasible.

Many bone turnover markers are cleared renally, with the notable exception of tartrate resistant acid phosphatase 5b (TRAP5b). They are therefore not

recommended for testing in the setting of renal failure. There are also potentially concerns that collagen remodeling occurring in the setting of fibrotic or tissue remodeling diseases of other tissues, such as systemic sclerosis, congestive heart failure, or dilated cardiomyopathy may impact BTM levels and mask their ability to reflect bone metabolism.

In addition to sources of preanalytic variance, other demographic factors strongly affect BTMs. BTMs are generally high in growing children, reflecting the active ongoing skeletal growth and modeling, that often reaches a peak during puberty. Men in their 20s and 30s generally display higher BTM levels than young women, likely due to the greater total skeletal mass present undergoing remodeling. However, this reverses later in life as postmenopausal women experience an increase in resorptive BTMs because of ongoing bone loss.

For most other analytes, laboratories typically construct reference ranges using patient groups closely matched for demographics, especially age and sex. In the case of BTMs, this poses a particular challenge because many patients tested are older, with a particular emphasis on postmenopausal women. However, bone dynamics in older women, even those otherwise considered healthy, may not be conducive to maintenance of healthy bone mass and, therefore, the usual ideal practice of comparing patient results to an age-matched reference range may be falsely reassuring.

A VALUABLE TOOL

While bone turnover markers are subject to numerous preanalytic factors that complicate their interpretation, they can provide useful information to guide clinical decision-making for risk assessment or management of osteoporosis or other diseases of skeletal fragility. While there is not currently evidence supporting routine BTM testing for all postmenopausal women or osteoporosis patients, BTMs remain a valuable tool when testing is carefully applied. ■

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Recent studies suggest that an increase in bone turnover markers is associate with all-cause and cancer morality in older men.



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Gender Inclusion

AS AN ESSENTIAL PREANALYTICAL PROCESS

BY DINA GREENE, PHD, DABCC, FAACC, AND MATTHEW D. KRASOWSKI, MD, PHD

Humans are socialized to interact with people differently based on their gender expression—and those preconceptions also impact individuals' experiences within the healthcare system. Clinical professionals must work not only to address their own biases regarding patients' gender identities, but also to ensure they are providing appropriate gender- and sex-specific medical care.

For this reason, AACC and the College of American Pathologists recently sponsored a taskforce of physicians and laboratory scientists to develop guidance for gender inclusion within the practices of laboratory medicine and pathology. The taskforce will outline tangible steps that laboratories can take to reduce discrimination and improve the healthcare experience for transgender people.

As we await this forthcoming guidance, we hope laboratory staff have already begun to embrace gender diversity, beginning when patients first present to the lab.

UNDERSTANDING IDENTITY, GENDER, AND SEX

Humans define themselves and others with identities: "I am a basketball player;" "She is an artist;" "They are Mexican." Identity is defined as "the fact of being who or what a person or thing is." Often, these traits appear naturally, even as our cultural expressions are complex amalgams of nature and nurture. Gender is a function of the social, psychological, cultural, and behavioral aspects of being a man, woman, or nonbinary human. It is not a choice or a biological assignment, but rather an inherent identity that significantly contributes to a person's sense of belonging. In contrast, sex refers to the chromosomal make-up that prescribes the development of gonads and endogenous sex-hormone expression.

Cisgender people have experienced only congruence between their sex assigned at birth and their gender identity. Even so, cisgender men and women will have different medical experiences based on their sex and gender. Sex-specific medical care is important for cancer screening, fertility testing and treatment, and workups for other anatomical-based conditions. Gender-specific medical care is a function of socialization and current sex-hormone composition (endogenous and/or exogenous).

Some well-recognized healthcare disparities relate to sex and gender biases within medicine.

Gender impacts how likely a person is to receive standard-of-care cardiology services, for example. For many years, clinicians were taught that women with acute coronary syndromes present in an "atypical" or clinically abstract manner, potentially leading to delayed diagnoses and treatment. In fact, men and women simply present

This article is part of a special collection on health equity, diversity, and inclusion in laboratory medicine.
Guest Editor: Dina Greene, PhD, DABCC, FAACC, LetsGetChecked and University of Washington, Seattle.



**Creating an inclusive
environment for
every patient is part
of high-quality
care.**



with different signs and symptoms. In addition, we now know that high-sensitivity troponin is an excellent biomarker for acute coronary syndrome in women. But historic teaching patterns and unconscious biases may lead to people who present as masculine being triaged differently than those who present as feminine.

IMPLICATIONS FOR LAB MEDICINE

In laboratory medicine and pathology, we often are tasked with generalizing populations. Our reference intervals are derived using practical approaches, such as defining “normal” as the middle 95% of the population distribution. For tests with sex-specific distributions, we derive and use separate reference intervals for men and women. When electronic medical records (EMRs) indicate

man with natal reproductive organs will. For the latter example, the EMR may indicate that the patient is male. Ensuring that laboratory information systems (LISs) do not cancel tests based on anatomical assumptions is important for providing equitable care.

Similarly, prostate-specific antigen (PSA) and human chorionic gonadotropin (hCG) are often thought to apply only to men and women, respectively. However, if a transgender woman has a PSA result of 100 ng/mL, this result should be flagged, irrespective of the sex/gender marker that the lab receives. Because the lack of standardized interfaces between the EMR and LIS may prohibit a laboratory from identifying a patient’s assigned sex, results for critical tests that fall outside of the reference interval should always be flagged.

Some tests have sex-specific reference intervals that are driven by endogenous hormone concentration. Testosterone stimulates erythropoiesis, for example; therefore, there are clearly observable differences in hemoglobin and hematocrit levels between boys and girls that begin at puberty and continue throughout adulthood. That means that transgender men on stable testosterone hormone therapy will have hematology results similar to cisgender men, whereas transgender women on stable estradiol therapy will have values similar to cisgender women.

Other tests are less straightforward. The concentration of creatinine, a byproduct of muscle mass, tends to be higher in men than women. While testosterone contributes to muscle mass, lifestyle factors can also play a large role. For instance, a transgender man who lifts weights and takes testosterone during gender transition has multiple factors that may influence creatinine relative to baseline. Selecting appropriate reference intervals for creatinine in patients receiving gender-affirming therapy, and more importantly, determining which sex-specific variable to use in eGFR equations, is a topic of current discussion between the fields of clinical chemistry and nephrology.

Even though laboratorians generally work “behind the scenes,” there are many ways we can improve inclusion of gender diversity within clinical practice. Normalizing that sex and gender are different can go a long way towards creating an accepting clinic experience. It’s also important to keep in mind that the pre-analytic process begins when a patient presents to the lab. Creating an inclusive environment for everyone means embracing quality from the start. ■

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Developing a simple, standardized approach for identifying sex and gender in our electronic systems is fundamental to improving care.

that a person is male or female, the applicable reference interval is triggered in the system. However, whether an EMR differentiates between sex and gender is inconsistent, varying among and within institutions.

Developing a simple, standardized approach for identifying sex and gender in our electronic systems is fundamental to improving care and respecting people of all genders. Sex fields should be used as needed for organ inventory, while gender fields should direct healthcare professionals on the appropriate pronouns to use for patients at the time of sample collection. Similarly, reference intervals and pathology reports should include gender neutral language. Using patients’ preferred names whenever interacting with them benefits everyone, including those who are gender diverse.

Anatomy often dictates the type of screening a person needs. For example, cervical cancer screening applies only to people with a cervix. A cisgender woman who has undergone a complete hysterectomy will no longer qualify for regular screening, but a transgender

CURRENT DISCUSSIONS, FUTURE POSSIBILITIES

Electronic medical records and lab information systems increasingly include functionality to record a patient’s sex assigned at birth, gender identity, and sexual orientation in addition to legal sex. While there is still wide variability across products, the availability of these sexual orientation/gender identity (SOGI) fields opens possibilities for more sophisticated approaches for flagging and interpreting test results.

For instance, a clinician’s interpretive comment about changes to a patient’s hemoglobin/hematocrit that are possibly due to gender-affirming hormones could be appended to the test results of a person identifying as transgender or nonbinary in the gender identity field. For anatomic pathologists, SOGI fields within the EMR and LIS could allow these professionals to quickly recognize that a specimen which seems discordant with a patient’s legal sex could be explained by the fact that the patient has had gender-affirming hormones and/or surgery.



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BY KEVIN FOLEY, PHD, DABCC, MT, SC(ASCP)

Putting Your Electronic Medical Record to Work for Lab Stewardship

The time to deal with duplicate or nonbeneficial lab orders is at the point of order entry. Once an order is placed and pending in the lab information system (LIS), it is difficult to undo, cancel, or modify. Thus, the electronic medical record (EMR) has great utility in offering real-time decision support and guidance on lab testing for ordering providers.

Our laboratory system has been using the EMR to enhance lab stewardship for several years. One key to our success is having a physician-led department of medical informatics that works closely with our LIS analyst team. Together they review, build, monitor, and update decision support tools that we implemented within our EMR, Epic.

It may feel like we laboratorians spend more time working within the constraints of our EMR and LIS than the systems spend benefiting our workflows. But it doesn't always have to be that way. Here are four ways we put our EMR to work for our lab stewardship program.

The Answer Is “No”

The most direct measure to tackle unneeded lab testing is a simple ban. Over the years, we have banned, or put “hard stops,” on several tests. Some examples are high-sensitivity C-reactive protein (hsCRP), serum homocysteine, and H. Pylori IgG tests. Instead of simply deleting these order records in Epic, it is preferable to keep an order for a period of time, and have it trigger an alert that informs the clinician who ordered the test why it is no longer available. Figure 1 shows an example.

In our system, any lab test, including these banned tests, could still be ordered as a miscellaneous lab test. However, if ordered via this route it would be reviewed and likely not allowed since the test would not be on our approved test formulary.

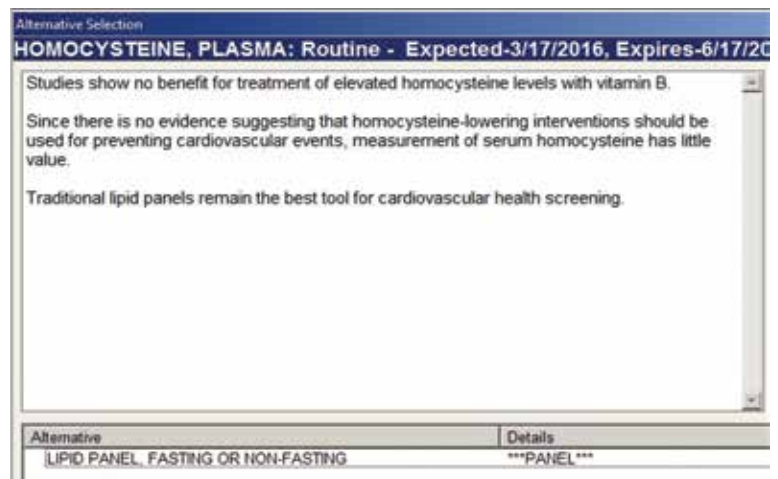
Reflex Rejects

Creating intelligent reflex options is more difficult, but it is a very useful and clinician-friendly way to reduce wasteful testing. In 2015, Oregon legalized cannabis use. We soon realized that despite THC being legal, we still were confirming the presence of THC in every positive urine drug screen. When a patient admits to using THC, and a positive THC screen result is expected, it does not make sense to send the sample for confirmatory

mass spectrometry testing. For this reason, we removed the reflex for THC confirmation from our urine drug screen panels. However, we did create a special urine screen that preserved the THC confirmation reflex but limited this option only to the addiction medicine department. They argued that confirmatory testing was still useful given their unique addiction counseling context.

Another example of adjusting orders to reduce waste was implementing a question-based algorithm for gastroenteritis. We created an algorithm that asks four questions at the time of order entry to determine which test is performed. Based on the answers to questions such as “Has the patient traveled outside the U.S. in the last 30 days?” and “Has the patient been hospitalized

F1 A “hard stop” alert in the EMR for a plasma homocysteine order. Note that the only available alternative is a lipid panel.



or taken antibiotics in the last 30 days?” as well as questions about exposure to shellfish and untreated water, the lab directs the specimen for either *C. difficile* testing, viral PCR, bacterial PCR, extended bacterial PCR, or parasite PCR testing.

Dealing with Duplicates

Stopping duplicate orders is the Holy Grail of lab stewardship. Epic has a robust duplicate order checking tool that we use for high-volume tests such as complete blood counts (CBC) and the components of a basic metabolic panel. The degree of overrides for these duplicate alerts varies depending on location and environment (such as inpatient versus outpatient settings, and higher versus lower acuity patient demographics). But one can expect to see at least a 20–40% reduction in duplicate orders when duplicate alerts are enabled.

Our lab recently built an alert to curb ordering of differentials. While the CBC itself is commonly over-ordered, we also have an order for a CBC with differential that is over-used. The CBC with differential often requires manual review, which slows down the lab and generates unnecessary charges for the patient. In most cases a simple CBC will suffice. We

created an alert that not only informs the provider when the last CBC was ordered, but also automatically changes the next order from a CBC with differential to a simple CBC.

Automatic Notifications

The EMR can also be used to notify ordering clinicians (and the lab), of test interferences. We use an alert in our EMR that fires a notice to the provider when a patient has a serum protein electrophoresis test and has an active prescription for the drug daratumumab. Daratumumab is a monoclonal therapeutic that can present as a band on electrophoresis gels, confounding the measurement of existing monoclonal proteins in gammopathy patients.

We also created an alert for when a patient has their creatinine measured with an Abbott iStat device and the patient has an active prescription for hydroxyurea. Hydroxyurea has a known interference with the iStat creatinine method and will give a falsely elevated result when present in blood or plasma. Although iStats are only used in a few urgent care settings within our system, our EMR is programmed to reconcile the testing method with the patient’s prescriptions and alert the provider and the

lab. A message stating that the testing could not proceed at the desired location and needs to be sent to our central lab fires immediately at the time of order entry.

Labs also can add simple checks in the EMR to help ensure the right specimens are collected. We recently included a new prompt when ordering multiple sclerosis oligoclonal band testing. Now, a radio button must be clicked stating that it is a serum specimen. We implemented this after finding that several cerebrospinal fluid samples were sent without the accompanying requisite serum sample.

How to Avoid Too Many Alerts

Lab utilization and stewardship are no longer novel concepts. Over the years, our LIS and Informatics teams have built more than one hundred alerts to guide laboratory test ordering. Now we must be diligent about reviewing the alerts that were put into place at the start of our lab utilization program.

Some of these alerts have now been firing for more than 10 years. One such example is vitamin D. We had an alert aimed at reducing unneeded vitamin D orders. The alert worked well initially and solved the problem we were trying to fix. But alert fatigue happens quickly, and if the alert has served its purpose and is no longer being heeded, it needs to be retired, so we removed it.

Many other useful tips for optimizing (or eradicating) alerts to deal with alert fatigue are available (1). But a good rule of thumb is that a successful alert should lead to an order change at least a third of the time. Moreover, the lab stewardship team should measure the efficacy of alerts annually. ■

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Reference

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F2 A simple radio (option) button can be used as a “hard-stop” to alert the provider to handle the specimen or collect a specimen in a specific way.

MULTIPLE SCLEROSIS PANEL, OLIGOCLONAL BANDS, CSF RIG SYNTHESIS RATE + INDEX

Priority: Routine STAT

Status: Normal Standing Future

Expected Date: 1/5/2023 Today Tomorrow 1 Week 2 Weeks 1 Month 2 Months 3 Months 4 Months 1 Year Approve

Expires: 4/7/2023 1 Month 2 Months 3 Months 4 Months 1 Year

Specimen Source: TSSUE, OTHER, NOT IN DL...

Quantity: 1 The maximum orderable quantity for this procedure is 300

Comments:

Please collect a serum sample when collecting the CSF. Collection of the serum sample must be a plain red top tube and collected at same time as collection of CSF.

Please acknowledge collection of the serum sample. NO YES by RN or Clinician

(For support staff only) Verbal, protocol or written pre-approval (non-medication)?

PROTOCOL ORDER VERBAL ORDER WRITTEN ORDER

Fee Number:

Release to patient:

Additional Order Details

LABORATORY STEWARDSHIP FOCUS



AN INTERVIEW WITH MIKE ASTION, MD, PHD

Medical Necessity Policies: Creating Opportunities for Better Test Utilization and Fair Payment

Mike Astion, MD, PhD, has been working in collaboration with insurers since he worked at the University of Washington in 2007. He brought that experience with him to Seattle Children's Hospital, which launched PLUGS in 2013. The partnership includes analyzing laboratory insurance claims, performing evidence reviews, creating or reviewing medical necessity policies, advocating for specific CPT coding over nonspecific codes, improving preauthorization for genetic tests, and explaining successful lab-payer collaborations through webinars and publications (Table 1). Astion, who cofounded the PLUGS program, is medical director of laboratories at Seattle Children's Hospital and professor of laboratory medicine and pathology at the University of Washington in Seattle.

How do the perspectives of payers, labs, and patients differ?
Payers focus on restricting payment to medically necessary tests, while clinical labs want fair payment for those tests. Patients want to avoid financial toxicity. As outlined in a recent article in CLN (October 2021), insurers and labs have multiple ways to reduce financial toxicity, recent federal and state laws and initiatives are addressing this issue.

What is meant by medically necessary, and how does cost play a role?
Medical necessity refers to a test needed to diagnose or manage a health condition. Medical necessity policies determine clinical criteria for a lab test to be a covered benefit. In general,

payers base their definitions on peer-reviewed evidence. Since that is often lacking, they rely on guidelines based on research evidence and expert consensus. Cost effectiveness is included in some medical necessity policies. More commonly, costs are unaddressed, and evidence is primary. Practically, costs matter! If genetic tests cost a dollar, insurance companies would not regulate them through administrative and medical necessity policies. All payers prioritize policymaking where money is wasted. Since waste is abundant, payers are rewarded for creating policies. Importantly, administrative policies add another layer: They describe the requirements that the provider and patient must fulfill to access the medical necessity policy. This includes

medical documentation as well as submitting an accurate, correctly coded claim. For certain genetic and other expensive tests, there are often additional administrative requirements related to preauthorization.

What are the economics of medical policy writing?
An example illustrates the financial return. If a payer spends \$1 million annually on vitamin D testing and 20% is unnecessary, then the payer saves \$200,000 through a vitamin D policy that denies unnecessary testing. The payer's cost includes creating, maintaining, automating the policy in their claims system, and resolving patient grievances. This costs much less than \$200,000. Many tests are similar to this example. Therefore, payers and

LABORATORY
STEWARDSHIP
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T1 Collaboration between academic laboratory medicine group and the insurance industry

Project	Examples
Claims analysis to find fraud, waste, abuse	<ul style="list-style-type: none"> Excessive IgG allergy testing Overuse of Vitamin D testing Overly large test panels in multiple domains including cardiovascular disease risk, thyroid testing, and nutrition
Evidence reviews	<ul style="list-style-type: none"> Review of Proprietary Laboratory Analysis (PLA) Codes
Reviewing medical necessity policies	<ul style="list-style-type: none"> Review specific payer policies (e.g., for specific genetic tests)
Creating new medical necessity policies freely available to insurers	<ul style="list-style-type: none"> Whole exome/whole genome policy Mitochondrial disease testing
Specific CPT coding	<ul style="list-style-type: none"> Specific CPT codes for celiac disease test

third-party benefits managers actively manage testing.

How does this affect patients?

Policies are long and difficult to access and understand. There is no insurance industry standard on policy access, contents, and size.

It is challenging even to locate policies. Tests are rarely listed by name. For example, a specific tumor marker test may be inside a larger tumor marker policy, or in a genetic testing policy, but not searchable by the specific test name. Therefore, access often involves receiving help from the payer.

Moreover, policies contain medical vocabulary, so the patient requires help unless they have a medical education. Additionally, policies often are nonspecific about how scientific evidence links to coverage criteria.

Policies lack a simple summary, and their length is a challenge on its own. For example, a search of “tumor marker policy” for one insurer has >1000 references, covers 169 tumor markers if inclusion criteria are met, and denies >100 markers always. If there is potential coverage, it is hard to locate the pertinent policy section. In the pertinent section, it is difficult to discern if criteria are met.

How does PLUGS approach writing and reviewing medical necessity policies?

There are two aspects to the PLUGS approach. First, we provide guardrails against abuse without unduly blocking medical practice. Second, we allow wider guardrails for patients with severe illness.

Why not just require high-grade evidence? Because the US is not a single payer system with one interpretation of evidence. It is not realistic for physicians and labs to conform to differing views of multiple payers. Each payer cannot force a lab to practice that payer’s version of evidence-based medicine—a lab cannot dance simultaneously to that many kinds of music.

A guardrails approach is an answer to this problem. If insurers take a more generous approach to the evidence, and focus on guardrails that block abuse, then mainstream labs can succeed. Using an automobile analogy: a lab driving down the middle will usually not notice variations in guardrails.

In addition, broader guardrails should be given to specialists caring for severely ill patients. Patients with multiple medical conditions fit poorly into the categories covered by evidence. While it is never appropriate for these patients to experience laboratory quackery, it is fine for physicians to order a few more tests and monitor more frequently.

What is most challenging about developing medical necessity policies?

Guidelines and other expert opinions on utilization often are based on weaker grades of evidence, including consensus. We specifically try to avoid denying a test based on a lack of high-grade evidence when the standard of care is to provide that test.

This arises with older tests and panels used as markers of organ damage. For example, it is difficult to find guidelines on the frequency of monitoring patients who have diseases affecting multiple organs. When patients are extremely ill, the standard of care may require frequent monitoring with batteries of tests, but the peer-reviewed evidence for intense monitoring is limited.

Can you further compare the standard of care with evidence-based medicine?

This is a challenging aspect of insurance. The standard of care and evidence-based medicine are related but not identical. The standard of care refers to the expectations of a well-educated clinician to diagnose, treat, and monitor a condition. The standard of care is established through consensus among experts and is influenced by guidelines from professional and governmental organizations. Ideally, the standard is based on robust evidence, but often it is not. The standard of care is a clinical expectation, and violations are foundational to malpractice lawsuits. Therefore, insurance policies should support the standard of care.

Evidence-based medicine (EBM) uses scientific evidence to guide clinical decisions. For insurers, EBM involves evaluating research evidence to decide coverage. Insurers differ on the evidence level required for

coverage, leading to coverage differences between payers.

PLUGS has a freely available exome/genome policy. With that policy, you did not begin with a wide guardrails approach. Why?

There are nuances to policy strategy. Our biggest success is the exome policy, which is now an exome/genome policy. When we started several years ago, insurers did not cover exomes and lacked a policy. Exome costs were thousands of dollars higher than common tests. Payers heavily considered cost. We realized we would be more successful starting with a policy with narrower inclusion criteria than that favored by our lab and PLUGS members. We focused on effectiveness rather than righteousness. Therefore, the approach to achieving coverage was to start slow and land something with a payer, then broaden the inclusion criteria as evidence strengthened. We were correct, and versions of our exome/genome policy now cover tens of millions of lives.

How do tests that begin as uncovered eventually become covered?

Insurers change from uncovered to covered because of four major factors: accumulation of independent evidence; new, favorable opinion in a national guideline; state or federal legislation; and patient grievances. Insurers dislike grievances because they represent dissatisfaction among customers.

Medical necessity policies are reviewed annually, offering a chance for a coverage change. If a national guideline newly supports coverage, it can still be a 3- to 12-month delay to incorporate into policy and program claims systems. During that delay, the patient is uncovered and pays the bill.

What is your future hope for medical necessity policies?

The hope is that there are more policies, and that they are based on guardrails to block abuse. They are easily accessible, short, and have a comprehensible summary. The policies are updated twice annually. The policies that produce the most denials would list the specific reason for denial. ■

Regulatory Roundup

Predictive Radiation Therapy Test Gets Medicare Advanced Diagnostic Laboratory Test Status

Laguna Hills, California-based Prelude Corporation (PreludeDx) recently announced that the Centers for Medicare & Medicaid Services (CMS) gave its DCISionRT test Advanced Diagnostic Laboratory Test (ADLT) status, a category reserved for innovative products with Medicare coverage that provide new clinical diagnostic information that cannot be obtained from any other test or combination of tests, among other criteria.

DCISionRT is the only risk assessment test for patients with ductal carcinoma in situ (DCIS) that predicts radiation therapy benefit, according to

PreludeDx. The test combines protein expression from seven biomarkers and four clinicopathologic factors and uses a nonlinear algorithm to account for multiple interactions between individual factors to better interpret this complex biological information.

DCISionRT's reporting software provides a woman's recurrence risk after breast conserving surgery alone and with the addition of radiation therapy. This new information may help patients and their physicians make more informed treatment decisions, the company said.



COLLECTION DEVICE FOR SARS-COV-2 TESTING SAMPLES RECEIVES FDA CLEARANCE

The FDA has granted 510(k) clearance for Pleasanton, California-based Mawi DNA's iSWAB-Respiratory Tract Sample Collection Media-Extraction Less (iSWAB-RC-EL) device, the company announced.

The device is intended for stabilization and inactivation of human upper respiratory and saliva specimens suspected of containing SARS-CoV-2. It can be used for collection, transport, and storage at ambient temperature.

The device also enables surveillance testing of SARS-CoV-2 and

its variants in any clinical setting. Currently used for population-scale sampling to mitigate the impact of the virus's spread, iSWAB-RC-EL enables hospital and clinical lab personnel to skip the RNA extraction step in the PCR testing protocol. The biosampling device also offers a nontoxic formulation that inactivates viruses to decrease potential spread and exposure, especially among lab personnel processing samples.

FDA CLEARS TEST FOR CYP2C19 VARIATIONS

Ottawa, Canada-based Genomadix recently announced it has received FDA 510(k) clearance

for its Genomadix Cube CYP2C19 System (Cube CYP2C19 Test), an automated sample-to-result PCR test.

The Cube CYP2C19 Test helps clinicians to determine therapeutic strategy for drugs metabolized by the CYP450 2C19 genetic pathway. The Cube CYP2C19 Test identifies the CYP2C19 *2, *3, and *17 variations, if present, directly from a noninvasive buccal swab in 1 hour.

Company officials said the Genomadix Cube CYP2C19 System would help physicians to make informed decisions on selecting drugs for precision medicine, such as antiplatelet therapy in stroke and for cardiology patients.

The test runs on the Genomadix Cube, a platform capable of performing

tests for genetic, infectious disease, and environmental targets on a sample-to-result platform. The system's portable size, ease of use, and on-demand processing capability enables users to generate time-critical results in a near-patient setting, according to the company.

BREAST CANCER TEST GETS CE MARK

Calgary, Alberta-based Syantra recently announced it obtained the CE mark for its Syantra DX Breast Cancer Test, a blood test that detects an active breast cancer signature.

The CE mark allows Syantra to market its test in the European Union and other countries that recognize the designation.

The test evaluates gene expression patterns of 12 unique biomarkers through a quantitative PCR process that uses proprietary software including machine learning-derived algorithms.

Company officials said the test may help improve detection in high-risk women, especially those with genetic predisposition to breast cancer, dense breasts, or diverse ethnic backgrounds. For these women, standard screening mammogram may be inadequate.

COVID-19 TEST GETS EMERGENCY USE AUTHORIZATION (EUA)

The FDA recently granted EUA to the MedArbor Diagnostics SARS-CoV-2 Assay.

The test is a real-time PCR test intended for the qualitative detection of nucleic acid from SARS-CoV-2 in nasopharyngeal swab, oropharyngeal swab, anterior nasal swab, mid-turbinate nasal swab, nasopharyngeal wash/aspirate, and nasal aspirate specimens from individuals suspected of COVID-19 by their healthcare provider, according to an FDA fact sheet. The test should be ordered by healthcare providers, the fact sheet says.

The test's performance, based on evaluation of a limited number of clinical specimens, has not been established in all circulating variants. Performance at the time of testing may vary depending on the variants circulating, including newly emerging strains of SARSCoV-2 and their prevalence, which change over time, the FDA adds.

LUNG CANCER PCR COMPANION DIAGNOSTIC APPROVED IN JAPAN

China-based Riken Genesis Co., Ltd. (AmoyDx), and Precision Medicine Asia Co., Ltd. (PREMIA) recently announced Japanese Ministry of Health, Labor, and Welfare (MHLW) approval of their AmoyD® Pan Lung Cancer PCR Panel (AmoyDx PLC Panel) as a companion diagnostic for RET fusion-positive non-small cell lung cancer (NSCLC), for seliperatinib capsules 40 mg and 80 mg.

The AmoyDx PLC Panel is based on PCR technology. It simultaneously can evaluate the presence of activation alterations in 11 driver genes when all genes on the panel are approved as companion diagnostics.

The AmoyDx PLC Panel has received approval for the identification of activating alterations in seven driver genes for 12 associated targeted therapies in NSCLC.

With its high sensitivity and short turnaround time, the AmoyDx PLC Panel is expected to be an important clinical diagnostic in guiding treatment opportunities for NSCLC patients, the companies said.

COVID-19 AND FLU COMBO TEST APPROVED IN AUSTRALIA

Emerlyville, California-based Lucira Health, Inc. recently announced that its Lucira COVID-19 & Flu Home Test has been included in the Australian Register of Therapeutic Goods (ARTG) for use by healthcare professionals in a point-of-care setting, during the southern hemisphere's flu season.

The Lucira COVID-19 & Flu Home Test is a molecular test that has demonstrated similar performance for SARS-CoV-2 and influenza compared to highly sensitive lab-based PCR tests in clinical trials. The easy-to-use, all-in-one combination test delivers results in 30 minutes or less from one shallow nasal swab.

Company officials said they believe that the combination test's speed and accuracy will help Australian patients access treatment earlier in the course of the infection.



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Oxford Nanopore and bioMérieux Partner on Infectious Diseases

Oxford Nanopore and bioMérieux announced that they have teamed up to explore bringing nanopore sequencing to the infectious disease diagnostics market.

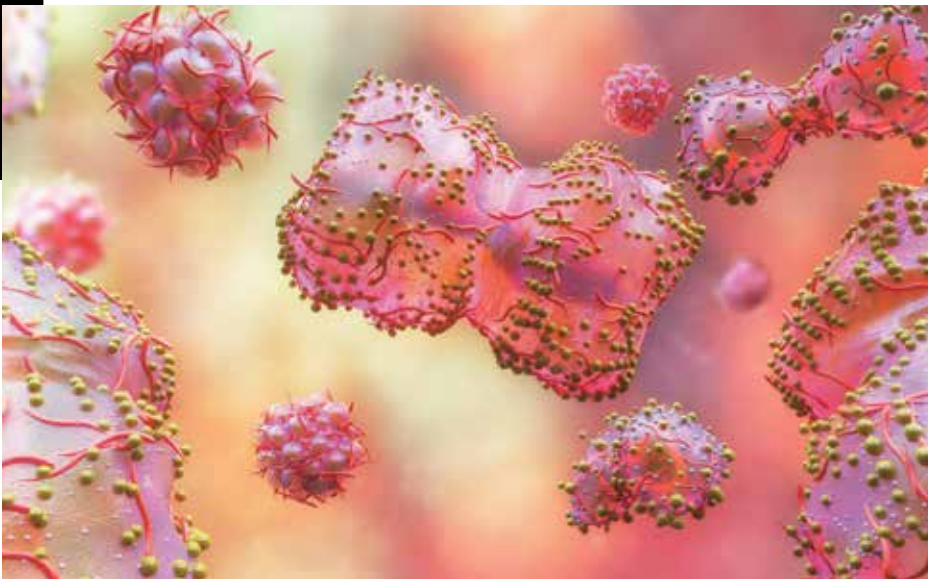
The companies aim to advance patient care by providing access to nanopore-based clinical research and in vitro diagnostic solutions.

Initial areas of collaboration will include a test for determining antibiotic resistance of tuberculosis, an assay to identify pathogens in normally sterile clinical samples, and validating Oxford Nanopore's sequencing platform with the bioMérieux Episeq CS application for rapid infection outbreak

monitoring in patient-care settings.

Oxford Nanopore officials said the partnership will allow their company to "offer rapid and accurate identification of pathogens and associated antimicrobial resistance, at scale, and better equip the specialists for whom speed and access to comprehensive data is key."

bioMérieux officials noted that the partnership allows their company to explore new technologies that hold promise to improve diagnostics and patient care, such as sequencing.



DEVYSER DIAGNOSTICS, THERMO FISHER TARGET POST-TRANSPLANT MARKET

An agreement between Devyser Diagnostics AB and Thermo Fisher Scientific gives Thermo Fisher exclusive rights to commercialize, under combined brands, Devyser's post-transplant portfolio of next-generation sequencing (NGS) products in North America and Europe, the companies announced.

Devyser retains the rights to commercialize its post-transplant products in the U.S. via its own service laboratory in Sweden, as a service to U.S. laboratories. Devyser will also continue to manufacture all products.

Devyser officials said the agreement will give clinical labs, clinicians, and patients in the U.S., Canada, and Europe broad and fast access to Devyser's NGS-based products for post-transplant monitoring. The agreement also serves as a quality stamp for the company and its products.

Thermo Fisher's position in the U.S. and European markets and commercial infrastructure and resources benefit Devyser, while Devyser's sensitive assays and streamlined work process give labs the ability to provide faster results.

The company's post-transplant products are pending In Vitro Diagnostic Medical Devices regulation certification for the European market, Devyser officials added.

Thermo Fisher officials said Devyser's post-transplant NGS offerings are unique and complement their existing, One Lambda-branded products and support better patient outcomes.

The transplantation market is growing rapidly due to a growing older population and higher incidence of relevant diseases. There is a shortage of organs globally and many patients are currently on waiting lists for new organs, the companies noted.

QUEST DIAGNOSTICS TO ACQUIRE HAYSTACK ONCOLOGY

Quest Diagnostics and Haystack Oncology recently

announced an agreement for Quest to acquire Haystack.

Founded in 2021, Haystack has developed a circulating tumor DNA (ctDNA)-based technology specifically for minimal residual disease detection (MRD), after 20 years of research and development. MRD tests detect ctDNA in the bloodstream of patients following cancer surgery and treatment.

Published research demonstrated an earlier version of the Haystack technology's ability to better identify patients with residual disease for adjuvant chemotherapy after surgery for stage II colon cancer, thereby reducing chemotherapy use in the overall patient population without compromising recurrence-free survival.

When the acquisition closes, Quest expects to adapt the MRD test developed at Haystack as the basis for new clinical lab services available beginning in 2024. Development efforts will focus initially on MRD tests for colorectal, breast, and lung cancers.

Quest Diagnostics officials said that Haystack's liquid biopsy technology, combined with Quest's strengths in screening, pathology, and sequencing, will leverage Quest's expertise and scale in oncology, genomics, and pathology and position Quest to lead in the fast-growing MRD category.

SPIN-OFF OFFERS POINT-OF-CARE PCR TEST

Curative recently announced the spin-off of Sensible Diagnostics, which aims to commercialize a point-of-care PCR testing platform.

Its Sensible PCR platform is designed to support Curative's legacy next-generation testing operations as an easy drop-in upgrade for current point-of-care testing workflows. Results are ready in 10 minutes, according to the companies.

With prices that are competitive with lateral flow antigen testing and a design that requires fewer process steps, Sensible Diagnostics' platform is setting out

"to make lateral flow immunoassay testing a thing of the past," the companies said.

They added that the platform would be launched with a respiratory test designed to extend to all types of infectious disease testing.

Sensible Diagnostics and its point-of-care testing platform came to fruition out of Curative's COVID-19 testing business.

Curative is no longer in the diagnostic testing business and is currently offering a health insurance plan in Texas.

MAYO INKS SPATIAL BIOLOGY DEAL


Alpenglow Biosciences recently announced a collaboration with Mayo Clinic to use Alpenglow's 3D spatial biology platform to accelerate drug development and advance clinical diagnostics.

Alpenglow's end-to-end 3D spatial biology solution includes patented high-throughput 3D imaging, cloud-based bioinformatics pipelines, and artificial intelligence (AI)-powered spatial analysis.

Recent research has applied Alpenglow's 3D spatial biology platform to analyze human lung cancer samples from patients treated with immunotherapy, revealing novel 3D spatial insights that the team aims to correlate with treatment response.

Alpenglow officials said that while tissue contains insights into disease processes and therapeutic mechanisms of action, slide-based pathology misses most of that information. Alpenglow's technology uncovers the missing information by digitizing entire tissues down to sub-cellular resolution and can generate insights about it with AI.

Mayo officials said they will integrate Alpenglow's 3D spatial biology platform with multiomics approaches including multiplex immunofluorescence and single-cell sequencing to predict response to therapy and patient prognosis using Mayo's biospecimen repositories.




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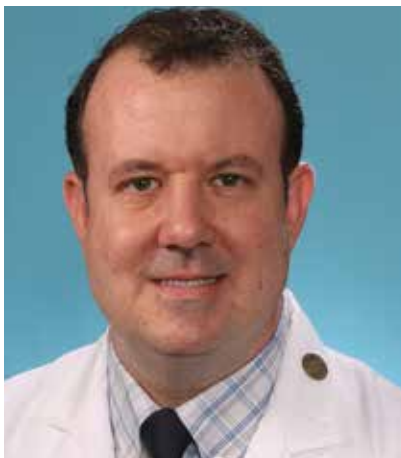
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Ask The Expert

Hyperbilirubinemia Management in Newborns



EXPERT

By Stephen Roper, PhD, DABCC

Why screen for hyperbilirubinemia?

A: Elevated concentrations of unconjugated bilirubin in blood (typically >30 mg/dL) can induce a type of permanent brain damage called kernicterus. Conditions in newborns that cause excessive bilirubin production, such as maternal antibodies to

red blood cell antigens and inherited red blood cell disorders—that cause decreased clearance of bilirubin in the blood—including low albumin and decreased activity of conjugating enzymes—are associated with an increased risk for hyperbilirubinemia and subsequent neurotoxicity. Fortunately, hyperbilirubinemia is treatable, and with prompt recognition and intervention, many cases of kernicterus can be prevented.

What guidance is available for managing this condition?

Last year, the American Academy of Pediatrics (AAP) updated its guidelines for managing hyperbilirubinemia in newborns 35 weeks of gestation or older (Pediatrics 2022;150:e2022058859). Like the previous version published in 2004, the 2022 guidelines focus on prevention, risk assessment, monitoring, and therapy for hyperbilirubinemia. In 2009, the AAP added further commentary to endorse universal pre-discharge bilirubin screening by total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) measurement (Pediatrics 2009;124:1193–8). Since then, the incidence of devastating neurologic impairments associated with unconjugated hyperbilirubinemia has decreased in major U.S. health systems.

What's new in 2022?

Recognizing the impact of previous recommendations, the 2022 guidelines reaffirm universal screening by TSB or TcB, update treatment thresholds, and clarify which risk factors dictate follow-up practices. The 2009 updates first suggested universal TSB or TcB measurement, but the 2022 guidelines go further by promoting TSB as the definitive test needed for the escalation of care. Before that, the 2004 guidelines promoted visual assessment for jaundice (skin blanching via digital pressure) every 8 hours in newborns, and immediate TSB or TcB measurement was advised if jaundice was observed before 24 hours of life (HOL) or seemed excessive for the infant's age; beyond 24 HOL, visual assessment and TcB were the main screening methods promoted.

The 2022 guidelines specify that bilirubin measurement should be

made between 24–48 HOL or prior to discharge (whichever is earlier) for infants not visibly jaundiced in the first 24 HOL. While TcB is still approved as a screening technique because it is non-invasive and reasonably accurate near decision limits, the new guidance decreases reliance on visual assessment and clarifies situations when TSB should be assessed. For example, the expert group now encourages measuring for TSB when TcB is within 3 mg/dL of age-specific phototherapy threshold or >15 mg/dL.

Another important change is related to monitoring the rate of increase between two sequential TSB or TcB measurements (when available). In the 2022 guidelines, a rise of ≥ 0.3 mg/dL in the first 24 HOL or ≥ 0.2 mg/dL after 24 HOL is considered to raise the risk for developing significant hyperbilirubinemia and should prompt additional workup to evaluate for an underlying hemolytic condition.

How will the guidelines affect pediatric labs?

Depending on local practices and the population served, the new guidelines may modestly affect TSB volumes. Newborns with a positive result on the direct antiglobulin test (DAT) will be tested more frequently, in accordance with 2022 guidelines. Thus, institutions that do not use TcB likely will see an increase in TSB requests for DAT-positive newborns. However, the overall number of TSBs will likely decrease at institutions that use TcB because the thresholds for phototherapy and exchange transfusion are slightly higher than previous nomograms. Accordingly, outpatient newborns who present for well-child visits to community pediatricians may present with more jaundice than in previous years, leading to additional referrals for TSB measurement.

Stephen Roper, PhD, DABCC, is an associate professor of pathology & immunology and pediatrics at Washington University School of Medicine and the associate director of pediatric laboratory services at St. Louis Children's Hospital in St. Louis.

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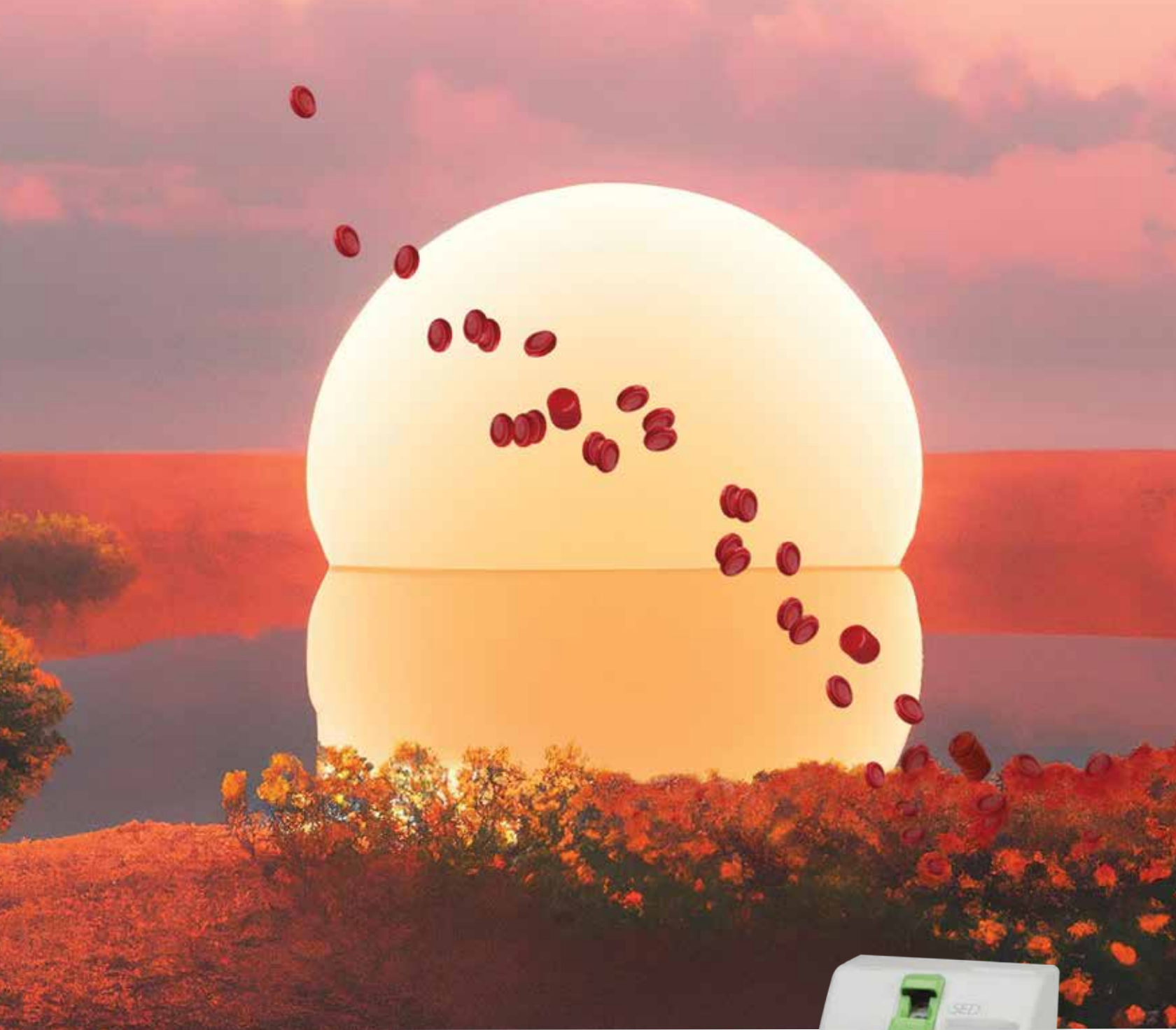
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