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The COVID-19 pandemic has been a strong force in decentralizing diagnostics, as it has driven trends ranging from a lab personnel shortage to an increase in over-the-counter (OTC) at-home testing.

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**On the cover:** Luis M Molina / iStock
AACC Urges Caution on Congress's LDT Regulation Push

AACC and 18 other stakeholders are asking Congress not to rush into a decision on regulation of laboratory developed tests (LDTs). Congressional leaders, including Senate health committee Democratic Chair Patty Murray of Washington and ranking Republican Richard Burr of North Carolina, are considering a plan to package changes to the regulatory model for LDTs into upcoming legislation on Food and Drug Administration (FDA) user fees, called the Medical Device User Fee Agreement (MDUFA). Such a move could short-circuit debate on controversial LDT legislation.

“Legislation to reauthorize MDUFA will reflect an agreement negotiated between the FDA and the medical device industry it fully regulates, entailing policy issues and considerations that have been discussed and debated before that agreement is even transmitted to Congress,” a letter from the AACC-led stakeholder group says. “These negotiations involve different stakeholders than those relevant to the reform of the regulatory oversight of LDTs...Further, MDUFA reauthorization will proceed on an expedited basis because of both the FDA’s agreement with medical device stakeholders and the necessity to reauthorize legislation before the current agreement expires.”

AACC and other groups worry that a rush to tackle LDTs as part of MDUFA would lean on an existing bill Burr has supported, the Verifying Accurate Leading-edge IVCT Development (VALID) Act of 2021. AACC’s letter called the VALID Act a “complex bill proposing dramatic modifications to current oversight mechanisms and thus has the potential to significantly impact many clinical testing laboratories, public health laboratories, healthcare providers, and patients throughout the United States.”

AACC and other stakeholders have criticized the VALID Act because it would create duplicative regulation of laboratory services under FDA. Laboratories and LDTs already are regulated under CLIA and the Centers for Medicare and Medicaid Services.
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Although most contemporary immunoassays are extremely robust and display excellent sensitivity and specificity, they are still susceptible to interferences such as heterophile or human antianimal antibodies, vitamins/supplements, medications, or other unidentified interfering substances in the patient specimen. Depending on the type of immunoassay employed (competitive vs. sandwich) and mechanism of interference, results may be falsely increased or falsely decreased. Clinical laboratorians and physicians may suspect interferences when lab test results are inconsistent with the clinical presentation or with other clinical or laboratory findings. It is critical that laboratories have the ability both to detect and rule out assay interference as a source of error.

There are standard tools the laboratory can use to troubleshoot spurious results. Common approaches used to rule out an assay interference include: 1) serial dilution of the sample to verify analyte recovery upon dilution; 2) alternate testing methods to assess comparability of results between methods; and 3) commercially available kits to pretreat samples and remove possible interferences such as antianimal or heterophile antibodies or biotin.

Although these approaches are valuable, labs must consider several caveats and limitations. Strategies for developing a robust investigation protocol and avoiding red herrings, or misleading results, are described below.

Validating Dilution Protocols to Aid in Detecting Assay Interference
Assessing recovery of the analyte upon dilution of the specimen is a powerful tool for interference investigations. A common pattern observed when an interfering substance is present is that the analyte will not recover upon initial dilution of the sample.
Upon subsequent dilutions, the analyte concentration, adjusted for dilution, will plateau once the interfering substance is sufficiently diluted to a concentration where it does not affect the assay. If the analyte does not recover appropriately upon serial dilution of the sample, an interfering substance should be suspected.

However, labs need to know the expected recovery in samples without interference to correctly interpret results. Some assays do not dilute in a linear fashion or are very sensitive to matrix effects introduced by the diluent. The diluent and dilution protocol must be validated in control samples to establish expected recovery.

It is best to adhere to the manufacturer’s recommendations for diluent when possible. Measuring the analyte concentration in the diluent is also necessary as some diluents may contain measurable analytes, which will yield misleading recovery results.

Under normal circumstances, sample dilution is reserved for situations where the analyte concentration is above the analytical measurement range (AMR). However, when using dilution as a tool for investigating interference, the lab may need to dilute samples with much lower analyte concentrations. Furthermore, dilutions at the low end of the AMR may exhibit poor recovery. Regardless of the diluent chosen, the lab should validate its use by diluting waste patient samples with a similar analyte concentration to that of the sample with suspected interference to establish expected recovery.

**Using Alternate Testing Methods to Investigate Potential Assay Interference**

The use of alternate testing methods can be useful, as assay manufacturers use different antibodies and reagents that are not usually susceptible to the same interferences. If significantly different results are obtained, an interfering substance may be present that affects one of the assays.

When interpreting results obtained from alternate methods while troubleshooting a suspected interference, labs must understand how the results would compare in patient samples with no interference present. For example, known bias between two methods needs to be accounted for. The laboratory should use method comparison data to establish expected agreement between methods and set criteria for differences that would be considered suggestive of interference. Comparable results between methods are strongly supportive evidence for ruling out interference.

**Using Commercially Available Reagents and Kits to Detect Assay Interferences**

Finally, samples can be treated with commercially available reagents to investigate the potential for interference by comparing results obtained pre- and post-treatment. For example, heterophile antibody blocking tubes or interference-specific blocking reagents from companies, such as Scantibodies or Veravas, can be used to remove heterophile antibodies or biotin from the patient sample.

However, the lab must demonstrate that the product does not affect the assay. Negative controls (waste patient samples) should be used to validate products either prior to or in conjunction with investigating the sample with suspected interference. Ideally, the lab would also confirm that the reagent removes the interference in a positive control. This is feasible for interferences such as biotin, which can be spiked into a sample to create a positive control. However, this may be impossible for heterophile or human antianimal antibody interference. Once the lab confirms that treating the sample does not affect measurement of the analyte in control patient samples, the commercial kit can be a useful troubleshooting tool for identifying antibody- or biotin-mediated interferences.

In collaboration with their clinical colleagues, laboratorians play a critical role in providing quality laboratory results and investigating questionable test results. While the lab’s troubleshooting toolbox includes valuable techniques, careful consideration must be given to the limitations surrounding these experiments in order to appropriately interpret results and draw conclusions about interfering substances. The ability to confidently rule out an assay interference and provide assurance of valid results is equally as important as being able to detect an assay interference.

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Machine Learning Improves Urine Culture Classification

Deep convolutional neural network analysis may be useful to clinical microbiology laboratories, which increasingly use automation and technical advancements to optimize testing efficiency and improve performance, according to recent research (Clin Chem 2022; doi: 10.1093/clinchem/hvab270).

Deep convolutional neural networks are a type of machine-learning algorithm used for feature extraction, object identification, image classification, and tracking. The networks combine convolution and processing components. The convolution component uses feature maps to learn different image representation, while the processing component consists of a fully connected multilayer perceptron—a type of neural network unit—that processes learned features and makes a prediction.

Labs’ decisions to classify urine cultures as insignificant growth, contamination, or growth consistent with a urinary tract infection is subjective. The researchers identified and quantitated subjective labeling of urine cultures using a deep-learning approach, BacterioSight, to improve harmonization and quality of urine culture interpretation in a clinical microbiology laboratory.

Researchers used BacterioSight on routine clinical urine cultures from two large institutions. BacterioSight displayed performance on par with standard-of-care-trained technologist interpretations. BacterioSight’s accuracy ranged from 97% when compared with standard-of-care involving a single technologist to 100% when compared with the gold standard: consensus by a group of technologists.

Training and testing performed within the same institutions performed well, giving area under the curve (AUC) of 0.98 or greater for negative and positive plates. In contrast, cross-testing on images trained on one institution’s images and tested on images from the other institution showed decreased performance, with AUC of 0.90 or greater for negative and positive plates.

The researchers said that their study can be a roadmap for how BacterioSight or other deep-learning prototypes can screen for microbial growth, flag difficult cases for review by multiple people, or verify a subset of cultures with high confidence. The results also highlight variability of image interpretation by technologists within and across institutions.

NEW EGFR EQUATION DRIVES CKD DISEASE CLASSIFICATION CHANGES

New equations used to calculate estimated glomerular filtration rate (eGFR) without consideration of race would move millions of U.S. adults into a new kidney function classification, mostly in the moderate stages of chronic kidney disease (CKD) (JAMA Netw Open 2022; doi: 10.1001/jamanetworkopen.2022.0460).

In the cross-sectional study, researchers used data from the U.S. National Health and Nutrition Examination Survey (NHANES 2011–2018) to compare estimates of CKD severity using the old and new eGFR formulas, with a focus on disease stage and the CKD-related complications anemia, acidosis, hyperphosphatemia, and hypertension.

Using the new formula, about 5.5 million adults were reclassified, researchers found. About 1 million
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Ionized Magnesium (Mg²⁺), not Total Magnesium (tMg), is the only physiologically active form of magnesium. Magnesium bound to protein, or chelated to phosphate, citrate, sulfate, or carbonate is inactive.

tMg is an unreliable substitute for Mg²⁺. Mg²⁺ may be abnormal while tMg is normal, and vice versa.¹,²

Mg²⁺ and Ca²⁺ can now be measured in the lab or at the point of care to provide a complete electrolyte analysis. Na⁺, K⁺, Ca²⁺, Mg²⁺, Cl⁻, HCO₃⁻

If you are measuring K⁺ and Ca²⁺, you should also be measuring Mg²⁺

Mg²⁺, Ca²⁺, and K⁺ ion abnormalities are common in critical care medicine.

Mg²⁺, Ca²⁺, and K⁺ ions are interdependent and play a role in numerous disease processes, including diabetes, hyperension, kidney disease, cardiovascular disease, cardiac arrhythmia, and sepsis.

Mg²⁺ is a vasodilator, Ca²⁺ is a vasoconstrictor. Both are synergistic in maintaining vascular and bronchial smooth muscle tone.

Mg²⁺ ion is an antagonist to Ca²⁺ ion entry into cardiomyocytes.³

Serial monitoring of Mg²⁺, Ca²⁺, and K⁺ ions are all important in correcting or avoiding cardiac arrhythmias and cardiomyocyte necrosis.⁴,⁵,⁶

Hypokalemia may be unresponsive to potassium repletion unless hypomagnesemia is first corrected.⁷

Contact us for a bibliography of more than 25 recent publications about the importance of Mg²⁺ in disease processes.

References:
Black people with CKD moved into a more severe category, and about 4.5 million people who are not Black moved into a less severe category. The new formula did not substantially change CKD-related complication prevalence estimates.

The researchers noted that their research was limited by use of single laboratory measurements. Limited numbers in some subgroups prevented precise estimates, especially of complications. Limited subgroup numbers also prevented separate analysis of smaller racial and ethnic groups. Findings could drive changes to CKD diagnosis and treatment for many patients, the researchers said.

STUDY SUGGESTS LOWER TROPONIN CUTOFF FOR EARLY COVID-19 CARDIAC DAMAGE

A high-sensitivity troponin 1 (hs-cTnI) level of 5 ng/L or more may be a manifestation of early cardiac damage in patients with nonsevere COVID-19, according to a recent paper (Sci Rep 2022; doi: 10.1038/s41598-022-06378-2).

To explore the manifestations of cardiac damage at presentation in nonsevere patients with COVID-19, the researchers grouped 113 patients with nonsevere COVID-19 according to the length of time between symptom onset to hospital admission. That time span was a week or less for group 1, one to two weeks for group 2, more than two to three weeks for group 3, and more than three weeks for group 4. The researchers compared clinical, cardiovascular, and radiological data on hospital admission across the four groups.

Group 2 patients in the second week after symptom onset had the highest levels of cardiac biomarkers. The proportion of patients who had a hs-cTnI of 5 ng/L or more in group 2 was 85.71%, compared with 37.04% for group 1, 51.85% for group 3, and 25% for group 4. Group 2 patients also had the highest levels of C-reactive protein (CRP) and lactate dehydrogenase.

Compared with patients with hs-cTnI under 5 ng/L, those with hs-cTnI of 5 or more ng/L had lower lymphocyte count and higher CRP. Patients with hs-cTnI ≥ 5 ng/L had a higher incidence of bilateral pneumonia and longer hospital length of stay.

Researchers say their study is likely the first to demonstrate the value of a cutoff lower than the 99th percentile of hs-cTnI to identify early cardiac damage in nonsevere patients with COVID-19. Results are similar to those of earlier studies that show the level of hs-cTnI increased significantly from 10 to 13 days after symptom onset in COVID-19 patients and that the cardiac biomarkers were highly related to lymphocyte count and CRP. These findings suggest that cardiac damage from COVID-19 is related to viral response and hyperinflammation.
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Maternal-fetal medicine owes much of its successes in recent decades to the contributions of the clinical laboratory. Yet recent controversy around noninvasive prenatal screening (NIPS) shows that laboratorians have work to do in order to ensure clinicians can translate advances in medical technology into better patient care.

In particular, when it comes to prenatal screening for rare conditions, the stakes are high, and the statistics can be confusing. The January 2022 New York Times article “When They Warn of Rare Disorders, These Prenatal Tests Are Usually Wrong,” has drawn attention to potentially misleading results of positive prenatal genetic screens.
for rare microdeletions. The authors highlight how the screening tests’ low positive predictive value contrasts with the information on some manufacturers’ brochures that claim their assays are “reliable” and “highly accurate,” offering “total confidence” for pregnant patients.

Six of the test manufacturers interviewed by the *Times* stated that patients with a positive screen should always review results with their healthcare provider and “cautioned that the tests are meant not to diagnose a condition but rather to identify high-risk patients in need of additional testing.” However, with these tests often performed outside the healthcare provider’s purview—and with limited time for interactions with their patients—the potential for misunderstandings abounds.

The lab community can help clarify these results by working with clinicians to improve understanding about what the prenatal screens are, the potential issues around screening results, and the most appropriate language to help clearly communicate results to healthcare providers and patients, experts told *CLN.*

**NIPS: ANEUPLOIDY VS. MICRODELETION**

Prenatal genetic screening has been available for decades. One of the earliest and most common NIPS tests is for trisomy 21 (Down syndrome). For women at higher risk for this chromosomal aneuploidy (having a third copy of chromosome 21), a definitive answer can be obtained via a diagnostic test. Historically, fetal cells would be obtained via amniocentesis and then karyotyped.

With the discovery of fetal cell-free DNA (cfDNA) in maternal blood, advances in DNA sequencing technology, and extensive bioinformatics, individual laboratories began offering NIPS for far less common genetic conditions called microdeletions—missing or extra pieces of chromosomes. Among these are Prader-Willi syndrome (1 in 20,000 births), Cri-du-chat syndrome (1 in 15,000 births), and DiGeorge syndrome (1 in 4,000 births).

NIPS for these rare syndromes is at the heart of the *Times* article because most positive screens for microdeletions would not be confirmed by positive diagnostic tests. In fact, they can be overwhelmingly incongruous, with some screens averaging only 15 diagnostically confirmed correct calls out of 100 screen-positive test results. Here is where things can get tricky for many clinicians and patients: Technically, these NIPS are not diagnostic tests, and they are not “wrong.”

If the results can be so confusing, why are these prenatal screens for very rare genetic conditions so popular? “A driving force for the growth of NIPS is the significant interest from patients and clinicians,” said Jonathan Genzen, MD, PhD, chief operations officer, ARUP Laboratories, and associate professor, University of Utah Department of Pathology, Salt Lake City. Another driving force is the commercial nature of these tests and manufacturers’ broad marketing efforts.

It is recommended that all pregnant individuals be offered information about prenatal screening and diagnostic testing—what assays are available and what information they can and cannot provide about a developing fetus. However, many professional societies, including the American College of Medical Genetics and Genomics and the American College of Obstetricians and Gynecologists, advise against prenatal screening for microdeletions.

From a laboratorian perspective, the problem with NIPS could be a matter of language: To accurately report a NIPS result, one must use statistical terminology that is not common knowledge and hope that it is correctly communicated to patients by their physicians or genetic specialists.

**NIPS STATISTICS 101**

The language used to describe NIPS performance is important and very specific. Manufacturers must release information about a screening test’s detection rate, false-positive rate, and estimated positive predictive value:

**Detection rate.** The detection rate (DR) refers to the proportion of all individuals with a specific condition that is correctly identified as being positive by a test. For example, if 100 tested individuals have a given condition and 99 test positive, the test’s DR is 99%. Another name for DR is sensitivity.

“In your reports to clinicians, make sure you use language like ‘screen positive.’ Very few physicians will see ‘screen positive’ and translate that to, ‘Your baby has this genetic issue.’”

—Glenn Palomaki
**False-positive rate.** The false-positive rate (FPR) indicates the proportion of all individuals without that specific condition that an assay correctly identifies as being negative. For example, if 10,000 tested individuals do not have the given condition and 100 test positive, the test’s FPR is 1%.

**Positive predictive value.** The positive predictive value (PPV) combines DR and FPR with the prevalence of the specific condition. PPV represents the proportion of individuals with a positive test who have the specific condition. For example, a PPV of 50% means half of those with a positive test truly have the specific condition. Even though the DR and FPR remain constant, the PPV of a test will vary based on the prevalence of the condition in a defined population. In general, the rarer the condition, the lower the PPV.

The authors of the *Times* article focused only on the PPV of NIPS for microdeletions. Prader-Willi syndrome (PWS) has a very low prevalence of about 1:20,000 and NIPS provided a relatively low PPV of 15%. “With such a low prevalence,” said Glenn Palomaki, PhD, professor in the department of pathology and laboratory medicine, Women & Infants Hospital, Alpert Medical School of Brown University, Providence, Rhode Island, “even an excellent test could have a low PPV.”

These statistics can seem contradictory and could be the reason why some manufacturers highlight DR and FPR in their informational brochures. If the prevalence of PWS were much higher at 1:400 (the prevalence of Down syndrome), the PPV of that same test would increase to over 90%.

Statistical concepts like DR, FPR, and PPV are taught to clinical professionals but are not well understood by the general public. Therefore, it is imperative to communicate the purpose and limitations of NIPS—particularly for uncommon disorders such as microdeletions.

**COMMUNICATING SCREENING RESULTS**

Screening results for microdeletions, especially positive screens that are not diagnostically confirmed, have confused and stressed patients, prompting potentially difficult discussions and decisions—all within a finite gestational timeline.

“**Sources for Reliable, Independent NIPS Guidance**

**American College of Obstetrics and Gynecology (ACOG)**

www.acog.org

ACOG produces practice guidelines for healthcare professionals and educational materials for patients, provides practice management and career support, facilitates programs and initiatives to improve women’s health, and advocates for members and patients.

**Genetic Support Foundation (GSF)**

geneticsupportfoundation.org

GSF is a not-for-profit organization whose mission is to improve the quality of healthcare by providing up-to-date, objective genetic information to patients, providers, and healthcare organizations, supporting those in need of genetic services, and facilitating the adoption of best genetic practices.

**Society for Maternal and Fetal Medicine (SMFM)**

www.smfm.org

SMFM is a nonprofit organization that supports the clinical practice of maternal-fetal medicine by providing education, promoting research, and engaging in advocacy to optimize the health of high-risk pregnant women and their babies.

“The NYT article authors got a lot of criticism for their use of the word ‘wrong’ when referring to microdeletion screening results,” said Katie Stoll, MS, LGC, executive director of the Genetic Support Foundation, based in Olympia, Washington. “The way the test reports are often phrased makes it seem like the presence of the condition is certain, and so if a patient gets a positive screen and a subsequent negative diagnostic test, the patient often does feel the screening results are wrong.”

Stoll, who still counsels patients, added: “We’re talking with people about their pregnancies. Misunderstandings can result in tragic or misguided decisions—a lot of anguish. These issues have been here since cfDNA testing began about a decade ago. The *Times* article drew attention to it—attention that I think is overdue.”

“Sometimes the healthcare providers don’t have the time or resources to really explain what a screening test means to their patients,” Palomaki said. His advice to laboratorians? “In your reports to clinicians, make sure you use language like ‘screen positive.’ Very few physicians will see ‘screen positive’ and translate that to, ‘Your baby has this genetic issue.’”

It is also worth noting that patients often see laboratory results through their electronic health records before they talk with their provider. “In the future,” Palomaki added, “this is something labs may need to address to ensure screening results are very readable and clear for the lay public.”

“Clinicians should have resources to better understand and communicate screening test results to patients, and laboratories performing such testing should make sure that informational resources and test reports provide thorough, understandable, and patient-centric explanations,” Genzen added. “The Food and Drug Administration may describe this in the context of ‘labeling’ of tests. I’d suggest it’s also just good patient care and medical practice.”

While prenatal screens for microdeletions offer new opportunities for increasing patient knowledge about their pregnancies, positive screening results are not indicative of a genetic syndrome. Clinical laboratorians should take caution and care when communicating screening information to clinicians and patients.

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From Cells to Spells

A brief history of HLA testing in the clinical laboratory.

BY TIFFANY BRATTON, PHD, DABCC, FAACC, FACHI
Human leukocyte antigen (HLA) testing has been a staple of transplant medicine since the 1960s, when researchers discovered that crossmatches could reliably predict transplant allograft rejection (1). Although methods have changed dramatically since then, the premise that it is unethical to perform a transplant in the absence of HLA testing remains.

Interest in transplant immunology, specifically in the understanding of HLA and its implications for transplantation, has only increased over the past 60 years. Early on, the understanding was that the donor had to be a “match” for the recipient. While this concept is correct overall, in that the donor and recipient must be compatible, our understanding of what compatibility looks like has evolved considerably.

Let us take a brief tour of the history of HLA testing and its evolution from cells to spells.

**MAKING A MATCH**

From the late 1960s through the early 1980s, compatibility was determined by cytotoxicity dependent crossmatch (CDC). Donor serum was added to recipient cells, and if the cells remained viable, then the pair was considered compatible—a “match.” This method worked remarkably well, with transplant outcomes improving from ~35% mortality within the first year of transplant in the pre-crossmatch era (1963–1969) to <18% in the immediate years following implementation of the CDC (2). Notably, mortality within the first year post-transplant is ~5% today (3).

The basic premise of the CDC is that the presence of donor-specific anti-HLA antibody in the recipient serum induces complement fixation resulting in donor cell death (Figure 1). The production of HLA antibody in the context of a foreign graft relies on allore cognition. Various antigen-presenting cells present processed antigen to CD4+ T-cells that trigger an immune response. Upon T-cell activation, the CD4 helper T-cells release various cytokines that, in addition to activating CD8 killer T-cells, also activate progenitor B-cells that will begin to produce antigen-specific antibodies. In most cases this is a donor HLA peptide, leading to the production of donor-specific HLA antibodies.

Vascular endothelial cells are the preferential target of the immune response due to the abundance of antigens they express. When antibodies bind to antigens within the graft endothelium, complement molecules, particularly C1q, bind to the antigen-antibody complex and activate an intricate cascade of reactions. These result in the formation of the membrane attack complex (MAC) that disrupts the integrity of the cellular membrane resulting in cell lysis.

Cell death in situ in the CDC is certainly predictive of a poor outcome for the allograft in vivo, where activated complement can also be responsible for the recruitment of neutrophils, macrophages, and inflammatory markers that further damage surrounding tissue. This process results in inflammation, tissue injury, and thrombosis, leading to antibody mediated rejection and, ultimately, graft failure (4).

**IMPROVING SENSITIVITY WITH FLOW CYTOMETRY**

The CDC became the cornerstone of compatibility in transplantation. In the mid-1980s, however, a new flow cytometric crossmatch (FLXM) technique was developed that was found to be far more sensitive than the CDC (5). In this method, donor serum is still added to recipient cells, but now instead of adding exogenous complement to facilitate antibody-mediated cell death, an antihuman IgG antibody with a fluorescent tag is added. The mixture is then run through a flow cytometer, and increased fluorescence is indicative of incompatibility between donor and recipient (e.g., recipient has donor-specific HLA antibodies). The FLXM was more sensitive than the CDC; however, in 1999 an article was published highlighting the lack of specificity and questioning the clinical utility (6). At that time, an understanding was emerging that not all antibodies are created equal.

Until the lack of specificity of the FLXM was understood, the HLA was thought of as the only antigen on the cell surface. We now know that there are many antigens on the surface of a cell, all of which can bind antibodies of certain specificities (Figure 2). It is these other antigens that contribute to FLXMs that appear to be clinically irrelevant.

This figure shows the basic premise of the cytotoxic dependent crossmatch (CDC). In the CDC, the presence of donor specific anti-HLA antibody in the recipient serum will bind to HLA on the donor cell surface. Bound anti-HLA antibody fixes complement, specifically the C1q protein, leading to donor cell death.
These particular, non-HLA antibodies generally do not cause damage to the allograft, so a transplant between a donor and recipient that demonstrates a positive FLXM can still have outcomes identical to those of a pair with a negative FLXM. Therefore, it is critical to identify when a FLXM is positive due to HLA antibodies versus non-HLA antibodies.

SOLID PHASE TESTING ADDS SPECIFICITY
In the mid-1990s, researchers developed the solid phase testing methodology in which recombinant HLA antigens are conjugated to polystyrene microspheres (Figure 3). These beads can then be added to a patient’s serum, and any HLA antibody specific to the antigens represented will bind to the beads. A fluorescently labeled secondary anti-human IgG antibody can then be used to identify which beads—and therefore, which antigens—are positive (i.e., which specific HLA antibodies a patient has in circulation). Notably, upon the widespread utilization of solid phase testing, it was possible to distinguish exactly which HLA a recipient had antibody against at the antigen level.

In parallel to the development of solid phase testing, many laboratories began using molecular methods for HLA typing. These methods revealed that there was much more to HLA antigens than initially understood. Far more polymorphisms were discovered by molecular methods than had previously been distinguished by serological methods. For example, one of the first HLA antigens identified by serology was designated HLA-A2. However, when molecular methods entered, it was discovered that A2 had several polymorphisms that had not been serologically determined. Thus, these were designated as alleles of A2 (HLA-A*02:01, HLA-A*02:06, etc.).

The nomenclature went from a locus- (e.g., A) and antigen- (e.g., A2) based system to an allele-based system of locus (A), antigen (A*02), and allele represented by the four-digit designation (A*02:06). Notably, while >25,000 HLA alleles have been characterized, only the most frequently occurring 60 to 70 serologically determined HLA antigens are currently identified by solid phase testing.

THE ERA OF VIRTUAL CROSSMATCH
As a complement to the great specificity of the solid phase HLA antibody testing and molecular typing methods, the mid-2000s ushered in the era of the virtual crossmatch (VXM). By knowing the specific HLA antibodies in the circulation of the recipient and the HLA genotype of the donor, the compatibility of the pair could easily be predicted. It was found that the VXM had better specificity than the FLXM and that outcomes of transplants that proceeded based on VXM had equally good outcomes (7).

Currently, as we begin the 2020s, the assessment of donor/recipient compatibility relies on VXM-acceptable mismatch strategies, with positive VXM/unacceptable mismatches defined by the presence of donor-specific HLA antibodies targeting the HLA antigens of the donor as determined by the HLA genotype. It is important to remember, however, that a negative VXM—indicating a compatible donor/recipient pair—does not mean that the pair is HLA matched. In fact, it has been demonstrated that increasing the HLA mismatch results in development of de novo donor-specific HLA antibodies (DSA) post-transplant. These are correlated with antibody mediated rejection and worse outcomes (8).

For this reason, the VXM/acceptable mismatch approach to deceased donor kidney allocation has been challenged by proponents of HLA epitope matching algorithms that claim to offer a more precise assessment of compatibility.

UNDERSTANDING EPITOPES
To date, HLA has been primarily thought of as a group of antigens. However, as understanding of antigen/antibody interactions has progressed, HLA perhaps should be recognized as a grouping of epitopes. An epitope is defined as the region of an antigen to which an antibody binds (Figure 3). Each antigen can have multiple epitopes; conversely, a single epitope may be present on multiple antigens.

Each individually identified HLA antigen will carry a “private” epitope. This is the single nucleotide polymorphism, resulting in a single amino acid change, that will
distinguish the allele from others of the same serological group. However, cross reactive groups (CREGs)—where several antigens will react serologically with a single serum—have long been recognized among HLA antigens. Understanding the presence of epitopes has now revealed that many of these CREGs represent a single epitope binding to a single antibody. It is now easier to think of an HLA antigen as a collection of epitopes, all of which are shared with other HLA antigens. Under this framework, it has become clear that “matching” donors and recipients at the antigen level is insufficient.

The concept of epitopes within the field of transplant immunology was brought to the forefront by the work of Rene Duquesnoy (9). However, for many years the field was skeptical of this new point of view. It wasn’t until almost a decade later, when epitopes were proven to be predictable based on the structural, physicochemical properties of the amino acid polymorphisms, that the epitope-based theory of HLA became widely accepted (10). Not long after, several software algorithms were developed to help better understand the level of epitope matching, or mismatching, between donor/recipient pairs. The first was HLA Matchmaker by Duquesnoy (9) which was soon translated to the Epitope Registry (11).

Development of de novo DSA post-transplant correlates with the level of epitope mismatch between the donor and recipient, also known as epitope load (12). However, HLA Matchmaker and the Epitope Registry only account for the antigenicity of the epitope—how the epitope interacts with an antibody. In the context of de novo DSA, it is also critical to consider the immunogenicity of the epitope or its ability to induce an antibody response (12).

In a 2011 publication, Kosmoliaptsis et al. reported that the physicochemical polymorphisms of amino acids, such as hydrophobicity and electrostatic properties, were also predictors of an alloantibody response (10). They found that the HLA amino acid mismatch score (AMS) and electrostatic mismatch score (EMS) were associated with the development of DSA against donor HLA Class II mismatches after renal transplant, but only the EMS correlated with the risk of HLA Class I DSA development. These data indicate that differences between donor and recipient HLA amino-acid sequences—as well as the physicochemical properties of the epitope mismatches—enable better assessment of the risk of de novo DSA development and subsequent graft failure than conventional HLA matching.

TIME TO REDEFINE DONOR/RECIPIENT COMPATIBILITY?

The impact of epitope load on DSA formation and graft survival has led to the suggestion that compatibility of donor/recipient pairs be redefined as epitope matching or the level of epitope load. Indeed, there may be several advantages to this approach. Firstly, it may allow increased access to transplantation for highly sensitized individuals—those with high levels of pre-existing anti-HLA antibodies. Determining compatibility based on the epitope load would, theoretically, allow for organ allocation to highly sensitized patients despite absence of pre-existing DSA. The donor epitope repertoire would be considered for compatibility, rather than simply the mismatched antigens. This would potentially allow for more acceptable allele combinations, thereby expanding the donor pool (13).

Epitope considerations may also be beneficial for recipients who are less sensitized. Perfect donor/recipient HLA allele matching is clinically impractical in the context of over 25,000 HLA alleles across 11 HLA gene loci. In contrast, with a smaller number of epitopes that may be shared across different HLA alleles, accomplishing compatibility at the level of the epitope may be more feasible (14). However, the overall feasibility of determining compatibility based on epitope load still faces many challenges.

The first step toward implementing epitope matching relies on the availability of allele-level HLA genotyping. Genotyping of a deceased donor is highly time sensitive, and for this reason, laboratories choose their methods primarily for a rapid turnaround time and offer only intermediate level typing at best. That is, these methods often cannot resolve
between common alleles.

At times, the allele-level typing is imputed based on associations between alleles at other loci that are well documented in large populations. However, recent studies have shown that imputations are often inaccurate, and the inaccuracies are more pronounced when applied among patients of non-Caucasian self-reported ancestry (14). This limits the accurate assignment of epitopes in deceased donors as well as in recipients being typed by low resolution methods, which is still common at many centers.

The feasibility of epitope matching in the context of deceased-donor transplant is also limited by time. It is often necessary to utilize more than one software package to both identify the epitopes and then assign the epitope load of the donor. The laboratory must then cross-reference this information with the pre-formed DSA to completely rule out those epitopes, as well as determine the remaining epitopes of most concern to inform acceptable mismatching—a time-consuming endeavor. Moreover, while increased donor epitope load has been correlated with worsened outcomes, not all epitopes have thus far been shown to be deleterious. That is, the antigenicity of some identified epitopes is still in question; antibodies are likely to bind strongly to some epitopes and only very weakly to others. Understanding which epitopes are which is going to be critical to an acceptable mismatching strategy.

Finally, while efforts are underway to identify the most immunogenic epitopes, what has not been considered is the risk of allograft injury associated with re-exposure to epitopes, which may accelerate immune response and injury (14). Patient sensitization after prior transplant, transfusions, pregnancies, etc. is difficult to account for, and it is possible that recipients may experience a strong memory response to highly immunogenic donor epitopes even in the absence of detectable existing DSA. It is equally likely that a recipient may have no response to previously encountered epitopes that are not very immunogenic.

Our understanding of transplant immunology has evolved tremendously from the days of the CDC into the current epitope era. The concept of compatibility itself has evolved from relatively simple in terms of “matching” at the cell level to something incredibly complex in the context of epitopes and acceptable mismatching.

As we consider the current obstacles to allocating organs based on epitope load, it may seem akin to casting a magic spell. However, in the 1960s, predicting transplant outcome based on mixing serum and cells seemed like magic as well. There is only a thin line of understanding between magic and science, and as the field of transplantation develops a laser focus on improving long term outcomes, it is only a matter of time before our understanding evolves again.

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Laboratories around the country are dropping the race modifier in estimated glomerular filtration rate (eGFR) calculations of kidney function. They are changing to new formulas recommended by the National Kidney Foundation (NKF) and American Society of Nephrology (ASN) Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases.


Measuring serum creatinine for an eGFR is recommended as the first step in assessing kidney function by clinical practice guidelines. In an article published simultaneously in the Journal of the American Society of Nephrology and the American Journal of Kidney Diseases, the NKF-ASN task force recommended that all U.S. laboratories adopt the new creatinine formula “because it does not include race in the calculation and reporting, includes diversity in its development, is immediately available to all labs in the U.S., and has acceptable performance characteristics and potential consequences that do not disproportionately affect any one group of individuals.”

The task force also recommended national efforts to facilitate increased use of cystatin C measurement as a confirmatory test because combining filtration markers provides more complete information for clinical decisions.
The use of a race multiplier—which required inputting whether a patient was “African-American or non-African-American”—in eGFR equations had come under increasing scrutiny for its lack of recognition that race is a social construct rather than a biological one. Spurred by worries that the modifier was also potentially contributing to racial disparities in access to kidney treatment, many institutions dropped it from their eGFR equations, leading to inconsistency in eGFR estimates among institutions.

STANDARDIZED REPORTING
The new creatinine equation offers laboratories “a way to standardize the reporting of eGFR,” said to Greg Miller, PhD, a member of the NKF-ASN task force, a former AACC president, and professor of pathology and codirector of clinical chemistry at Virginia Commonwealth University in Richmond.

“We are hoping that we can convince laboratories that they should quickly adopt the new CKD-EPI 2021 equation, not only because it eliminates the potential racial disparity concern, but it also would make for a more consistent practice of patient management across the country,” Miller said.

Miller headed an NKF working group that published a “practical guidance” to help laboratories implement the new equations. The paper was published online in December 2021 and will appear in the print version of Clinical Chemistry in April (Clin Chem 2021; doi: 10.1093/clinchem/hvab278). The paper contains detailed recommendations on how to communicate the reasons for the change to stakeholders, how to program new parameters into laboratory information systems, and more.

Miller said that his and other institutions have already made the change. “The transition is actually surprisingly easy from an IT point of view, because the form of the new equations is the same as the form of the old equations. All you have to do is change the coefficients,” Miller told CLN.

APPARENT DIFFERENCES
The use of a race coefficient dates back to the Modification of Diet in Renal Disease (MDRD) study reported in 1999, in which all patients had their GFR measured by the kidney iothalamate clearance, considered a gold standard of function but not a practical test for widespread use compared with creatinine. The researchers concluded that self-identified Black individuals had higher creatinine levels vis-à-vis a given GFR, so they inserted a correction factor in the MDRD estimating equation.

In 2009, the Chronic Kidney Disease Epidemiological Collaboration did a similar study with comparable results and published the widely used CKD-EPI 2009 formulas with a similar race-based correction factor.

“At the time, this adjustment was thought to be an advancement because an important group, with high risk for CKD progression, was included in studies of measured GFR,” wrote the authors of the initial report from the NKF-ASN task force. However, the correction factors meant that if a Black and non-Black patient had the same creatinine level, the Black patient would be reported with a more favorable eGFR, and less likely to be considered for treatment.

RACIAL INEQUITIES
As concerns over racial inequities in healthcare grew—as did recognition that Black individuals experienced kidney disease at higher rates than White individuals—the use of the correction factor came under increasing scrutiny. Beth Israel Deaconess Medical Center (BIDMC) in Boston was one of the first places to act. In the spring of 2016, nephrologist Melanie Hoenig, MD, an associate professor of medicine at Harvard Medical School, was explaining the racial coefficient “when a medical student asked pointedly, ‘Why would there be a correction factor for a healthier value for the group at greatest risk of kidney disease?’”

The question inspired Hoenig and her students to explore the literature review, engage in conversations with stakeholders at BIDMC, and conclude that “the use of race in clinical medicine is flawed and problematic. Ultimately, we agreed to change the language of the report to remove race, but we provided two values generated by the eGFR formula to try to reintroduce the notion that the formula reports an estimate.”

A handful of other institutions made similar moves—often also initiated by medical students and residents—and several articles and editorials appeared questioning the use of the race modifier. But the issue gained immediacy after the reaction to the killing of George Floyd in May 2020 took the racial justice movement to a new level.

In August 2020, the ASN and NKF formed their joint task force

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to reassess the use of race. The task force followed an exhaustive process that considered 26 different potential strategies suggested by a variety of experts. But the breakthrough came when the CKD-EPI Collaboration researchers went back to reanalyze the data sets they had previously used along with data from newer studies to create its updated formulas.

**AACC FORMS TASK FORCE**

For its part, AACC formed an eGFR and Race Equity Task Force to examine the issue. Chaired by Hoenig, the task force included individuals with expertise in clinical laboratory medicine, nephrology, primary care, pharmacy, and evidence-based medicine. They performed a systematic literature review to determine whether there was evidence “supporting the use of the Black race modifier in creatinine-based eGFR calculations.”

The task force published its findings online in December 2021, prior to appearing in the April print issue of *Clinical Chemistry*, and concluded: “There is little evidence supporting the inclusion of a race modifier in eGFR calculations. Although the use of the Black race modifier may have improved the accuracy of the formula in the original population studies, the Black race modifier does not demonstrate any analytical or clinical benefit in clinical diagnoses and treatment for an individual patient, and rather may contribute to healthcare inequities and social harms” (Clin Chem 2021; doi: 10.1093/clinchem/hvab279).

Hoenig said that this work was different from but complementary to the work of the NKF-ASN task force: “I think it was important for AACC to have its own look at this issue. This is the first time all these papers have been put together. The formulas have been used for decades, so it is important to take a really hard look and say, ‘What is the evidence?’”

Hoenig’s institution changed to the formulas recommended by the NKF-ASN task force in mid-February.

**LABS IMPLEMENT THE CHANGE**

Lakshmi V. Ramanathan, PhD, service chief of the clinical chemistry service, attending chemist, and director of point-of-care testing at Memorial Sloan-Kettering Cancer Center in New York City, said that her institution has already made the change.

As a member of the NKF laboratory engagement group, she was already aware of the issue, but waited until the new formulas were published in the *New England Journal of Medicine* to act.

“Once the equations were available, we had a discussion with our nephrologists, and they agreed that we should go forward,” Ramanathan said. “There was a lot of work that our computer staff had to do to make sure the equation was right. We did a lot of cross checks for accuracy. Then on a Sunday, when it was a little quiet, the computer systems upgraded with the new equations.”

Laboratory medicine and renal medicine sent an email notifying physicians about the new equation, and the transition went smoothly. “We have had no real pushback or any questions,” Ramanathan said.

Many large institutions, including the Johns Hopkins Health System, University of Maryland Schol of Medicine, and Oregon Health & Science University, announced the switch to the new formulas on their websites.

Miller said that his institution was coincidentally implementing a new computer system, so it was just a matter of incorporating the new equations into the new computer system. “It was a relatively easy transition,” he said. “I have talked to colleagues at other institutions that have already switched to the new equation, and they have reported the same thing, that everybody was receptive to the change and just started using the new equation. It has just seemed like the right thing to do.”

Miller hopes that the focus on the CKD-EPI 2021 equation can bring order to a rather chaotic current approach to eGFRs. The *Clinical Chemistry* guidance article notes: “In a 2019 survey by the College of American Pathologists, 23% of 6,200 laboratories reporting eGFR-creatinine used an incorrect equation that is not suitable for use with standardized creatinine measurements, 34% used the CKD-EPI 2009 equation, and 43% used the MDRD Study 2006 equation re-expressed for standardized creatinine measurement.”

The new CKD-EPI 2021 equation offers an opportunity for laboratories to standardize to the most up-to-date practice, as well as to take a step toward lessening racial disparities in healthcare, Miller said.

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“This is the first time all these papers have been put together. The formulas have been used for decades, so it is important to take a really hard look and say, ‘What is the evidence?’” —Melanie Hoenig
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Patient blood management (PBM) is a multimodality, multidisciplinary approach to stewardship in transfusion medicine. It involves optimization of anemia and hemostasis with a goal of avoiding unnecessary transfusions. Now considered standard of care, PBM is patient-centered and can improve quality while reducing costs. The recent intermittent national blood shortages make PBM more important than ever (1).

One effective approach to curb unnecessary blood transfusions is clinical decision support (CDS) (2). Multiple large, randomized controlled trials support a restrictive hemoglobin threshold for red blood cell (RBC) transfusion. Many different individuals within a hospital system have privileges to decide whether to give or withhold a transfusion. In tandem with appropriate education efforts, CDS can influence their transfusion decisions based on the best available evidence and reduce over-transfusion events (2).

CDS, however, does not sufficiently address all PBM practices by itself. For example, a patient scheduled for a complex cardiothoracic (CT) surgery procedure 3 weeks from now may ultimately require multiple RBC transfusions intraoperatively. For that same patient, a proactive approach to PBM could result in zero RBC transfusions. Treating iron deficiency anemia before surgery, using cell salvage, and antifibrinolytic agents together could obviate the need for any transfusion, and the differential blood utilization between these two examples can occur despite the use of appropriate transfusion thresholds.

As a transfusion medicine specialist interested in data-driven PBM and a data visualization expert, we wanted to evaluate PBM practices more holistically. For example, when comparing blood utilization among surgeons within a department, surgeons with higher average blood use per case may justifiably feel the comparisons are not fair because they operate on the most complex patients, who are more likely to bleed. For fairer comparisons, we developed a risk-adjusted benchmarking method using diagnosis-related group (DRG) billing code weights that modeled the association between patient complexity (DRG weight) and blood utilization (3).

Sharpening Understanding With Data Visualization

Although the benchmarking method added useful context, we realized this concept could be taken much further. To create more meaningful comparisons, we turned our attention to advanced data visualization in a complex patient population: CT surgery. Data visualization involves graphical representations of data to facilitate understanding and insights. Our goal with advanced data visualization was to create a new approach to visualizing PBM practices that is rapid, flexible, in-context, and tied to patient outcomes. What if we could build such a tool and have potential end users help with the design? Give the people what they want.

While we had several ideas for what a novel data visualization tool might look like, we took a unique approach to glean insights into perspectives of other potential end users: surgeons and anesthesiologists. We held a 3-hour creative visualization opportunities (CVO) workshop facilitated by our data visualization expert and PBM expert (4). This involved an introduction to PBM and discussion of current workflows, followed by creativity techniques, such as "wishful
PLM approach numerous times during the pandemic to stay prepared and meet patient needs.

We are currently in the early deployment phase of the Sanguine prototype at our institution, but feedback from anesthesiologists and surgeons has been enthusiastic. Sanguine is available as an open-source tool at github.com/visdesignlab/Sanguine.

Next steps include collaboration with outside institution beta sites as well as adding surgeon and anesthesiologist names to the tool. Previous studies have shown that including names can motivate behavior change. Our colleagues have also expressed interest in knowing where they stand.

Lastly, blood utilization is probably a useful surrogate marker for quality in high blood loss surgeries. This, combined with the fact that we designed Sanguine with other end users in mind, means that Sanguine can be used as an advanced quality tool to evaluate surgical practices. We incorporated outcomes known to be important to surgeons and anesthesiologists, such as mortality, risk of needing extracorporeal membrane oxygenation, stroke, prolonged ventilation, intensive care unit length of stay, and more. Our surgeon and anesthesiologist colleagues have told us that Sanguine provides information and insights that do not currently exist from their national benchmarking organizations.

While not our original intent, it has become apparent that Sanguine provides a glimpse into practice quality beyond PBM that, to our knowledge, does not currently exist. We have observed significant practice variation, and whether Sanguine would be universally well received in this regard by some potential end users remains to be seen. For example, will increased transparency potentially cause surgeons concern? This is possible. If the goal is to provide a next generation benchmarking tool to best serve patients, then transparency at this level may be inevitable. The question may not be whether such a tool should exist, but how institutions can use it to provide the most benefit, carefully and constructively.

References
Supply Chain Meltdown? Laboratory Stewardship to the Rescue

Supply chain challenges have plagued the clinical laboratory throughout the COVID-19 pandemic. Increased, unpredictable demand for laboratory testing has coincided with global delays and raw material shortages. The pandemic exposed the weaknesses of “just in time” inventory management, leaving many laboratories without inventory. Laboratories worldwide have endured alternating shortages, from nasal swabs, viral transport media, and pipette tips, to molecular testing reagents.

In the spring of 2021, the lab industry confronted its biggest challenge of the pandemic: The global shortage of blood collection tubes. This article is about how our lab at Ochsner Health System responded using principles of laboratory stewardship.

A Different Kind of Fear
Upon hearing of the FDA’s alert on June 10, 2021, about citrate tube shortages, the laboratory teams at Ochsner predicted that the problem would extend beyond blue tops. Our fears were confirmed in the fall when we noted increased allocations and difficulty obtaining inventory from our primary tube supplier. We were critically low on inventory of blue, green, gold, and purple tops, often with only 1–2 days on hand before the next limited shipment arrived.

Our lab teams felt that if we could survive four COVID waves, staffing shortages, and a category 4 hurricane, we could endure anything. But this? This was a different kind of fear. How can a lab run with no blood collections? How can we tell our clinical teams they may be forced to treat patients without diagnostic testing? How can we manage patient expectations, particularly after their care has already been delayed repeatedly? Being the messenger of scarcity to our overwhelmed colleagues felt insurmountable.

Fortunately, we are lab people. The Ochsner laboratory has a strong, sustained value-based infrastructure to rely upon. Thus, we were able to quickly adopt some of the established tenets of laboratory stewardship to navigate the challenge.

Data Collection and EMR Collaboration
The first step toward a solution was understanding the nature of the problem by collecting and analyzing data. We relied on our Epic electronic medical record (EMR), laboratory information system, and laboratory management to create a tube utilization snapshot of the previous month. This illustrated how many tubes of each type were used daily at every location in the system.

The data highlighted three principal targets for intervention: rainbow draws, extra tubes, and physician ordering patterns. The rainbow and extra tube data revealed an average monthly wastage of more than 20,000 tubes, while the physician-focused reports highlighted individual providers with aberrant ordering patterns.

As we explored our options for interventions, we learned that for data to suffice to sustain tube inventory. We needed to use the painful interventions of restricting laboratory testing for both inpatients and outpatients. This proved a formidable task in a stressed healthcare system.

Best Practices and Published Guidelines
Eliminating rainbow draw and extra tube collection were the first interventions. These were palatable since they did not require a major change in patient management; they relied predominantly upon practice changes from nursing and phlebotomy teams. But after several weeks, it was obvious that these efforts would not suffice to sustain tube inventory. We needed to use the painful interventions of restricting laboratory testing for both inpatients and outpatients.

This proved a formidable task in a stressed healthcare system. Physicians and patients were highly attuned to COVID-19-related care delays and were more fearful of underdiagnosis than overdiagnosis. Patient-centric, evidence-based recommendations were required to ensure collaboration and practice changes from clinical teams.

Our laboratory team looked to the Choosing Wisely initiative and Britain’s National Health Service retesting interval guidance to make recommendations. Our experts in endocrinology, primary care, cardiology, and hospital medicine then vetted and approved the changes.

Collaborating with clinical leaders, we restricted daily orders on stable hospitalized patients for common labs such as complete blood count, comprehensive metabolic panel, c-reactive protein, lipids, sedimentation rate, lactic acid, lipase, ferritin,
procalcitonin, and iron studies. In outpatients, we deactivated low-yield or obsolete tests including free T3, reverse T3, and vitamin D. We also imposed order interval restrictions on lipid panels (6 months), A1C (3 months), prostate-specific antigen screening (6 months), and thyroid peroxidase antibodies (no repeats).

To make these changes, we partnered with our EMR analysts, who analyzed each order set. They identified those requiring modification by either removing obsolete tests or removing the daily option for common tests. epic was able to generate both hard stops and best practice advisory guidance for appropriate testing intervals.

A Solid Foundation in Good Governance
Our laboratory governance was foundational to ochsner health’s success in managing this systemwide stewardship initiative. the care variation committee contains multiple specialties and geographic regions. Monthly meetings have focused on improving laboratory value and care by reducing variation and employing evidence-based guidelines to optimize resources. the committee members were accustomed to debating utilization, and this frequently produced effective compromises. this group vetted and voted on the proposed restriction and achieved majority agreement. the care variation committee not only validated our suggestions but also provided an effective forum for complaints and discussion by clinicians.

Strategic Communication
Tailored communication to diverse teams across multiple geographic regions was the cornerstone of our tube-management strategy. the first task was to rapidly inform clinical services of the situation’s seriousness through two systemwide email distributions occurring 2 weeks apart. To increase readership, these were distributed from the chief medical officer and senior executive team. the communications emphasized the global nature of the shortage, expected duration, and projected impact to critical testing if no interventions were taken. We also explained our plans to restrict testing and manage inventory, along with a strong request to clinical teams to make mindful test ordering a part of their daily patient care goals.

Pathology leaders participated in biweekly departmental chair meetings and staff meetings of primary care, hospital medicine, and surgery. this allowed clinical teams to ask questions about effects on their departments. for example, primary care favored restrictions on some screening labs for routine health maintenance, yet they feared backlash from patients due to unmet expectations. Lab and executive leadership responded by collaborating with primary care on a script that addressed key discussion points and questions patients might have once they learn of the lab shortages. this acknowledged physician concerns and decreased the physician’s communication burden.

Nursing and phlebotomy required a different communication strategy as their impact was not on order restrictions but on proper collection. this was accomplished by nursing and lab operational leaders who collaborated on illustrated tip sheets highlighting the importance of proper blood draw technique and tube filling, recognizing that a rejected tube is a wasted tube. We used data compiled from individual phlebotomists, locations, and draw sites to communicate to team leaders which areas and individuals had a high rejection rate and/ or extra tube rate, thus promoting targeted interventions to improve competence.

Our True North
Our experience maintaining tube inventory has been both gratifying and imperfect. We continue to have days where the inventory becomes dangerously low, and some physicians have remained unhappy with lab ordering restrictions. However, overall, using the stewardship interventions, teamwork, and communication strategies described here, we have maintained our true north of providing testing to all patients who truly need it.

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**Handheld SARS-CoV-2 Saliva Test Earns CE Mark**

Canary Global has received the CE mark for its DigiGENE COVID-19 Rapid Molecular test kit, a self-collected, multi use, rapid point-of-care molecular test that uses saliva to detect SARS-CoV-2.

The test is now cleared for sale and distribution in the European Union. It processes four samples simultaneously, yields a positive result in 5 minutes, and a negative result in less than 20 minutes. DigiGENE says the test is suitable for settings where quick, accurate results are needed for large numbers of people. These settings include schools, airports, event venues, international border crossings, and businesses.

The kit consists of a handheld, reusable digital reader and disposable testing cartridges that feature digital detection technology capable of analyzing multiple targets to detect SARS-CoV-2. This lab-on-a-chip technology combines loop-mediated isothermal amplification, smart sensors, and cloud-based analytics.

With a limit of detection of 600 copies of RNA per mL, this molecular test is on par with most lab-based PCR tests, according to the company. It requires neither special lab equipment nor professional operators. Users get an immediate, verified test result sent to their mobile devices. HIPAA-compliant results from the test can also be sent to public health authorities for contact tracing and surveillance purposes.

DigiGENE says it is now preparing to submit the test kit for Food and Drug Administration review, with an eye toward emergency use authorization for use at home and at the point of care.

### MAMMOTH BIOSCIENCES GETS FDA EUA FOR FIRST CRISPR-BASED HIGH-THROUGHPUT SARS-COV-2 TEST

The Food and Drug Administration (FDA) has granted emergency use authorization (EUA) to Mammoth Biosciences’ Detectr Boost SARS-CoV-2 Reagent kit, a high-throughput solution that combines the sensitivity of CRISPR with laboratory automation for SARS-CoV-2 testing.

According to the company, the Detectr Boost platform is a turnkey, CRISPR-based molecular diagnostic system that enables high-throughput, sample-to-answer testing with PCR-equivalent performance and minimal hands-on time. Together with the Agilent Bravo BenchCel DB liquid handling platform, the Detectr Boost SARS-CoV-2 Reagent kit detects SARS-CoV-2 RNA in nasopharyngeal, anterior nasal, mid-turbinate nasal, or oropharyngeal swab specimens from individuals with COVID-19.

### FDA CLEARS SEPSIS QUALITY CONTROL PRODUCT

Streck recently announced that the Food and Drug Administration (FDA) has cleared its MDx-Chex for BCID2, which provides quality control designed to meet standards for verifying performance of the BioFire BCID2 panel for sepsis.

MDx-Chex for BCID2 is a patient-like, full process control designed to validate each sample processing step included in the pouch for BioFire’s BCID2 panel. The control kit contains 43 bacteria, yeast, and antimicrobial resistance gene targets. They are packaged in two separate vials, one for gram-negative bacteria and one for the gram-positive bacteria and yeasts detected by the BioFire BCID2 assay. The microorganisms are...
intact, inactivated, and suspended in a matrix of stabilized red blood cells, white blood cells, and blood culture media components, which are designed to challenge the lysis and purification processes like a patient sample.

Company officials say the cleared control will enable labs to perform all crucial sample processing steps needed for nucleic acid amplification tests and instrumentation.

**FDA CLEARS MOLECULAR TEST AND WORKSTATION FOR SEXUALLY TRANSMITTED INFECTIONS**

The Food and Drug Administration (FDA) recently granted 510(k) clearance to the Rheonix automated Encompass MDx workstation, along with the company’s STI TriPlex assay and Male Urine Collection Kit for the detection of sexually transmitted infections (STIs).

The fully automated Encompass MDx workstation enables multiplexed sample-to-answer detection, and is designed to simplify laboratory workflows and reduce the burden on laboratory technicians.

The Rheonix STI TriPlex assay is approved for simultaneous detection and differentiation of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis*. Rheonix will also seek FDA approval for additional syndromic diagnostic panels that leverage the Encompass MDx workstation’s ability to perform simultaneous detection of multiple target organisms from a single clinical sample.

Other assays in the Rheonix pipeline include a multiplexed test for simultaneous detection of respiratory pathogens including SARS-CoV-2, influenza, and respiratory syncytial virus; a panel of leading organisms that cause gastrointestinal infection; and STI assays with expanded targets and sample types.

**MICROBIOME TEST CE-MARKED AND LAUNCHED ON NEW PLATFORM**

The microbiome diagnostics company Genetic Analysis (GA) recently announced that it has received the CE mark for its GA-map Dysbiosis test on Magpix, a new platform from the company Luminex.

The Magpix instrument is the most affordable among Luminex’s xMAP instruments and enables up to 50plex using MagPlex Microspheres. It has already become a widely used platform for performing other tests.

The availability of GA-map on the Magpix instrument system complements GA’s new availability on the Luminex LX200 instrument. It provides a less costly option to customers who plan to install a Luminex system for GA-map testing only, and it also enables Magpix customers to add microbiome testing to their current test portfolios.

**SEEGENE’S ALLPLEX RESPIRATORY PANEL RECEIVES CANADIAN INTERIM APPROVAL**

Seegene, a South Korean molecular diagnostic company, has earned approval of its Allplex SARS-CoV-2 FluA/FluB/RSV assay under Health Canada’s Interim Order. The test is a multiplex real-time PCR assay that can both amplify and distinguish among influenza A, influenza B, respiratory syncytial virus, and SARS-CoV-2.

Noting the demand for SARS-CoV-2 tests, Seegene officials say the company is prepared to provide its Allplex test globally. The company also hopes that the assay will aid in the response to a surge in both flu patients and COVID-19 patients.

**NEWLY CE-MARKED TEST DETECTS SARS-COV-2 VARIANTS**

PathogenDx recently announced that its real-time SARS-CoV-2 PCR test Detectx-Cv+ has received the CE mark. The PathogenDx Detectx-Cv+ test is a molecular biology real-time PCR test coupled with DNA microarrays designed to detect the SARS-CoV-2 virus plus emerging variants of concern and of interest.

Company officials noted that as of 2021, the virus had mutated more than 30 times. Without genomic surveillance involving quick turnaround, data on new variants becomes too old to have public health value. The officials said that Detectx-Cv+ can identify both SARS-CoV-2 and its variants with a turnaround time of less than 6 hours, enabling same-day results. No high-end bioinformatics are required, officials added.
C2i Genomics, Twist Bioscience Partner on Whole-Genome Cancer Detection Reference Materials

C2i Genomics and Twist Bioscience announced a partnership to develop whole-genome cancer reference materials. The partnership aims to deal with a lack of standardized reference samples for analytical validation of whole-genome tests. Oncology has a critical need for advanced technology to help improve treatment decisions, the companies said.

The companies’ reference materials will enable diagnostic labs to better validate and monitor their whole-genome cancer screening and minimal residual disease (MRD) products’ quality. Under the partnership, C2i will integrate Twist’s library preparation into its MRD workflow. The new reference standards and kits will complement existing cancer reference standards and solve the need for lab validation and proficiency testing materials for cancer assays.

The collaboration involves C2i using artificial intelligence to identify a very large set of variants associated with cancer signatures. Twist will synthesize each of these variants to create a whole-genome sequencing-focused set of reference materials. Under the terms of the agreement, the reference standard kits will be available through Twist Bioscience.

BD ACQUISITION ADDS POST-TREATMENT MONITORING TO ITS BUSINESS

Becton, Dickinson and Company (BD) has acquired Cytognos, a Spanish company that specializes in flow cytometry solutions for blood cancer diagnosis, minimal residual disease (MRD) detection, and immune monitoring research for blood diseases.

The acquisition expands BD’s portfolio of blood cancer diagnostics, immune assessment tests, and informatics to deal with patient, clinician, and care provider needs and to better understand the immune system, immune response, and MRD. MRD monitoring is a key element of the patient care continuum that helps alert clinicians of cancer’s return and spur timely treatment, BD said.

Cytognos acquisition also gives BD exclusive access to advanced assays licensed from the EuroFlow Consortium, a network of hematologists and immunology researchers from more than 20 European universities and hospitals. BD has existing license agreements with EuroFlow for multiple existing assays. Currently, Cytognos’ in vitro diagnostic products are CE marked and available only in Europe.

ONCOCYTE AND THERMO FISHER AGREEMENT TO EXPAND ACCESS TO PRECISION ONCOLOGY

Oncoyte Corporation recently announced a development and co-marketing agreement for two distributed in vitro diagnostic (IVD) assays on Thermo Fisher Scientific’s Ion Torrent Genexus System. The agreement also grants Oncocyte rights to develop future companion diagnostics on the Genexus System.

Under the terms of the collaboration, Oncocyte will clinically validate Thermo Fisher’s existing Oncomine Comprehensive Assay Plus on
Having a reliable normal control is crucial at every stage of assay development. The AACC Universal Sample Bank provides these controls through serum and plasma samples collected from ethnically and geographically diverse adults (18+) under IRB-approved collection protocols.

**New this year**: AACC offers a COVID-19 Sample Bank featuring well-characterized sample sets from almost 700 individuals vaccinated and/or previously infected with SARS-CoV-2. The sample set can be used in the development of COVID-19-related assays and other clinical studies.

**Pre-COVID-19 Samples**
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“We received over 800 samples from unique healthy donors. The data provided was very valuable for my research and helped us establish new reference intervals for emerging biomarkers of cardiac and kidney disease.”

— Joe El-Khoury, PhD, DABCC, FAACC

For more information visit: [www.aacc.org/samplebank](http://www.aacc.org/samplebank)

International shipping is available.
the Genexus System, with an eye toward IVD clearance for use in tumor profiling and future submissions as a companion diagnostic.

As an IVD, the more than 500-gene assay will initially be able to provide physicians with information about patients’ tumors to assist with selecting targeted therapies in accordance with established clinical evidence, applicable clinical trials, and future approval.

Oncocyte also will develop its 27-gene expression DetermaIO test as a distributed kit on the Genexus System. DetermaIO may predict response to immuno-oncology therapies based on data demonstrating potential pan-cancer utility and improvement over current standard-of-care tests.

According to Oncocyte officials, up to 44% of newly diagnosed cancer patients may be eligible for immuno-oncology therapies, with additional patients potentially benefiting from other precision medicines. But many patients’ tumors are never sequenced to determine if they may benefit from these targeted treatments. Expanding available IVDs and developing them on instruments that make sequencing-based testing simple will benefit patients.

Thermo Fisher officials said the agreement with Oncocyte to validate and codevelop new IVD assays expands access to genomic profiling and expands the benefits of precision medicine to more patients.

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BIOCARTIS AND OPHIOMICS TO COLLABORATE ON LIVER CANCER TEST

Biocartis Group and Ophiomics have announced a collaboration focused on commercialization of HepatoPredict, a prognostic gene expression signature test to identify patients who will benefit from liver transplants. HepatoPredict will be distributed by Biocartis in Europe as a manual kit mainly for centralized expert laboratories.

Retrospective validation has shown the test increased the number of patients that can benefit from curative-intent transplantation by 32%. Further prospective and retrospective validation is ongoing, the companies said. Biocartis officials said that availability of a manual kit version of the Ophiomics test allows the company to help patients generate commercial traction immediately.

While the partnership will initially focus on Biocartis’s commercialization of the manual kit in Europe, it also aims to include development of a fully automated version of the test on Biocartis’ decentralized Idylla platform.
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How is point-of-care testing growing?

**A:** The COVID-19 pandemic has been a strong force in decentralizing diagnostics as it has driven trends ranging from a lab personnel shortage to an increase in over-the-counter (OTC) at-home testing. Infectious disease testing, once the realm of central labs, is growing increasingly common at the point of care (POC), a shift led by SARS-CoV-2 antigen tests. Most of these antigen tests use nasal swabs and detect nucleocapsid proteins of the virus. As long as these tests are used according to instructions, they deliver quick and early results to both patients and clinicians.

There are now POC tests for many diseases that are inexpensive, easy to use, robust, and widespread. Many POC tests use lateral flow immunoassay technology, where the built-in control works automatically. For professionals, POC tests are especially useful for emergency room staff and for first responses, for example, to diagnose traumatic brain injury.

Infectious disease testing is about 37% of the POC market. Flu testing is the largest contributor, and about 80% of flu testing in the U.S. is performed in the physician office setting. Testing for syphilis and gonorrhea by POC devices also has been a success story.

Another POC growth area is testing for drugs of abuse in urine or other body fluids that use immunoassay screening cups. These tests are also easy to use and include controls. In one POC kit, the assay components are incorporated in the cap of the cup. The user ensures a minimum volume of urine in the cup and tilts it to activate the test, with qualitative results in 5 minutes. Depending on the drug being tested and cut-offs used, POC tests may have greater than 90% concordance with the gold standard chromatography/mass spectrometry assays.

Urine dipstick technology is now available for albumin/creatinine ratio, a marker of kidney health. Serum creatinine and cystatin C, both kidney markers, also have POC tests. Even cystatin C, another kidney marker, is available on POC devices.

What are some of the current challenges for POC testing?

One challenge of POC testing is quality control and result reporting. Laboratories can deal with this challenge by employing wireless laboratory information system connectivity for POC devices. A second challenge is test errors; home tests should be made robust, with results as good as the central lab’s. But even central lab tests occasionally suffer from various kinds of interference. Analytical interference is observed in POC as well.

The solution here is similar to that used in the central lab: If a result does not match the clinical picture—or other test results—serial dilution of the sample can confirm suspected interference and deviation from linearity. Most assay reagents now contain various blockers, such as heterophilic antibody blockers, to reduce such interference.

Can home testing keep expanding?

The rapid proliferation and public focus on at-home testing for SARS-CoV-2 is unique. But history shows such expansion has been building for years. Home testing certainly is not new: Patients have used blood glucose meters since 1981. And since 2019, hemoglobin A1c has joined glucose testing in the POC diabetes market. Similarly, while home pregnancy tests have been on the market since 1976, the fast and easy-to-use tests that the public is familiar with came to market only in the 1980s.

POC tests for coagulation also have become essential and make self-monitoring of anticoagulants, such as warfarin, easier.

Of course, another exciting opportunity for at-home POC is molecular testing, even beyond SARS-CoV-2. POC has become established for fecal occult blood testing to screen for colorectal cancer. It is hoped that incorporating immunoassays and molecular testing in stool tests will increase early detection of colorectal cancer.

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