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Clinical
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News

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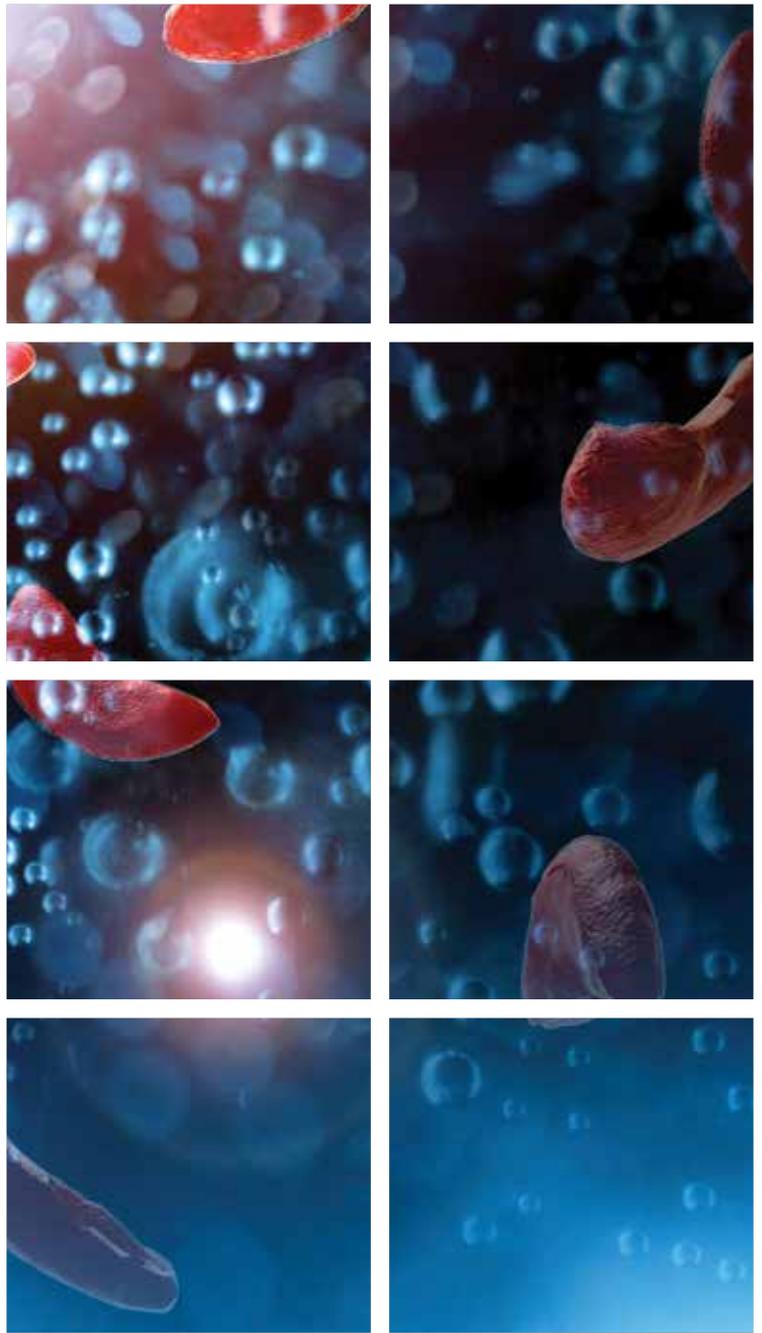
Combination of
CA-125 and HE4 markers
for women under 50

PAGE 8

Transforming Care for Sickle Cell Patients

The Future of Body Fluid Testing

Upgrading Pediatric Reference Intervals





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The general consensus in the literature is that noninvasive methods, including FibroTest, are very good for detecting severe liver fibrosis and cirrhosis and for ruling out fibrosis.

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Federal Insider

Future of LDT Regulation Hangs in the Balance

Even as a Senate committee has voted to include the VALID Act within a larger medical device user fee bill, the FDASLA Act, more than 100 medical and patient organizations have joined AACC in calling out problems with provisions in the bill. AACC has long argued that VALID would burden clinical laboratories with a new, duplicative layer of onerous costs and regulation and limit patient access to laboratory developed tests (LDTs). AACC believes any changes to LDT regulation should be accomplished through the Centers for Medicare and Medicaid Services (CMS), the agency that currently oversees LDTs through CLIA.

In a letter with 94 other healthcare organizations, AACC called on Congress “not to rush this very flawed, problematic legislation through the user fee reauthorization legislative process.”

The American Medical Association and the American Hospital Association (AHA) also have expressed concerns with the VALID Act. “The AHA is concerned that, if enacted in its current form, the VALID Act could lead to a loss of patient access to many critical tests and could dramatically slow down advances in hospital and health system laboratory medicine,” AHA wrote to senators.

With the Senate committee’s vote to keep VALID in the larger FDASLA bill, AACC and other groups remain focused on the next steps in the legislative process. At CLN press time, the bill had yet to arrive on the Senate floor. In addition, the House version of

FDASLA does not include VALID, and reconciling the law between the two chambers opens an opportunity to make changes.

AACC members have been meeting virtually with the offices of legislators in both the Senate and the House and have encouraged the laboratory community to participate in the association’s grassroots campaign: www.aacc.org/ldtaction.



COLORADO LAUNCHES FIRST STATE-BASED HEALTH PLAN UNDER NEW ACA PROGRAM

The Centers for Medicare and Medicaid Services (CMS) announced approval of Colorado’s request to create the “Colorado Option,” a state-specific health coverage plan that aims to increase health coverage enrollment and lower healthcare costs starting in 2023.

The new state health plan operates under a special section of the Affordable Care Act (ACA) allowing states to apply for state innovation waivers in order to pursue alternative strategies for health insurance.

Colorado’s plan will combine federal support and state subsidies and projects that approximately 32,000 residents will gain health insurance by 2027. The plan will be available to

those who purchase insurance on the individual market or to small employers with fewer than 100 employees. The state estimates it can lower premiums by up to 15% by 2025.

NEW GUIDANCE ON HIPAA AND AUDIO-ONLY TELEHEALTH

The Department of Health and Human Services (HHS) through its Office for Civil Rights (OCR) issued guidance on how healthcare providers and health plans can offer audio-only telehealth services and still meet Health Insurance Portability and Accountability Act of 1996 (HIPAA) privacy, security, and breach notification rules.

In its announcement, HHS noted that telehealth can significantly expand access to healthcare, but certain populations have trouble accessing

audio-video telehealth due to financial resources, English proficiency, disability, and availability of broadband internet access.

One critical clarification in the guidance is that the HIPAA Security Rule does not apply to audio-only telehealth services when the healthcare provider is using a standard telephone landline. Under HIPAA rules, landlines are not considered “electronic,” reducing the burden of security measures that would be required for internet-based systems.

The caveat: many providers may be using landlines that hospitals have replaced with Voice over Internet Protocol (VoIP) that use the internet or Wi-Fi. In these cases, audio-only communication is considered electronic transmission of protected health information and the full suite of HIPAA security rules come into play.

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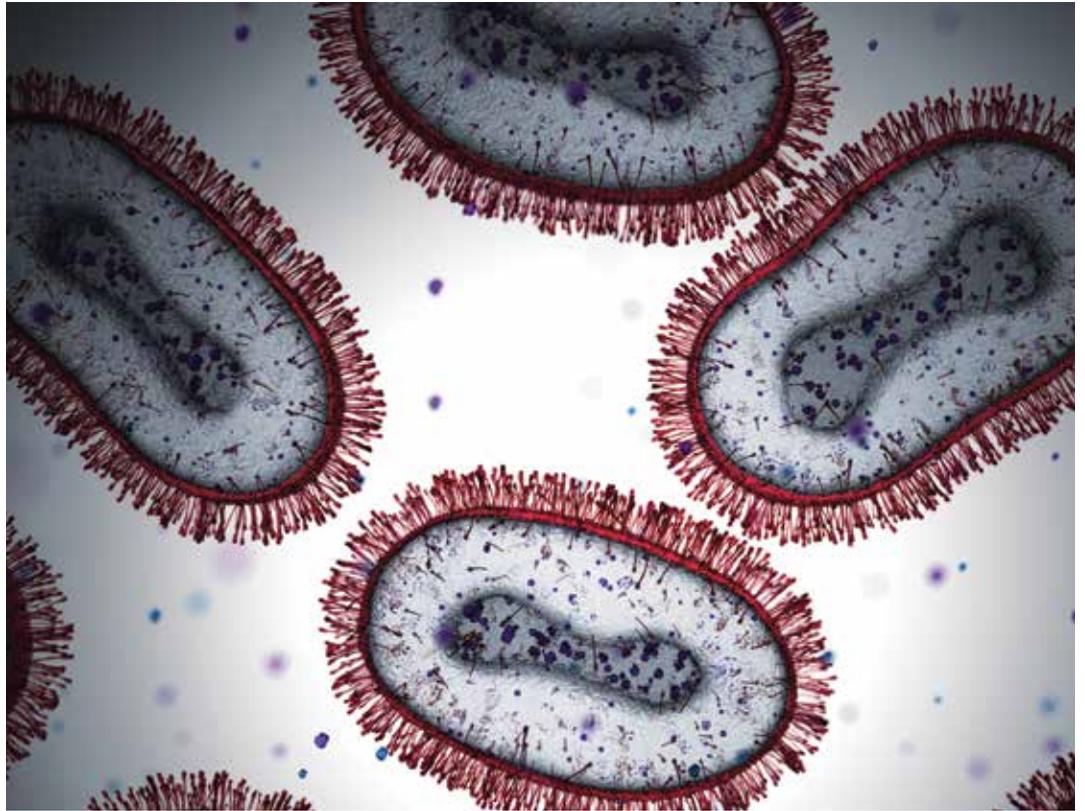
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Monkeypox Arrives in the U.S.—Now What?



Rodney E. Rohde, PhD, MS, SM(ASCP)^{CM}, SVCM, MBCM, FACS

For 2 years, everyone on planet earth has watched what is arguably the biggest global emergency in over a century unfold before our eyes. SARS-CoV-2, COVID-19, mRNA, “flattening the curve,” and other medical and laboratory jargon has become mainstream vocabulary. The pandemic of our generation has ebbed and flowed as most microbial outbreaks do, while humankind has experienced anxiety, heartbreak, hope, and exhaustion. Then, just as the world was beginning to hope for a pandemic ending, an old zoonotic agent reared its viral head: monkeypox.

The Current Outbreak

A confirmed case of monkeypox in the United Kingdom was reported on May 7, 2022. Cases have since popped up globally, from Spain and Germany to the U.S. and Canada. As of June 17, the U.S. reported 113 laboratory-confirmed cases in 20 states and the District of Columbia. Data from the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), and other public health authorities now indicate more than 1,300 confirmed monkeypox cases in 31 countries.

WHO is working with these countries, and others, to expand surveillance and provide guidance for monitoring and managing this outbreak. CDC scientists and others

are tracking cases that have been reported in several countries that don’t normally report monkeypox, including the U.S. Historically, this infection is acquired via close contact (skin to skin or skin to fomites, such as bed linen), animal exposure, or more rarely via respiratory droplets. Interestingly, early data with this outbreak suggest that gay, bisexual, and other men who have sex with men make up most cases. However, most experts believe this is due to close contact and not a classically defined sexually transmitted infection.

What Is Monkeypox?

What exactly is monkeypox, and should we be concerned about the latest pathogen to capture headlines? The monkeypox virus is taxonomically in the *Orthopoxvirus* genus in the *Poxviridae* family,

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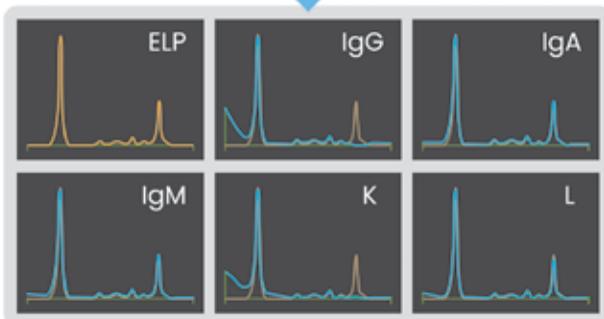
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including smallpox and cowpox. Like all poxviruses, monkeypox virions are large, enveloped, and “brick-shaped.” Encapsulated within each virion is a core containing a linear, double-stranded DNA genome and enzymes required for virus uncoating and replication.

Monkeypox is a misnomer because monkeys are not the main reservoir. A more well-suited name would be “rodent pox” since the virus is believed to mainly reside in rodents (e.g., squirrels and rats). While several rodent species are suspected to be susceptible to monkeypox, the virus has only been isolated from wild animals on two occasions: a rope squirrel (1985) in the Democratic Republic of Congo and a dead infant mangabey monkey in Cote d’Ivoire (2012).

Transmission of monkeypox virus to and between humans occurs when individuals contact an infected animal, person, or contaminated material (fomites). In addition to gaining entry to the body via broken skin (including wounds invisible to the naked eye), the virus can travel in large respiratory droplets via the mouth, nose, or eyes. Because droplets are heavy, and fail to fly more than a few feet, prolonged contact is required for efficient human-to-human spread. In other words, monkeypox is nothing like SARS-CoV-2, which is aerosolized and highly transmissible.

Monkeypox is a self-limiting disease resolving within 2–4 weeks. Incubation is between 5 and 21 days so variation often occurs in individuals experiencing symptoms. In early stages, monkeypox illness may present like influenza, resulting in fever, headache, muscle aches, and swollen lymph nodes, among other symptoms.

First, a rash forms, blooming on the face before spreading to other body regions, including the palms (hands) and soles (feet). Rash lesions progress in stages, starting as macules (flat lesions), progressing to pustules (raised lesions filled with yellowish fluid), and ending in scabs, which eventually fall off. These symptoms mirror those of smallpox, though less severe, and most people recover without issue. Additionally, unlike monkeypox, smallpox is not associated with lymphadenopathy.

Monkeypox has a fatality rate ranging from 1%–10%. Case severity in individuals depends on several factors, including viral strain, medical care access and quality, exposure extent, and health status, such as being immunocompromised.

Currently there are two known virus clades: the more virulent Congo Basin clade (up to 10% mortality) and the less virulent West African clade (up to 1% mortality). So far, all confirmed monkeypox cases belong to the West African clade. To date, all nonendemic countries, including the U.S., report no mortality. Due to its low mortality rate, low reproductive number (R_0 less than 1), transmission route (nonaerosol), and longer exposure time required for infection,

monkeypox is very unlikely to become a pandemic or major problem. Food and Drug Administration-approved antivirals and vaccines are available.

Laboratory Detection of Monkeypox

Monkeypox is a very rare infection, especially in the U.S., and diagnosis is challenging, given that signs and symptoms mimic many other diseases. To diagnose suspected cases of monkeypox, clinicians rely on real-time quantitative PCR (RT-PCR) assays using sample material from skin lesions. Testing is performed at Laboratory Response Network (LRN) laboratories in the U.S. and globally. No commercial assays exist to detect monkeypox virus. There are approximately 120 domestic LRN laboratory members, representing all 50 states. Additionally, the LRN includes several international laboratories. Most current LRN members are public health laboratories.

If possible, successfully vaccinated (i.e., smallpox vaccination within the past 10 years) persons should perform laboratory work that involves handling specimens that may contain monkeypox virus, but it’s not an absolute requirement. BSL-2 facilities with standard BSL-2 work practices should be used for typical laboratory and clinical work involving suspicious or confirmed cases.

CDC published on June 6 an RT-PCR procedure for laboratories interested in creating laboratory developed tests for the virus. The procedure includes sequence information for primer and probe development and cycling conditions, and is available at www.cdc.gov/poxvirus/monkeypox/lab-personnel.

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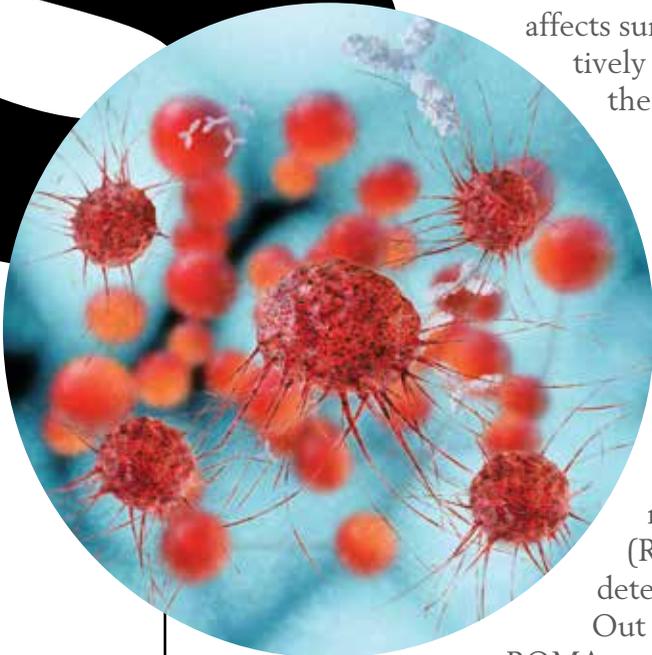


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The Sample



New Blood Biomarker Could Aid Ovarian Cancer Diagnosis

A recent study found that a blood test could help diagnose ovarian cancer faster and more accurately, particularly for women under the age of 50 (Cancers 2022; doi: 10.3390/cancers14092124).

Many women's nonspecific symptoms make early-stage ovarian cancer diagnosis difficult. Guidelines in many countries currently recommend CA-125 as a first-line test for ovarian cancer in women presenting with possible symptoms of the disease, followed by an ultrasound after abnormal CA-125 results. Specialist referral occurs after abnormal ultrasound.

Some women have false negative CA-125, a finding that delays diagnosis and affects survival. Meanwhile, human epididymis protein 4 (HE4), a relatively new blood biomarker for ovarian cancer, has shown promise in the hospital setting but has not been evaluated in primary care.

The researchers studied whether HE4 would improve ovarian cancer diagnosis in women with symptoms in a primary care setting. They investigated the diagnostic accuracy of HE4 alone and in combination with CA-125 for ovarian cancer in symptomatic women attending primary care by testing general practitioner-requested CA-125 samples in a large teaching hospital in Manchester, England. They tracked cancer outcomes for 12 months. Due to a low incidence of ovarian cancer in primary, the cohort was enriched with presurgical samples from 81 ovarian cancer patients. The researchers calculated Risk of Ovarian Malignancy Algorithm (ROMA) using an age of 51 as a surrogate for menopause and determined conventional diagnostic accuracy metrics.

Out of a total of 1,229 patients, 82 had ovarian cancer. Overall, ROMA performed best, with an area under the curve (AUC) of 0.96. ROMA performed particularly well in women under 50 years old. Among these patients, the combination of CA-125 and HE4 (with either marker positive) had a sensitivity of 100% and specificity of 80.1%. In women over 50, ROMA had a sensitivity of 84.4% and specificity of 87.2%.

The researchers call for validation of their results in a much larger sample.

■ RAPID GENETIC POINT-OF-CARE TEST COULD AVOID AMINOGLYCOSIDE TOXICITY IN NEWBORNS

Rapid point-of-care (POC) testing for a rare genetic variant could avoid toxicity in newborns treated with aminoglycosides for gram-negative infections, according to a recent study (JAMA Pediatr 2022; doi: 10.1001/jamapediatrics.2022.0187).

Newborns who get aminoglycosides and have the m.1555A>G

variant in *MT-RNR1* can suffer profound and irreversible hearing loss. But timeliness in treating these infections is also critical, with experts recommending antibiotics be delivered within an hour of any decision to treat sepsis. While current genotyping approaches can alert clinicians of the need for alternative antibiotics, they take several days and are not useful in acute settings.

The researchers developed a rapid genotyping platform for the m.1555A>G variant and assessed

whether the hospital could implement the technology successfully to avoid aminoglycoside-induced ototoxicity (AIO)—and without disrupting normal clinical practice in neonatal intensive care units. In a prospective implementation trial, they aimed to assess the proportion of neonates successfully tested for the variant among all infants prescribed antibiotics, whether implementation was negatively associated with routine clinical practice, and performance of the system.

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Among 751 newborns with a median age of 2.5 days, the test produced genotyping results for the m.1555s>G variant in 26 minutes. Preclinical validation demonstrated 100% sensitivity and specificity. Testing identified three newborns with the variant, all of whom avoided aminoglycosides. Overall, 80.6% of infants administered antibiotics were tested for the variant without disrupting normal clinical practice.

Based on the population frequency of the m.1555A>G variant, and worldwide use of aminoglycosides in more than 7 million neonates each year, the adoption of this POC test could potentially prevent thousands of AIO cases annually. There are other acute clinical scenarios where knowledge of an individual's genotype could be used to improve outcomes as well, the authors noted.

The researchers also pointed out that the SARS-CoV-2 pandemic has led to the proliferation of in vitro diagnostic systems that also could be redeployed for rapid genotyping.

COMPLEMENTARY CANNABINOID SCREENING METHOD PROPOSED

A universal screening assay and machine learning combination approach may complement conventional analytical methods for detecting synthetic cannabinoid receptor agonists (SCRAs), according to recent research (Clin Chem 2022; doi: 10.1093/clinchem/hvac027).

SCRAs are often much more active at the CB1 cannabinoid receptor than D9-THC, the prime psychoactive compound of the traditional recreational drug cannabis. Healthcare providers need information about SCRA user preferences, more toxic analogues, and rapidly proliferating new SCRAs because high CB1 cannabinoid receptor activity is associated with serious adverse health effects and emergency department visits.

Yet current SCRA screening strategies—like chromatography coupled to high-resolution mass spectrometry—are time consuming, expensive, and likely to miss low subnanogram per milliliter SCRA concentrations in body fluids. Meanwhile, activity-based bioassays have shown promise as a universal first-line screening tool for SCRAs that complement conventional targeted and untargeted analytical methods.

The researchers assessed an activity-based method for detecting newly circulating SCRAs, compared it with liquid chromatography coupled to high-resolution mass spectrometry, and evaluated their own machine learning models to reduce the screening workload by automating interpretation of the activity-based screening output. They tested their approach on 968 samples from adult emergency patients with acute recreational drug or NPS toxicity at a London hospital.

Of the 149 samples with analytically confirmed SCRAs, the approach had a sensitivity of 94.6% and a specificity of 98.5%. Findings also demonstrated rapid changes in the illicit drug market. The researchers detected six different SCRAs or their metabolites, only two of which they found in a similar 2019 study.

The model includes tradeoffs between having experts manually annotate samples or having to test more samples afterwards for confirmation. Expert review remains necessary to maintain high sensitivity and specificity of manual scoring. However, the machine learning approach could potentially speed up sample scoring and reduce workload, making it a good first-line screening approach to complement conventional analytic methods, the researchers noted.

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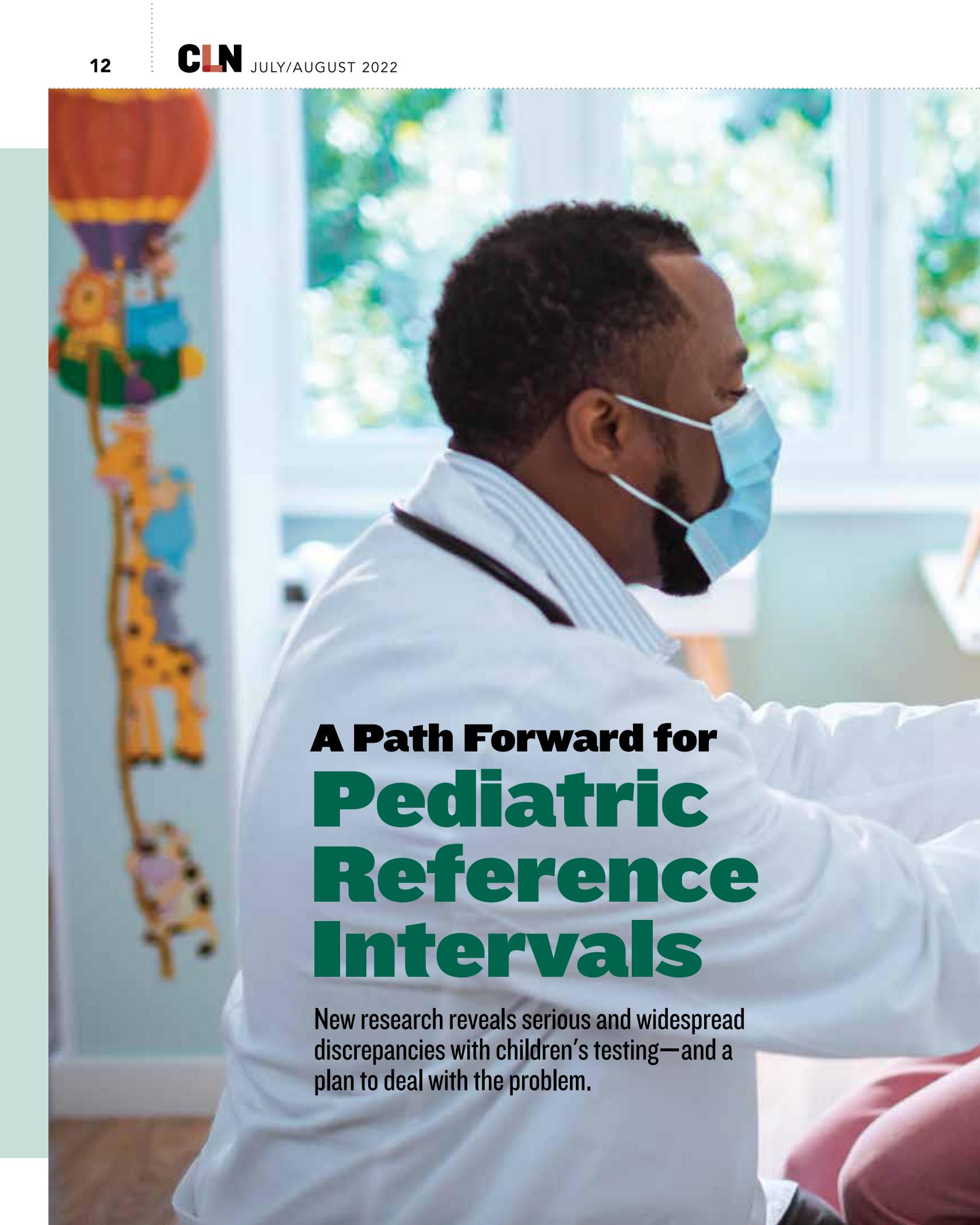


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A Path Forward for Pediatric Reference Intervals

New research reveals serious and widespread discrepancies with children's testing—and a plan to deal with the problem.



BY JEN A. MILLER

Most lab test results come with reference intervals—the range of numerical results that define “normal” from “high” or “low.” However, defining “normal” requires scientific evidence that demonstrates what healthy levels are for a range of chemicals in the body for different populations.

Establishing normal levels is especially challenging to accomplish for children. They’re not miniature adults, and their bodies are changing rapidly, sometimes wildly within a matter of days in the case of newborns.

“I don’t know which is worse: not having a range or having an inaccurate range,” said Amy Pyle-Eilola, PhD, lab director of Nationwide Children’s Hospital.

She, along with Hubert Vesper, PhD, director of clinical standardization programs at the Centers for Disease Control and Prevention (CDC) and Dennis Dietzen, PhD, lab director of St. Louis Children’s Hospital, recently published a paper in *JAMA Open Network* showing for the first time the breadth of significant inconsistencies with pediatric reference intervals (*JAMA Pediatr* 2022; doi: 10.1001/jamapediatrics.2022.0794).

They also identified some of the most pressing issues in this area, including the lack of data and how small studies can be interpreted the wrong way, especially by clinicians who find reference intervals online without any context, don’t consult a lab director, and make care decisions based on those intervals. The study also paves the way for the medical community to develop more reliable pediatric reference intervals, for the betterment of children’s medical care.



This has been an especially pressing need since the start of the COVID-19 pandemic, which also has coincided with a steep rise in pediatric cases of Multisystem Inflammatory Syndrome in Children (MIS-C).

For these conditions, “children usually get dozens if not more laboratory tests, and we’re stuck with trying to reconcile them for a condition that still is fairly nebulous,” said Alan Schroeder, MD, associate chief for research in the division of pediatric hospital medicine at Lucile Packard Children’s Hospital Stanford, who wrote the accompanying editorial in the same issue of JAMA Open Network. “Contextualizing lab results is so important, and trying to understand what’s normal for a kid really matters.”

THE CHALLENGE OF ACCURATE PEDIATRIC INTERVALS

Gathering enough data about every single stage of a child’s development is difficult, especially when children change so much, and so often. And even then, relying solely on numerical age doesn’t account for how children progress and develop on different timelines. “Just because you turn seven or eight years old, doesn’t mean your IGF goes up by ten points,” Pyle-Eilola said.

In their JAMA Open Network study, Pyle-Eilola’s group found that reference intervals published in scientific journals for free thyroxine,

thyrotropin, ferritin, cystatin C, estradiol, and testosterone were inconsistent, especially during developmental stages where children undergo rapid biochemical changes. Some pediatric reference intervals failed to account for the free thyroxine and thyrotropin surge in the first few days of life, which could lead to these newborns being diagnosed with thyroid disease.

Part of the problem is sheer lack of data. While sick children are often subject to a range of medical tests, parents aren’t often willing to have the same tests done on healthy children, especially babies, who by nature have very

small volumes of blood. Accurate ranges can’t be created based on the test results of sick children alone; healthy children need to be part of the sample set too.

“You need a lot of blood from a lot of people. In most cases, new parents aren’t about to let their child undergo phlebotomy,” Dietzen said. “If they’re sick, it’s not a great thing to do, and if they’re well, it’s a worse thing to do. By and large getting samples to do these studies is a big deal.”

The pediatric intervals that do exist also aren’t standardized across instrumentation, he added. “If somebody does a big study on thyroid stimulating hormone on a Siemens platform, and I have a Roche platform, I cannot take that data and put it onto my Roche platform because I don’t know how well it agrees,” he said. “It’s all over the place.”

The second part of the problem is that, despite these inconsistencies, existing reference intervals are still being used. That can put children at risk for inappropriate or harmful clinical care. At the very least, it means subjecting a baby or child to unnecessary visits to specialists, which most likely require their parent or parents to undergo additional travel to and from appointments, take off work, or find childcare for other children. At worst, children are given the

medication or treatment for a medical condition they don’t have.

“Abnormal tests lead to more abnormal tests and interventions, and it keeps going. In some cases it can be really harmful to patients,” Schroeder said.

It’s also easy for physicians to rely on these available pediatric reference intervals, even those who typically do their due diligence. Dietzen has found that clinicians who are what he calls “critical consumers of data” can still be unaware of the problem of interpreting data across platforms. “They typically don’t understand the equipment that’s present in the lab and how those reference intervals are generated,” he said. “The problem is they don’t know what they don’t know.”

Clinical laboratorians could “probably be better about making sure that people are aware” of the problem with these intervals, Schroeder said, and help out physicians who can be bombarded, even overwhelmed with data. At the time he wrote his opinion, Schroeder had a pediatric ICU patient who had undergone 65 individual laboratory tests by 6 a.m. Clinicians get “so much information and that’s just the lab on top of all of the patient’s vital signs,” he said.

That’s why it’s critical for standardize pediatric reference intervals, added Pyle-Eilola. “The problem is that clinicians don’t know to call and ask somebody.”

HOW TO CREATE ACCURATE PEDIATRIC REFERENCE INTERVALS

The answer starts with data—and a lot of it. “The holy grail is a continuous, smooth distribution of data from birth all the way into adulthood, and that is not where we are at today,” said Dietzen. “We end up having to make bins of data, and those bins are limited in how well they can describe the dynamic change of a pediatric population.”

In addition to raising awareness with both clinical laboratorians and clinicians about the problem with existing pediatric reference intervals, AACC and CDC have partnered on a project to create better reference intervals.

The effort includes using data from the National Health and

Papers in 2021 Continue to Show Certain Glucose Meters Cause Serious Adverse Events Due to Interferants

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AACE Clin Case Reports, 2021

"High Dose vitamin C treatment in combinations with Accu Chek II and Hemocue BGMs in patients with acute kidney failure may cause misinterpretation with potentially fatal consequences." ²

Clin Chem Lab Med, 2021

"Yet, vitamin C has been associated with multiple reports of factitious hyperglycemia and harmful iatrogenic hypoglycemia causing death in at least one report." ⁴

J Med Care Reports, 2021

"While the Nova StatStrip glucose meter effectively detected the presence of ascorbic acid interferant and suppressed glucose results, the Roche Inform II and Abbott Precision Xceed Pro demonstrated falsely increased results that could have impacted patient care (delayed PET scan) or possibly led to inappropriate patient treatment." ³

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2. Krabbe J et al. Significant interference on specific point-of-care glucose measurements due to high dose of intravenous vitamin C therapy in critically ill patients. *Clin Chem Lab Med*. 59(5) 2021.

3. Katzman B et al. Unintended Consequence of High-Dose Vitamin C Therapy for an Oncology Patient: Evaluation of Ascorbic Acid Interference with Three Hospital-Use Glucose Meters. *J Diabet Sci and Tech*. 15(4) 2021.

4. Lachance O et al. High-dose vitamin-C induced prolonged factitious hyperglycemia in a peritoneal dialysis patient: a case report. *J Med Case Reports* 2021.

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AACC Advocacy for Children's Health

Children's health has been a top priority for AACC's advocacy work with policymakers. In 2021, AACC with its partners succeeded in getting Congress to include report language recommending that CDC submit a plan to legislators on what resources the agency would need to start developing better pediatric reference intervals. CDC responded that they would need \$10 million annually. AACC and partners such as the American Academy of Pediatrics, the Children's Hospital Association, and other stakeholders, continue to work with key legislators in support of this effort.

Learn more about AACC's work in this area: www.aacc.org/advocacy-and-outreach/advocacy

Nutritional Examination Survey, which is conducted by CDC, to generate continuous pediatric reference intervals and provide them to laboratories, clinicians, and researchers. The project will also facilitate the adoption of these intervals by clinical laboratories through assay standardization.

"There is a need to correctly describe the biochemistry of child development, as well as to identify strategies to develop accurate and consistent pediatric reference intervals for improved pediatric care," the study authors wrote. "Continued communication and collaboration between clinicians and their laboratory colleagues ensures appropriate clinical test interpretation and patient assessment and remains essential to effective implementation of common [pediatric reference intervals], they added.

Canada has tackled this problem for more than a decade through the Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) project. Since 2009, it has

recruited more than 12,300 healthy children and adolescents, established pediatric reference intervals for more than 200 laboratory biomarkers, and created an online database and mobile application for free access to the CALIPER reference intervals.

Part of the success with CALIPER, said Pyle-Eilola, was in convincing parents to allow their healthy children to be part of it, which is why AACC working with CDC is critical and why more funding is needed to ensure a U.S.-specific set of standards that can be used across the country.

"We need a very large, nationwide reference interval study," she said. "These are really big problems that no single laboratory or organization can deal with. We need a large-scale approach, with federal funding, to make it happen."

"We just need Congress to love this idea to get it down the road," Dietzen added. ■

Jen A. Miller is a freelance journalist who lives in Audubon, New Jersey.
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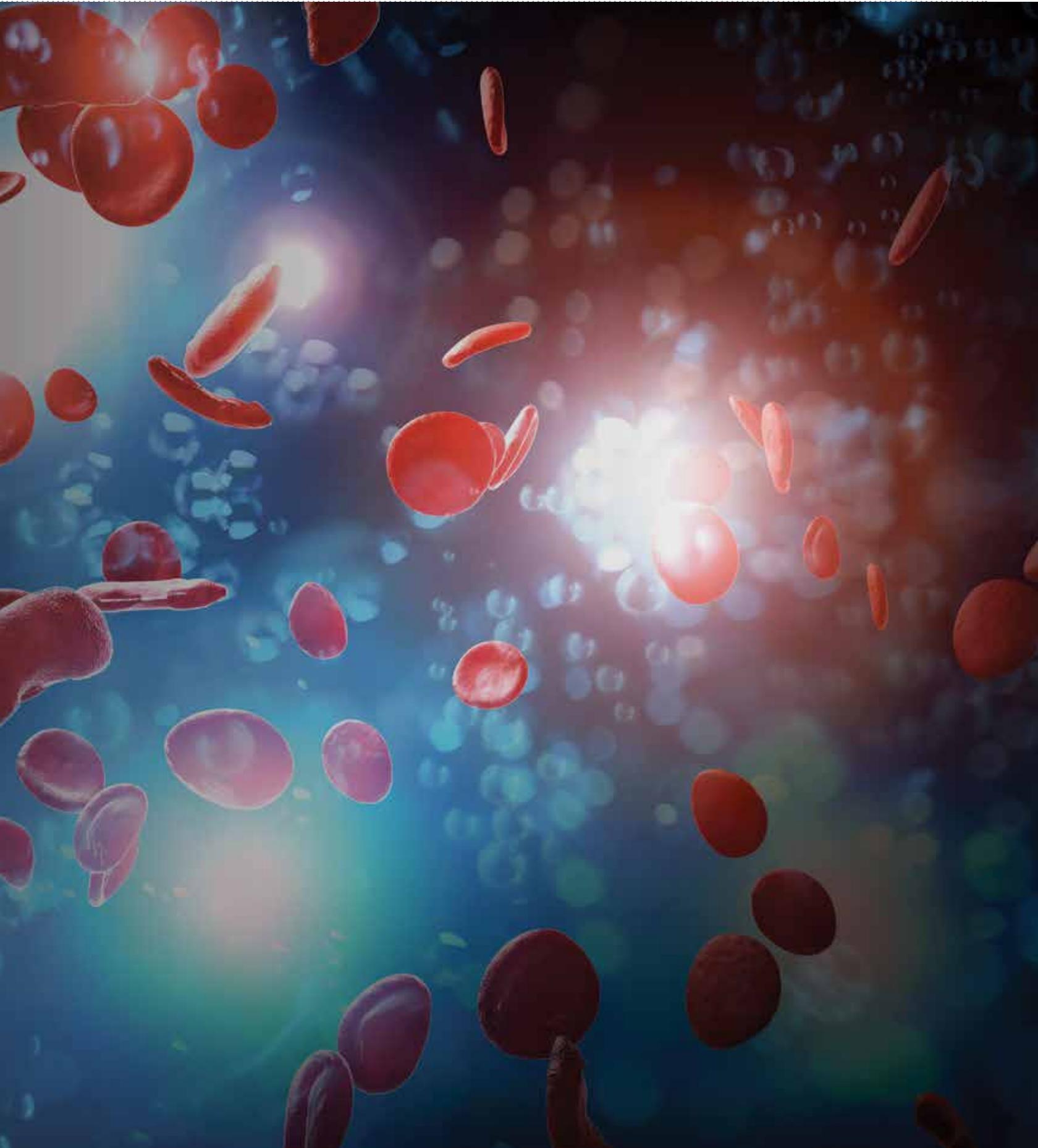
MANAGING SICKLE CELL DISEASE

As new treatments emerge, clinical laboratorians are key to ensuring that patients reap the benefits.

Over the last 50 years there have been great improvements in managing sickle cell disease (SCD) in the United States. In the 1970s, the median age of death for a person born with SCD was 14; today, the median age of death is in the late 40s.

Until 2017, treatment options for SCD largely consisted of red blood cell (RBC) transfusion and hydroxyurea, both of which can cause significant side effects (2,3). The Food and Drug Administration (FDA) recently approved three additional medications, increasing the available options for disease management to five. These include inflammation reducers such as L-glutamine; a new monoclonal therapy, crizanlizumab; and voxelotor (formerly GBT440), a novel drug that inhibits the hemoglobin polymerization process that causes RBC sickling (4–6).

In addition to these treatments, hematopoietic stem cell transplantation and gene therapies are potential curative treatments (7,8). This article provides an update on the current treatment options available and the current laboratory methods used to monitor patients with SCD.



BACKGROUND ON SCD

SCD is the most common inherited blood disorder in the United States, affecting more than 100,000 Americans and millions of people worldwide (1). SCD occurs as a result of changes to the protein hemoglobin, a major carrier of oxygen in the blood. The majority of adult hemoglobin is composed of hemoglobin A (HbA), with small amounts of hemoglobin A2 (HbA2) and hemoglobin F (HbF) (Table 1). SCD is an autosomal recessive disease caused by a point mutation in the β-globin gene that produces an abnormal hemoglobin S

(HbS) instead of wild-type HbA.

These mutations cause the production of dysfunctional hemoglobin that polymerizes in the setting of hypoxia into stiff rods, causing RBCs to take on a sickled shape (sickling). Sickled RBCs are unable to move through small blood vessels (vaso-occlusion) and are easily destroyed via hemolysis (1). As a result, tissue beyond the area of vaso-occlusion cannot receive oxygen and dies (ischemia), leading to extreme pain. Episodes of vaso-occlusion are known as pain crises and are the most common cause of morbidity in SCD.

SCD occurs when an individual inherits either two copies of HbS (HbSS) or one copy of HbS and a second malfunctioning β-globin gene, such as hemoglobin C (HbC), hemoglobin D-Los Angeles/Punjab (HbD-Los Angeles/Punjab), hemoglobin E (HbE), hemoglobin O-Arab (-Arab), or β-thalassemia, which is caused by either a mutation in one or more of the β-globin genes or deletion of an entire β-globin gene (Table 1).

UNDERSTANDING SCD TREATMENT OPTIONS

There are currently five available treatment options for managing SCD: RBC transfusions (simple or exchange); hydroxyurea (approved by FDA in 1998); L-glutamine (approved in 2017); crizanlizumab (approved in 2019); and voxelotor (approved in 2019) (2–6). These treatments work by targeting either the initial event and/or areas of downstream dysfunction (Figure 1).

RBC Transfusion

RBC transfusions are used for prevention and management of SCD symptoms, including acute chest syndrome, recurrent vaso-occlusive pain crises, acute stroke treatment, and stroke prophylaxis. The goal of RBC exchange is to reduce the relative percentage of HbS (HbS%) and to increase oxygen delivery to the tissues, thereby preventing sickling events and subsequent vaso-occlusion, hemolysis, and ischemia (2).

Hydroxyurea

In 1998, hydroxyurea was the first FDA-approved medication for the treatment of SCD after it was proven to reduce frequency of pain crisis in adults (3). Hydroxyurea is an inhibitor of ribonucleotide reductase and, similar to RBC transfusions, reduces the relative HbS%. Hydroxyurea does this by increasing the production of β-globulin, which in turn increases the percentage of HbF (HbF%) in the blood.

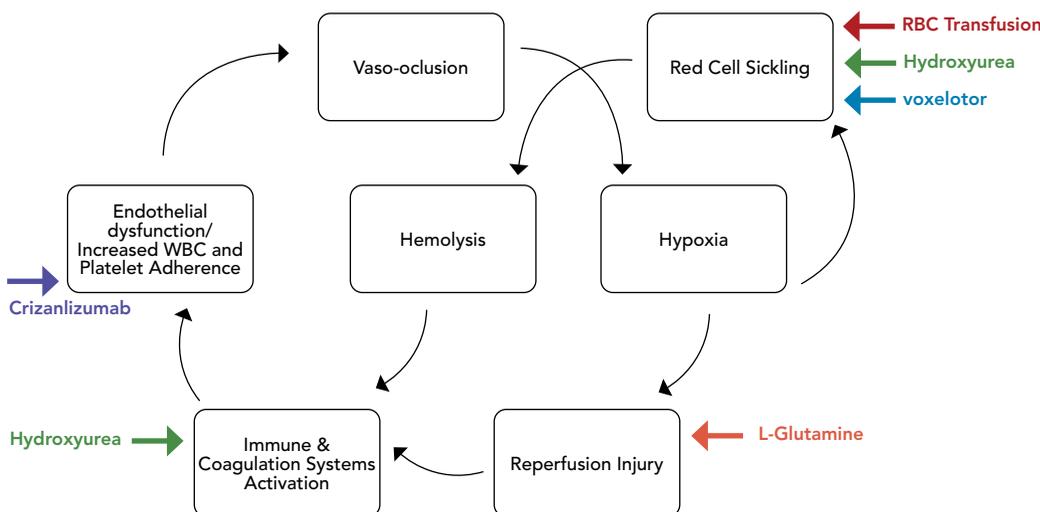
HbF is composed of two α and two γ subunits and is unaffected by the HbS mutation (Table 1). Increasing the HbF% in the blood decreases the HbS% and substitutes a hemoglobin that does not polymerize. Hydroxyurea also inhibits cell

T1 Common Hemoglobins

Hemoglobin	Structure	HBB mutation
HbA	$\alpha_2\beta_2$	None: Normal Hemoglobin
HbA2	$\alpha_2\sigma_2$	None: Normal Hemoglobin
HbF	$\alpha_2\gamma_2$	None: Normal Hemoglobin
HbS	$\alpha_2\beta^S_2$	c.20A>T
HbC	$\alpha_2\beta^C_2$	c.19G>A
HbD-Los Angeles/Punjab	$\alpha_2\beta^D_2$	c.364G>C
HbE	$\alpha_2\beta^E_2$	c.79G>A
HbO-Arab	$\alpha_2\beta^O_2$	c.364G>A

HBB: β-globin gene

F1 Current treatments for SCD target both the initial sickling event and areas of downstream dysfunction. Hemoglobin polymerization leads to sickling, which causes hemolysis, damage to the lining of the blood vessels (endothelium), and tissue ischemia. All of these activate the immune and coagulation systems, leading to increases in the numbers and activity of white blood cells and platelets and to endothelial dysfunction. Activated white blood cells and platelets adhere to the sickled red blood cells and increase risk of vaso-occlusion, creating a feed forward loop that contributes to disease severity. Current treatments for SCD target one or more of these mechanisms.



replication, reducing white cell and platelet counts. This reduces chronic inflammation and subsequently reduces the risk of vaso-occlusion.

Hydroxyurea is a tablet taken daily and remained the sole medication approved for the treatment of SCD for almost 2 decades.

L-glutamine

L-glutamine was approved by FDA for the treatment of SCD when it was shown to reduce frequency of pain crises both alone and in combination with hydroxyurea (4). L-glutamine is an amino acid necessary for the synthesis of nicotinamide adenine dinucleotide (NAD). Higher levels of NAD have been proposed to reduce oxidative stress resulting from ischemia reperfusion reactions in SCD, which would subsequently reduce chronic inflammation. L-glutamine is a pharmaceutical-grade powder that is mixed in a beverage or food and taken twice daily.

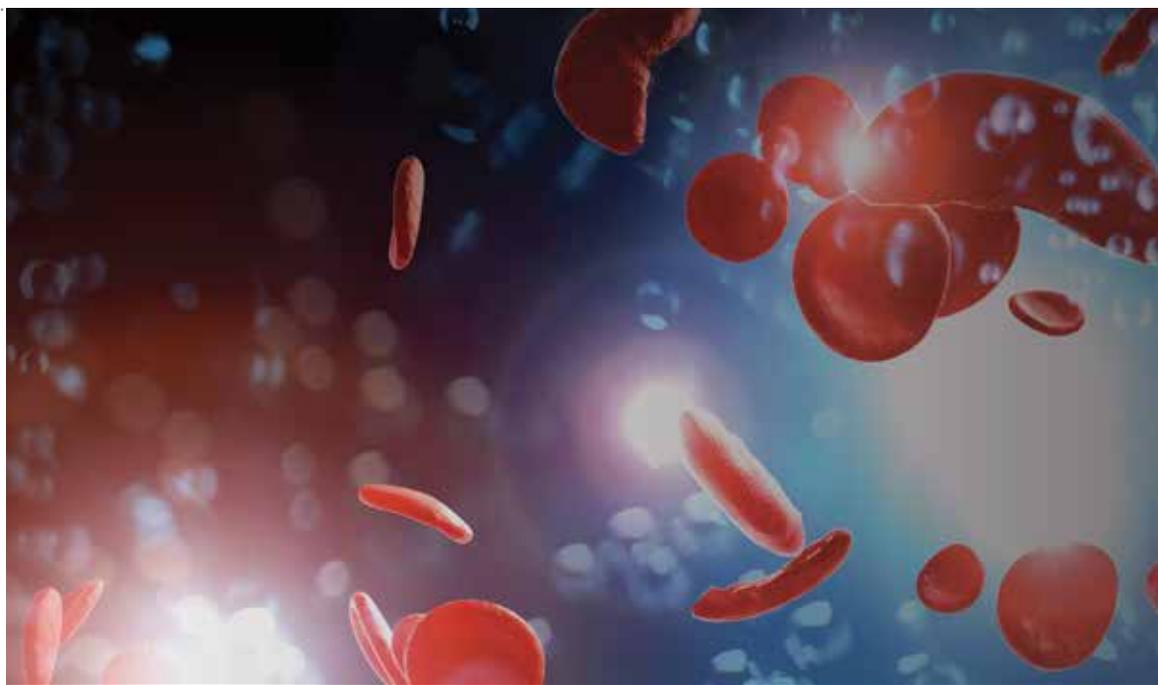
Crizanlizumab

Crizanlizumab is a monoclonal antibody for p-selectin, a cell adhesion molecule found on platelets and endothelial cells (5). It is taken as a monthly intravenous infusion and has been shown to reduce episodes of pain crises alone and in combination with hydroxyurea. By blocking p-selectin it reduces cell adhesion to the endothelium, subsequently reducing vaso-occlusive events (5).

Voxelotor

Voxelotor is a small molecule that reversibly binds to one α -globin chain within the hemoglobin tetramer and increases the hemoglobin affinity to oxygen (6). This increase in affinity is thought to prevent polymerization and reduce sickling events and subsequent hemolysis.

Voxelotor has been found to increase hemoglobin levels both alone and in combination with hydroxyurea. It was approved in late 2019 for the treatment of SCD in adults and pediatric patients >12 years of age, and in 2021 this approval was extended to patients >4 years of age. It is a tablet taken once a day for patients >12 and a tablet for oral suspension for patients aged 4–11 (9).



Only 18% of people living with sickle cell disease have a possible donor in the registry.

SCD TREATMENTS WITH CURATIVE INTENT

Hematopoietic Stem Cell Treatment

Allogenic stem cell transplants have been shown to cure SCD by replacing the patient's native bone marrow with a transplanted marrow that will produce RBCs with HbA that don't sickle. A study of 1,000 patients who underwent matched related donor transplants showed a 5-year survival of 92.9% and event-free survival of 91.4%.

While hematopoietic stem cell transplant is a possible curative therapy, there are currently significant barriers to using it for most patients with SCD. An estimated 18% of people living with SCD have a possible matched related donor, and only an additional 18% of people living with SCD have a possible donor in the registry. The rates of event-free survival are lower for patients whose transplant was from a nonrelated matched donor from the bone marrow registry (7).

Gene Therapy

Gene therapy may be a possible curative treatment option for those

who do not have a possible matched related donor for stem cell transplantation. Gene therapy works by taking the patient's own stem cells, modifying them, and then replacing the patient's native bone marrow with the modified cells.

Multiple modification methods and targets for modification are currently being studied, and it remains to be seen which methods will prove superior. Additionally, researchers have yet to determine whether the effects of gene modification will last long enough for this to serve as a curative treatment. However, studies haven't ruled out the potential for gene therapy to offer a curative treatment for some SCD patients either (8).

LABORATORY METHODS FOR MONITORING AND MANAGING PATIENTS

There are numerous methods available to diagnose hemoglobinopathies. The first is hemoglobin fractionation and consists of separating hemoglobin species based on charge and/or size. Hemoglobin fractionation can be performed by high-performance liquid chromatography (HPLC) methods,

capillary electrophoresis (CZE) methods, and gel electrophoresis methods (alkaline and acid gels and isoelectric focusing [IEF] gels).

HPLC separates hemoglobin fractions based on charge, whereas with CZE and gel methods, separation is based on both size and charge. HPLC and CZE are high resolution quantitative techniques. Gel methods, on the other hand, are low resolution compared to HPLC and CZE, although they can be semiquantitative.

Mass spectrometry and molecular methods (sequencing and deletion/duplication) are extremely powerful techniques for diagnosing hemoglobinopathies and thalassemia, particularly those that are challenging to diagnose with HPLC, CZE, and gel methods. However, these methods

are for qualitative identification and do not quantify hemoglobin species.

Patients with SCD have historically been managed by RBC transfusions and/or hydroxyurea. Managing and monitoring patients on these treatments requires discrimination and accurate quantitation of the various hemoglobin species; therefore, HPLC or CZE are the preferred methods for following these patients.

Gel methods, molecular genetics, and mass spectrometry methods are powerful tools for diagnosis but are not as well-suited for managing SCD. The 2021-B College of American Pathologists (CAP) hemoglobinopathy peer evaluation survey showed that 95% of respondents quantified hemoglobin species via HPLC or CZE methods.

Monitoring RBC Transfusion

Typically, quantitation of HbS% is completed prior to transfusion (pretransfusion) to calculate the units of RBCs to be transfused. A posttransfusion HbS% measurement is used to determine efficacy of treatment. In addition to hemoglobin fractionation, iron overload is a concern for patients undergoing transfusions and iron and ferritin should be monitored. Alloantibodies should also be monitored to limit the potential of transfusion reactions, especially after repeated transfusions.

Managing Hydroxyurea Dosage and Monitoring Compliance

For patients treated with hydroxyurea, HbF% is used to monitor dosage and compliance. In addition to hemoglobin fractionation, patients treated with hydroxyurea are monitored with serial CBC measurements to determine efficacy of treatment and guide dosing changes. As hydroxyurea doses are increased, HbF increases and inflammation markers decrease—and at high doses, neutrophil populations decrease and general leukopenia eventually sets in.

Typically, hydroxyurea dosing is increased until the patient's maximally tolerated dose (MTD) is reached. CBC parameters such as white blood cell and neutrophil counts are monitored to determine this point and to ensure that patients have sufficient leukocytes. As cells with HbF are typically larger than other RBCs, the mean corpuscular volume may also be used to monitor treatment efficacy.

Monitoring Stem Cell Transplants

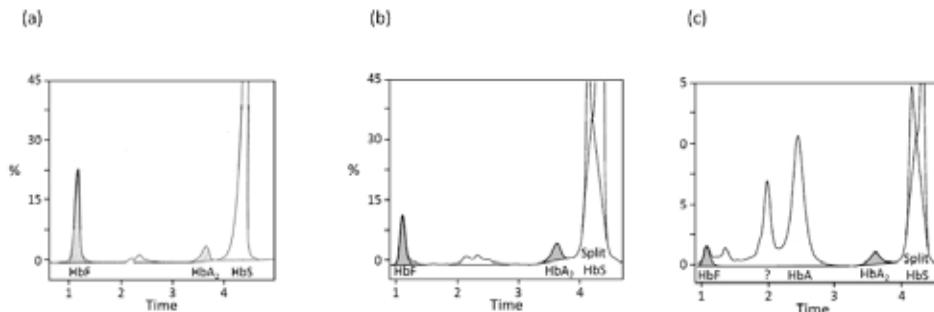
Hemoglobin quantification is often performed on patients who undergo stem cell transplant to assess the health of the graft.

Crizanlizumab

Crizanlizumab is a monoclonal antibody treatment approved in 2019. As crizanlizumab is delivered through an infusion, most monitoring is acute and centered around infusion-related reactions such as pain, gastrointestinal upset, and fever. It is also important to note that p-selectin is displayed on platelet surfaces and there have been reports

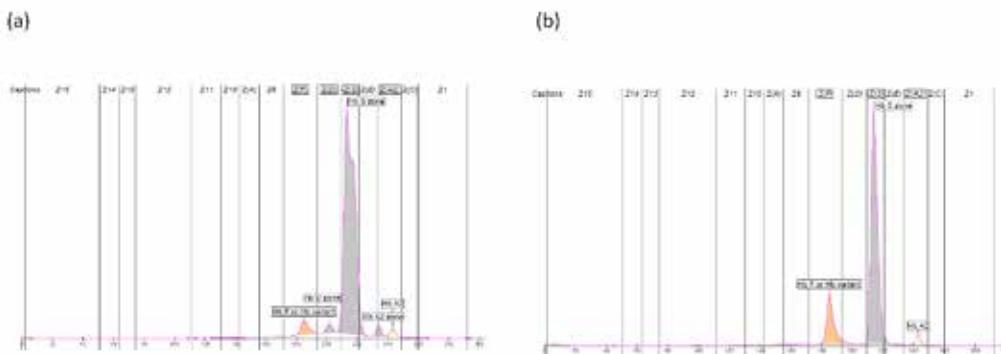
F2

Cation HPLC of A) HbSS patient, B) the same HbSS patient after treatment with voxelotor, and C) the same HbSS patient treated with voxelotor, post-transfusion.



F3

CZE of A) untreated patient with genotype HbSS and B) an HbSS patient treated with voxelotor.





Laboratorians at centers where patients are treated with voxelotor should be aware of how to recognize its interference and the impact it can have on reporting results.

of platelet clumping after administration, particularly for collections into EDTA-containing collection devices. Platelet clumping is a postcollection phenomenon and does not reflect an in vivo condition; however, it can falsely reduce platelet counts on automated analyzers. Because of this, platelet counts from tubes with citrate or heparin anticoagulant (which do not show this effect) may sometimes be used for monitoring in this patient population.

INTERFERENCE OF VOXELOTOR WITH HbS% QUANTITATION

In January 2018, a patient presented to the emergency department at Vanderbilt University Medical Center in sickle cell crisis. An emergent RBC exchange transfusion was scheduled and pre-exchange HbS% quantitation ordered. The patient had a reported diagnosis of genotype HbSS. Our laboratory noted an unusual chromatogram and paged the attending clinical chemists for a consult. Instead of a single distinct peak in the HbS peak region, there were two overlapping peaks that spanned the HbD and HbS windows, giving the appearance of a “split peak” (Figure 2b). Interestingly, a review of our patient’s previous chromatogram showed a well resolved HbS peak, consistent with his HbSS

genotype (Figure 2a). We discussed our findings with the clinical team and the patient ultimately received 10 units of RBCs. Our patient presented 2 weeks after his RBC exchange for follow up. In addition to the “split peak,” the hemoglobin fractionation chromatogram exhibited two additional distinct peaks near HbF and HbA (Figure 2c).

Upon further investigation, we discovered that the patient had recently been enrolled in a phase 3 clinical trial for voxelotor (NCT03036812) and was not taking the placebo. Given that the α -globin chain is not specific to HbS, we suspected that the additional peaks could be due to other voxelotor-hemoglobin complexes. Hemoglobin fractionation by CZE on the posttransfusion sample also demonstrated a “split HbS” peak and two additional peaks (Figure 3). With our colleagues, we conducted qualitative MALDI mass spectrometry studies that confirmed the presence of voxelotor-hemoglobin α chains in our patient’s sample (10).

To our knowledge, this was the first report that patients treated with voxelotor exhibited markedly altered HPLC and CZE chromatograms and additional peaks in IEF (10). To assess how voxelotor affects accurate quantitation, we performed in vitro spiking experiments to mimic



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voxelotor treatment and quantified the impact on HPLC, CZE, and acid and alkaline gels (11). These studies demonstrated that the formation of voxelotor-hemoglobin species affects accurate quantitation of multiple different hemoglobin species. The 2021-B CAP hemoglobinopathy peer evaluation survey showed that approximately 87% of laboratory respondents quantified hemoglobin species via HPLC, CZE, or gel methods that were evaluated in this study and would be unable to resolve this interference. The remaining HPLC and CZE methods were not evaluated in this study.

THE ROLE OF CLINICAL LABORATORIES IN PATIENT MANAGEMENT

Clinical laboratories should take an active role in ensuring that SCD patients get effective treatment. In the case of voxelotor specifically, laboratorians who are at centers where patients are treated with this

drug should be aware of how to recognize its interference and the impact it can have on reporting results. One potential way of communicating this interference to clinicians is the addition of a comment in the report notifying clinicians. One laboratory also has reported creating an automated order inquiry for quantitative hemoglobin fractionation that asks the clinician if the patient is taking voxelotor (12). Close communication between hematologists, transfusion medicine physicians, and laboratorians is crucial to successfully managing these patients.

A key question is whether the HbS-voxelotor complexes should be considered clinically equivalent to HbS for the purposes of transfusion or medication management, or if they should be treated as two distinct species, one sickling and one nonsickling. This will have implications for how results are reported, which currently available testing methods should be

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used, and if a separate field is needed to account for Hb-voxelotor complexes.

The ability to accurately detect Hb-voxelotor complexes is exciting due to the potential for monitoring patient compliance, dose titration, and quantitative measurements that can be linked to patient outcomes. However, clinical consensus and guidance are still needed on how to report hemoglobin species in patients treated with voxelotor (11). ■

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REFERENCES

1. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. *N Engl J Med* 2017;376:1561–73.
2. Chou ST, Alsawas M, Fasano RM, et al. American Society of Hematology 2020 guidelines for sickle cell disease: Transfusion support. *Blood Adv* 2020;4:327–55.
3. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *N Engl J Med* 1995;332:1317–22.
4. Niihara Y, Miller ST, Kanter J, et al. A phase 3 trial of L-glutamine in sickle cell disease. *N Engl J Med* 2018;379:226–35.
5. Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. *N Engl J Med* 2017;376:429–39.
6. Vichinsky E, Hoppe CC, Ataga KI, et al. A phase 3 randomized trial of voxelotor in sickle cell disease. *N Engl J Med* 2019;381:509–19.
7. Gluckman E, Cappelli B, Bernaudin F, et al. Sickle cell disease: An international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. *Blood* 2017;129:1548–56.
8. Abraham AA and Tisdale JF. Gene therapy for sickle cell disease: Moving from the bench to the bedside. *Blood* 2021;138:932–41.
9. Oxbryta (voxelotor) package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213137s006lbl.pdf (Accessed May 2022).
10. Rutherford NJ, Thoren KL, Shajani-Yi Z, et al. Voxelotor (GBT440) produces interference in measurements of hemoglobin S. *Clin Chim Acta* 2018;482:57–.
11. Rutherford-Parker NJ, Campbell ST, Colby JM, et al. Voxelotor treatment interferes with quantitative and qualitative hemoglobin variant analysis in multiple sickle cell disease genotypes. *Am J Clin Pathol* 2020;154:627–34.
12. Godbey EA, Anderson MR, M Bachmann L, et al. How do we monitor hemoglobin S in patients who undergo red blood cell exchange and take voxelotor? *Transfusion* 2021;61:1680–3.

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Remaining Hurdles in Body Fluid Testing

Potential issues with assay analytical sensitivity and deriving decision limits are just two of the many challenges clinical laboratories still face.

BY DARCI R. BLOCK, PHD, DABCC, FAACC

For decades, body fluid testing has been a routine practice within clinical laboratories both large and small, and in the past 10–15 years especially, major strides have been made in understanding the practicalities of testing these fluids. The first Clinical and Laboratory Standards Institute (CLSI) document on the analysis of body fluids in clinical chemistry was published in 2007 (3). It summarized the usefulness of measuring a wide variety of analytes in a host of body fluids, and it was recently revised to include a robust tutorial on analytical validation, as well (1–5). Following the initial release of that CLSI document, the College of American Pathologists created a specific body fluid checklist item (COM.40620) to guide laboratories more specifically in the analytical validation of alternate specimen types, and academic research was published in the peer reviewed literature depicting performance characteristics of body fluid validation studies (6).

Despite these advances, many hurdles remain for the clinical chemistry laboratory performing body fluid testing today, from streamlining ordering to implementing literature-derived decision limits. Here we discuss important considerations that labs should take into account when facing these challenges, as

well as the most up-to-date approaches to tackling them.

ORDERING PRACTICALITIES: HOW DO YOU SAY POTATO?

First, let's be real. Many of us have endured electronic health record (EHR) or lab information system (LIS) upgrades lately that also ripped off the band-aid of manual (often paper-based) ordering systems for body fluids. And honestly, this shift away from manual ordering isn't always a good thing. In the haste of optimization, we may miss the simplicity of such manual processes because it turns out that body fluids are collected in so many different settings that electronic systems just do not seem to be as flexible as the oldpen-and-paper systems. These settings include scheduled and unscheduled procedures in the operating room, in radiology, in the emergency department, at the bedside, and in exam rooms. This heterogeneity confuses the EHR and LIS and frustrates the people who rely on them.

The laboratory has a handle on which tests are most useful to perform for each of the specific body fluid types and has likely validated those types that are most often received and deemed useful. These become the "routine orderable" body fluid tests. There is a delicate balance between listing the entire dictionary of

human anatomy and offering enough descriptors to differentiate the body fluid sources adequately. The lab should assist with designing the ordering screens for tests that are offered and provide input for configuration of the dropdown lists and/or ordering buttons to match those analytes often ordered together. For example, total protein and lactate dehydrogenase (LDH) would have pleural fluid listed

If you want to have a good debate, ask your colleagues to explain the difference between body fluid type versus source.

first. There should also be an option for anatomic locations (e.g., left and right). Oops, the list just doubled in length. What is more, this must be done in concert with multiple laboratory sections (e.g., microbiology, cytology, hematology) that do not often share workflows or sometimes even nomenclature paradigms. If you want to have a good debate, ask your colleagues to explain the difference between body fluid type versus source. The challenge is satisfying

everyone's needs and being able to do it in two clicks. Good luck!

The logical way to offer these tests is within procedure order sets such as lumbar puncture, thoracentesis, arthrocentesis, etc. The cerebrospinal fluid (CSF) tests can be quite numerous, and this list can get rather unwieldy. Further stratification, in consultation with neurology and informatics, can help to organize the list into frequent (perhaps with tests selected by default), common (tests listed but not default selected), and rare (specialty and other esoteric tests may or may not be listed depending on how click happy your clinicians are). There may be further opportunity to subdivide by indication such as "infectious disease" and further differentiate tests for viruses, fungi, etc. The challenge here is coming up with a strategy that suits all users and whose comprehensiveness meets their expectations, and then convincing a programmer that it is worth it. Again—good luck!

Even after the above efforts, these order sets may or may not be available everywhere ordering is performed; thus, old school search and find also needs to work. When in doubt, get your downtime form out. The bottom line is that the cleaner and more thoughtful the upfront ordering is, the more useful the label

logic that prints specimen labels can be, and the more organized the results display ultimately will be.

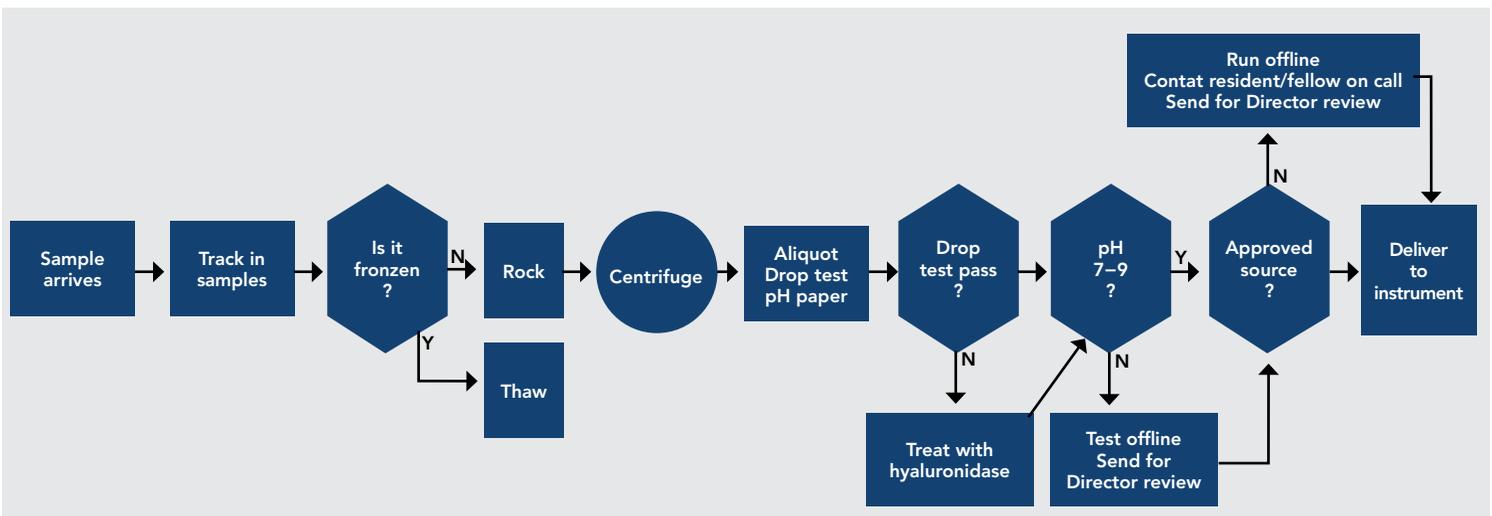
PROCESSING PRACTICALITIES: YOU WANT ME TO WHAT?

The goal of specimen processing is to prepare the sample for analysis and do all that is necessary to reduce the risk for error. When it comes to processing body fluids, one really must wonder how different it can be from processing other "normal" specimens received in the laboratory. What seems simple, however, is actually a fairly involved manual process (Figure 1).

For example, we now appreciate that there is some amount of order and label reconciliation that may need to occur once a specimen arrives at the laboratory. Because these specimens are procured from a broad variety of settings and collectors, it is also reasonable to expect variations in container types and sizes.

It may be necessary for lab staff to aliquot the sample into instrument-ready tubes and affix a new label. Next, one may wonder if it is necessary to centrifuge the sample. At times, the cellularity of the sample may be minimal, and if the tube is destined for cell counting, of course, skip the centrifuge. However, body fluids often come with all manner of particulate, including cellularity,

F1 Body Fluid Process Workflow



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Type 1 Diabetes

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viscosity, and of course, color. A best practice is to centrifuge all body fluid samples and then dispense the supernatant into a new tube. Admittedly, this might be overkill, but at the very least the sample should not be left in contact with a noticeable pellet on the bottom of the tube that could interfere with instrument sampling.

This brings us to the next hurdle. Different instruments and sampling mechanisms can have different sensitivities to sample viscosity. Many manufacturers use mechanisms intended to sense fibrin clots that could potentially clog the probe or cause missampling. This triggers a warning to the operator not to trust these results, which ultimately prevents the reporting of inaccurate results. These mechanisms are calibrated for “approved fluids” such as serum or plasma as well as urine or CSF. However, body fluids can demonstrate extreme viscosity much higher than serum. The viscosity of water at 20°C is 1.0 centipoise (cP) and “healthy” serum is <1.5 cP. Serum from patients with hypergammaglobulinemia with or without symptoms of hyperviscosity syndrome will have a viscosity that is >3.0 cP and >10 cP in case reports. These highly viscous samples produce “clot” errors when aspirated on automated analyzers for testing. Laboratorians also describe fluids that are so viscous, they are unable to draw them into a normal pipette, much less an instrument set to aspirate 2 µL.

All this to say, when processing body fluids, it is wise to perform an assessment of the viscosity. The goal is to prevent potential damage to instrument probes and avoid the potential for mis-sampling that does not generate the error flag because of the wide difference between how the system was designed and what we are introducing from highly viscous body fluids. A quick and simple “drop test” using a pipette to evaluate the shape of the body fluid drop as it exits a pipette tip back into the test tube is sufficient (7). The rounder and less elongated the drop is, the closer the viscosity is to water and the less likely it is that the sample will cause issues with the instrument. What are the options for those viscous samples that do not pass the drop test? This has not been studied extensively; however, some suggestions are offered in the CLSI guideline. These include dilution, freeze-thaw, and treatment with hyaluronidase, which is an enzyme that cleaves the glycosidic bonds converting hyaluronic acid into less viscous monosaccharides (5).

When the laboratory is doing their manual viscosity check, it may also be prudent to consider a cursory check of pH, as this has been demonstrated to influence the measurable activity of enzymes (8). A low pH of <7 can be observed in many different sample types, some of which are obvious, such as gastric fluid, and some of which, like peritoneal fluid, aren't. The concern is that low pH will diminish enzyme

activity, rendering it unrecoverable with neutralization despite having elevated concentrations to start with. Therefore, result comments can be applied to help communicate the potential impact on results or cancellation of testing after clarifying the intent of testing with the provider. In summary, the hurdles for processing body fluids are the numerous manual tasks that do not fit into routine workflows. These can take significant time and effort, depending on the number of body fluid orders a testing laboratory receives.

TESTING PRACTICALITIES: MIND THE GAP

As mentioned earlier, there has been significant progress in understanding the practicalities of testing when it comes to body fluids. Guidance is now available for how to conduct an analytical validation (5). Numerous validation studies that demonstrate minimal matrix interferences and acceptable imprecision to meet clinical reporting needs have also been published.

The testing hurdle at this juncture is an underappreciation for limitations in the measurement range for assays that are designed for serum but used for body fluids. In many cases the measurement range is suitable for both. However, there could be a concern for analytes that have lower abundance in body fluids as compared to serum or plasma, such as LDH, total protein, albumin, and cholesterol. It is true that for a given instrument manufacturer, the laboratory can choose which application (serum versus urine versus other) best suits the intended measurement range. However, body fluid concentrations for analytes such as those listed above tend to be approximately 50% of serum concentrations, so the urine or CSF assay that measures orders of magnitude lower is typically not helpful.

In a recent body fluid method comparison between five different instrument vendors, Roche, Abbott, and Siemens produced measurable albumin results for all samples while Beckman and Ortho produced undetectable results at lower concentrations owing to the differences in measurement range (9). Table 1 summarizes the manufacturer's measurement ranges and median albumin

T1 AMR for Albumin and Total Protein

Analyte	Serum AMRa	Urine AMR	Median (IQR) Body Fluid Concentration ^b	Median (IQR) Serum Concentration ^b
Albumin (g/dL)	0.4–10.5 Abbott 1.5–6.0 Beckman 1.0–6.0 Vitros 0.3–6.0 Roche 0.1–8.0 Siemens	~x10 ⁻⁴	1.0 (0.6–1.8)	4.1 (3.6–4.5)
Total protein (g/dL)	0.8–18.4 Abbott 3.0–12.0 Beckman 2.0–11.0 Vitros 0.5–12.0 Roche 0.1–12.0 Siemens	~10 ⁻¹	2.6 (1.5–3.7)	6.6 (6.1–7.0)

Analytical measurement ranges (AMR) for albumin and total protein for different assay/instrument manufacturers compared to observed median (IQR: interquartile range) analyte concentration in body fluids and serum.

^a Adapted from Block DR, Cotten SW, Franke D, et al. *Am J Clin Pathol* 2022 (9).

^b Abstract submitted to the 2022 AACC Annual Scientific Meeting in Chicago.



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1. Taylor SN et al. *Expert Rev Mol Diagn.* 2021;21(3):333-42. 2. Ejegod DM et al. *Am J Clin Pathol.* 2021:1-9. 3. BD Onclarity™ HPV Assay for the BD COR™ System Product Insert [L011461]. 4. HTD1-21-0406 BD COR™ Hands-On Setup Time. 5. BD CTGCTV2 for BD COR™ System Product Insert [L012506].

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The hurdle today when testing body fluids is the appropriateness of the measurement range.

concentration in body fluids compared to serum.

In summary, the hurdle today when testing body fluids is the appropriateness of the measurement range, which is reliant on instrument and assay manufacturers, and the willingness of the laboratory to pursue further modification of the assay to accommodate quantitation of body fluid analytes at a lower concentration so that meaningful interpretation can be made.

REPORTING PRACTICALITIES: DID SOMEONE SAY MEANINGFUL INTERPRETATION?

As laboratorians, we strive to provide the most meaningful interpretive guidance for laboratory results that we possibly can. This is because we care deeply about satisfying patient needs and improving outcomes. This includes researching and verifying or establishing the most applicable

reference interval data available to best serve each patient demographic we encounter. Reference intervals tend not to apply since most body fluids present in pathologic volumes amenable to collection are not associated with any state of “health.” Therefore, we rely on providing decision limits and interpretive comments to aid in the interpretation of body fluid test results. Table 2 summarizes three general approaches that have been taken to derive body fluid decision limits.

All of the decision limits identify presence or absence of a condition (such as triglycerides to identify chylous effusion) or differentiate one condition from another (such as transudate from exudate). Many decision limits were derived by comparing to the analyte concentration measured in serum. This opens a set of questions that are not easily answered, including how best to ensure a blood sample is collected and how near to the time of the body fluid collection that blood should be collected. Limited evidence suggests within 24 hours is best and for the reasons outlined above, ensuring this is done is nontrivial.

Many body fluid analytes have been studied, and decision limits are available in the published literature. The number of studies vary from the time-tested Light’s criteria to the

scant number available for certain analytes like lipase (10). Most are rather dated, and their methods sections are often ill-described, which means that the largest risk in using published decision limits is transferring them into practice. On the other hand, when the concentration measured in body fluids is compared with a measured serum concentration or expected serum concentration, the risk is theoretically lower since one could postulate that the ratio between body fluid and serum should be equal, independent of method. This assumption proved to be true for many analytes in a body fluid method comparison study performed by my lab; however, it did not hold true for every method and analyte studied (9). For example, creatinine demonstrated bias in several but not all body fluids, with one method at elevated concentrations (>3 mg/dL) that was not observed in serum or at lower concentrations, suggesting that the ratio of >1.0 to detect the presence of urine may need to be adjusted. A similar observation was made with glucose and urea suggesting further study is warranted.

Unfortunately, there is no gold standard body fluid method available so establishing a source of truth is impossible. Therefore, literature-derived decision limits are actually the best option for providing interpretive guidance for body fluid tests, but laboratories should be cognizant of the reputability of these decision limits and understand the risks in transferring them into practice today.

CONCLUSIONS

Body fluid test ordering is a challenge for everyone, so don’t feel bad if you experience problems with it. Body fluid processing is a time-consuming and manual endeavor that really is best considered a labor of love. Be mindful of the analytical sensitivity of the assays used to measure body fluid analytes by looking for an abundance of undetectable or “less than” results in body fluids not affecting the serum test. And lastly, laboratories should be wary of blindly transferring body fluid decision limits into practice from published studies, as bias between methods has been found that could affect interpretation. ■

T2 Summary of Interpretive Paradigms for Interpreting Body Fluid Results

Interpretive Paradigm	Description	Measurement	Source	Theoretical Risk in Transferring From Literature	Example Analytes
Definitive value	Measure analyte in body fluid alone	Body fluid only	Literature	High	Bilirubin, Cholesterol, Triglycerides
Compare to serum	Measure analyte in body fluid and serum. Interpret as a gradient or ratio.	Serum and body fluid	Literature	Low	Albumin, Total Protein, Amylase, Lipase, Bilirubin, Glucose, LDH, Creatinine, Urea
Compare to normal serum values	Measure analyte in body fluid alone. Interpret based on expected concentration in serum (e.g., upper limit of reference interval).	Body fluid only	Literature	Low/medium	Amylase, Lipase, LDH

LDH: lactate dehydrogenase.

REFERENCES

1. Light RW. The Light criteria: The beginning and why they are useful 40 years later. *Clin Chest Medicine* 2013;34:21–6.
2. Wians FH. To test or not to test? Opening Pandora's box. *Lab Med* 2004;35:707.
3. Clinical and Laboratory Standards Institute (CLSI). Analysis of body fluids in clinical chemistry; Approved guideline. CLSI document C49–A. Wayne, PA: CLSI 2007.
4. Ritchie JC. Is it time to remove the stigma of LDT from body fluid chemistry assays? <https://www.aacc.org/science-and-research/scientific-shorts/2011/is-it-time-to-remove-the-stigma-of-ldt-from-body-fluid-chemistry-assays> (Accessed July 26, 2011).
5. CLSI. Analysis of body fluids in clinical chemistry; Approved guideline. CLSI document C49–B. Wayne, PA: CLSI 2018.
6. Block DR, Ouverson LJ, Wittwer CA, et al. An approach to analytical validation and testing of body fluid assays for the automated clinical laboratory. *Clin Biochem* 2018;58:44–52.
7. Block DR, Florkowski CM. Body fluids. In: Rifai N, ed. *Tietz textbook of clinical chemistry and molecular diagnostics*. 6th Ed. St. Louis, MO: Elsevier 2018;925–e35.
8. Nandakumar V, Dolan CT, Baumann NA, et al. Effect of pH on the quantification of common chemistry analytes in body fluid specimens using the Roche cobas analyzer for clinical diagnostic testing. *Am J Clin Pathol* 2021;156:722–7.
9. Block DR, Cotten SW, Franke D, et al. Comparison of five common analyzers in the measurement of chemistry analytes in an authentic cohort of body fluid specimens. *Am J Clin Pathol* 2022; doi: 10.1093/ajcp/aqab218.
10. Block DR, Algeciras-Schimmich A. Body fluid analysis: Clinical utility and applicability of published studies to guide interpretation of today's laboratory testing in serous fluids. *Crit Rev Clin Lab Sci* 2013;50:107–24.

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BY JAMES HELLEWELL, MD, MS, AND RICHARD GILROY, MD

Resolving the Ammonia Paradox

A paradox is a statement or proposition that, despite sound (or apparently sound) reasoning from acceptable premises, leads to a conclusion or action that is senseless. In the ammonia paradox, measuring ammonia levels in confused cirrhotic patients with hepatic encephalopathy (HE) is, to paraphrase Adrian Reuben, MD, an action that creates greater confusion in those ordering the test than the confusion present in the patient (1).

Uncertainty creates, in the provider, a desire to resolve it. Tests are ordered to improve certainty and reasons to test include establishing a diagnosis or prognosis, to guide management based upon the result, or to exclude a diagnosis. With ammonia levels, the clinician is hoping the level will provide any or all of these.

In noncirrhotic patients with fulminant hepatic failure, when the ammonia level is greater than 150 µg/dL it does predict prognosis (cerebral edema or death) and a

need for a higher level of care like a transplant program. However, in those with cirrhosis, the ammonia level has little, if any, predictive or clinical value in HE for multiple reasons (2) (Table 1).

The Ammonia Level Project

Until recently, providers ordered approximately 14,000 ammonia level tests annually in the Intermountain Healthcare system. This is despite several publications and numerous local educational endeavors about the absence of the test's value in patients with HE. Further analysis confirmed that approximately 90% of the 14,000 were ordered inappropriately.

With the ammonia level project, the idea for change started with the observation that providers frequently referred patients for ammonia level assessment. Preliminary analysis identified that the emergency department (ED) appeared to order the test most frequently. Further analysis showed ammonia level results were often a

prerequisite before admission and low levels appeared to generate additional tests, like head CT scans.

Some patients admitted with HE underwent serial ammonia levels during their hospitalization. In certain instances, despite clinical resolution of HE, patient discharges were delayed while awaiting normalization of the level. When asked, all parties involved stated that someone associated with the patient's evaluation or management needed the result—although hepatology, the consulting service in several cases, was not interested in the result.

Designing and Testing an Intervention

We approached the process in three phases (Table 2). Initially we deployed educational programs for the ED and hospitalist services, shared reading material on HE and ammonia levels, and conducted interviews with involved parties seeking to understand the reason for ordering the test. The impact of this first phase on tests

F1 Ammonia Decision Support Solution

Ammonia Level Indication

Ammonia levels are often ordered in situations where they do not assist care, such as to assess confusion or response to therapy in patients with known cirrhosis (Ge, Runyon, Serum Ammonia Level for the Evaluation of Hepatic Encephalopathy. JAMA 2014; 312(6):643–644).

You may choose to cancel the order, or provide an indication for it using the **Document** button below.

Alert Action:

Cancel Ammonia Level

Ammonia Level Indication

Despite NOT being indicated to assess confusion or responses to therapy in adult patients with a diagnosis of cirrhosis, greater than 12,500 ammonia levels, often multiple in any individual patient, were ordered in the system in patients with cirrhosis in 2018.

Click cancel to go back or document reasons for use below and sign form.

"Other" reasons may be appropriate. The information documented will be viewable in the patient.

- Confusion or an altered level of consciousness in a patient without cirrhosis
- Acute liver failure (ie. acute change to liver enzymes or function in patient without cirrhosis)
- Drug or medication induced confusion (e.g. valproic acid)
- Family history or concern for urea disorders or an inborn error metabolism
- Other

ordered was limited and reduced the number of tests minimally.

For the second phase, we identified the electronic medical record (EMR) as a common step in placing ammonia level orders. Given the objective to reduce inappropriate ordering, we selected an order time decision support solution.

The intervention consists of two parts. First, upon ordering an ammonia level test, an informational alert suggests the clinician consider the appropriateness of the test. Second, if the clinician chooses to proceed with testing, a prompt appears to enter the indication for testing and is required to proceed (Figure 1).

In reviewing provider ordering patterns before and after implementation of the EMR based intervention, it was noted that some providers were influenced by the solution more than others (Figure 2, online) and some groups more than others (ER physicians ~45% reduction versus outpatient physicians 3.5%). This suggested an opportunity to further reduce inappropriate orders with additional interventions, such as report cards to providers showing their ordering frequency as compared to their peers.

The average number of tests dropped from 1150 to 650 per month after implementation of the EMR based intervention. At a cost of \$42 per test, savings approach \$250,000 a year. Additional benefits yet to be confirmed include reduced

ED length of stay (LOS)—increased ED bed availability—as well as shorter time to treatment initiation, reduced hospital LOS, and reduced subsequent testing, such as head CT.

In an era that requires prioritization of value-based care principals, initiatives to reduce inappropriate testing are increasingly important. At Intermountain, reduced inappropriate ammonia level testing has yielded cost savings without diminishing. The initiative has enhanced value. There are many opportunities, across multiple clinical settings, to which these principals can be applied to generate substantial savings while maintaining the highest quality of care. We only ask that you look for these and then tell us your story of success.

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References

1. Reuben A. There is nothin' like a Dame. *Hepatology* 2002;35:983–5.
2. Ge PS, Runyon BA. Serum ammonia level for the evaluation of hepatic encephalopathy. *JAMA* 2014;312:643–4.

T1 Managing Cirrhotic Patients With Hepatic Encephalopathy

Unnecessary tests lead to waste and drive up costs. With hepatic encephalopathy (HE) in a patient with cirrhosis, appropriate management does not require an ammonia test but rather a medical history and evaluation that focuses upon:
<ul style="list-style-type: none"> • What occurred before development of HE (new medications, medication changes, medication non-compliance [lactulose], new gastrointestinal bleed symptoms, or signs and/or symptoms of infection)
<ul style="list-style-type: none"> • Review of medications (in particular opioids or sedatives)
<ul style="list-style-type: none"> • Clinical examination for signs of infection, melaena, ascites, pneumonia, or abdominal pain
<ul style="list-style-type: none"> • Paracentesis if ascites is present in the presence of HE
<ul style="list-style-type: none"> • Comprehensive metabolic panel to assess for electrolyte changes or an acute kidney injury
<ul style="list-style-type: none"> • Complete blood count to explore for shifts in white cell count or a new drop in hemoglobin
<ul style="list-style-type: none"> • Review of prior events of HE for precipitating events
<ul style="list-style-type: none"> • Occasional imaging studies for those with atypical HE presentations with localizing symptoms

T2 A Stepwise Laboratory Stewardship Process

Phase 1

1. Deploy educational programs for the ED and hospitalist services.
2. Share reading material on HE and ammonia levels.
3. Conduct interviews with involved parties seeking to understand the reason for ordering the test.

Phase 2

1. Obtain frequency and demographic data (test volumes, ordering provider, association of cirrhosis ICD-10 diagnosis) and conduct sample analysis to determine test appropriateness.
2. Evaluate test accuracy, which in the case of ammonia levels is notoriously inaccurate due to challenges with collection and processing.
3. Recognize the opportunity, and with the data from step 1, write and present a brief to the stewardship committee defining the Subject, Background, Assessment, and Recommendation. Before investing in a change, a proposal must be vetted.
4. Identify a team of equally invested partners, with differing yet valued skill sets. In this instance, the Laboratory Stewardship Co-Chairs (Senior Medical Directors for Medical Specialties and Laboratory) and other leaders from Lab Operations, ED Operations, and Clinical Informatics.
5. Establish the objective (reducing inappropriate tests), set meeting schedules (schedule created with first meeting), and define timelines (set reasonable goals from start to implementation).
6. Having previously established why, develop the process of how to effect change (i.e., design the intervention).
7. Communicate the change to those who will be affected by the intervention (e.g., hospitalists, ED physicians, gastroenterologists).
8. Implement the intervention on the previously determined date.
9. Create a dashboard of variables of interest to measure effectiveness of the intervention.
10. Calculate economic benefits, direct (reduced test costs) and indirect (reduced length of stay [LOS] in ED, reduced number of head CTs).

Phase 3

1. Review the dashboard for populations in whom the intervention did not work (provider report by specialty).
2. Revise the approach to address deficiencies (share report cards of their actions versus their peers).
3. Recalculate economic (direct and indirect) and clinical benefit.
4. Tell the story to the institutional leadership and colleagues.
5. Petition others to consider their world for similar opportunities.
6. Develop new projects with new partners.

Phases 1 and 2 are nearing completion. The organization currently is conducting phase 3.

LABORATORY STEWARDSHIP FOCUS



BY SAM HUANG, MD, AND JESSIE CONTA, MS, LGC

How to Successfully Navigate the Insurance Denial Appeal Process for Genetic Tests

Seattle Children's Hospital (SCH) implemented a laboratory test stewardship program with focus on genetic testing in 2012. Key to the program has been the hospital's ability to standardize the prior authorization process and integrate it with the test stewardship review program. Given genetic testing's relative cost and evolving coverage policies, aligning test requests with payer requirements has been critical to reducing financial liability for patients, families, and the institution (1).

However, annual surveys revealed that providers were frustrated with the insurance authorization process, specifically with the burden of navigating denials and appeals. For example, one respondent commented that "sometimes it takes time to get the paperwork with the [denial] reason ... and what a provider may do to appeal the denial isn't always clear."

In the spirit of continuous performance improvement, we sought to improve the current denial and appeal process through targeted interventions to support providers and their teams, and ultimately increase the likelihood of a successful appeal.

Defining the Problem

Coverage of a genetic test is based upon the policies and the specific benefit structure of a patient's health plan. Common reasons for denials include not medically necessary (NMN) and investigational/experimental (I/E) (2). Understanding the specific denial reason and tailoring the appeal

accordingly helps prioritize the efforts of busy teams. It also informs communication with patients about what to expect.

An appeal letter demonstrating how a patient fits the policy is effective when the denial reason is NMN because it addresses details that the payer may have lacked in its initial review. Payers are less likely to overturn denials for other reasons, such as I/E. Other denials simply are not appealable. For example, if a request

is denied because genetic testing is not a covered benefit, no amount of persuasion will change the outcome.

We completed a baseline assessment via interviews with staff and providers within departments that coordinate a high volume of genetic test requests, including both genetics and nongenetics specialties. This revealed a gap in understanding about the implications of the denial reason and how to target appeals accordingly. In fact, providers were

T1 Demystifying Insurance Jargon

Denial Reason	What This Means for You	What You Can Do Next
Not Medically Necessary: Genetic testing is a covered benefit, and the payer has a specific coverage policy, but the payer assessed that the patient does not meet its coverage criteria.	This type of denial is the most likely to be overturned if the patient meets the specific coverage criteria. The goal of the appeal is to provide any missing elements or additional information to support how your patient meets the policy.	<ul style="list-style-type: none"> ✓ Review the insurance payer policy used in the denial letter, if provided. ✓ Submit a letter explaining why your patient meets the payer criteria or why your patient's case is exceptional. ✓ Focus on your patient's specific situation. Generally, insurance payers want to know how testing will affect the patient, not about the technical validity of the test.
Investigational/ Experimental: The payer either does not have a coverage policy for the test, or their policy states that this test is not covered.	This type of denial is unlikely (but not impossible) to be overturned. The goal of the appeal is to push the payer to update their policy, even if it's unlikely to affect this patient.	<ul style="list-style-type: none"> ✓ Submit a letter simply reiterating the medical necessity rationale in your clinic note and ask for an exception to the insurance payer policy for your patient. ✓ Prepare the family to seek financial assistance.

Excerpt from the general guidance document created to help teams understand denial reasons, their implications, and what to do next.

appealing genetic testing denials mostly in a test-specific or disease-specific manner, rather than focusing on the denial reason and policy.

We discovered that the reason for their approach was an entrenched library of appeal letter templates that had accreted over years. Filling out these templates is time-consuming, resulting in lengthy letters that feature abundant clinical detail and references to the literature—but a scattershot approach to arguing medical necessity. Unfortunately, the letters often did not end up addressing the specific coverage policy nor the reasons why the insurance company denied the test. This is neither efficient nor effective.

Our interviews also revealed that letter writers often did not review the payer's denial letter containing the denial reason and policy details. Some letter writers did not know to look for the denial letter. Others found it cumbersome to locate the letter in the electronic medical record (EMR) and so proceeded to compose appeals without referencing the denial information. Even with the letter in hand, they lacked guidance to translate the denial information into an effective appeal.

Over the past 2 years, the laboratory genetic counseling (LabGC) team piloted appeals guidance for genetic testing denials ordered by teams without clinical genetics expertise and support. This guidance focused on tailoring appeals based upon the denial reason. For example, in the case of a NMN denial, the LabGC team would review the specific insurance policy and the clinical features of the patient and help the provider focus the appeal on why the patient fit the policy or was otherwise exceptional.

Comparing the appeals success rate and completion rate between the LabGC-supported, nongenetics group and the genetics group yielded further insights to iterate the intervention. As expected, NMN and I/E were by far the most common denial reasons (52% and 44%, respectively), with similar frequency across both groups. LabGC support improved appeals success when compared with genetics group

appeals for both NMN (51% vs. 33%) and I/E (12% vs. 10%) denials.

Despite support, there remained a gap in the appeals completion rate between the nongenetics and genetics groups (approximately 70% vs. 90%, respectively). Teams still needed to take action to complete the appeal, and reported confusion about next steps, difficulties transforming the guidance into an appeal letter, and integrating the guidance with existing letter templates.

Tailoring the Intervention

Building on these experiences, we collaborated with the teams to develop and implement additional supports to make it as easy as possible to complete effective appeals. This dialogue also served as an opportunity to continue to educate the teams.

Teams needed to be able to identify the denial reason quickly and easily. We developed a job to aid providers find denial letters in the HER, and in collaboration with the Insurance Processing Department, modified the insurance outcome notifications to include a call-out box highlighting the denial reason and accompanying policy. We also modified the notifications for approvals and denials that cannot be appealed.

To help demystify the insurance jargon, we created a new quick reference document with general guidance organized by denial reasons and a short explanation about what to do next (Table 1). This document is directly linked from insurance outcome notifications, improving visibility and ease of access.

The LabGC review and case-by-case guidance expanded to support all genetic testing denials, not just those ordered by nongenetics teams. The suggestions are attached to the insurance outcome notification and build upon the principles laid out in the general guidance, ensuring the need-to-know information comes to teams in one communication.

We also created letter templates with prompts to transform that information into effective appeal letters. These included prompts by denial reason to help providers focus on the important information they needed to include and to serve

as a repository to incorporate the LabGC guidance. The templates are posted on our institution's laboratory stewardship website for teams to easily access and modify.

Measuring Success

Since implementing the new tools and process, we have received positive feedback. A check-in with teams from the high-volume specialties indicated improved awareness of the support tools, improved assessment of communication clarity, and better overall satisfaction with the denials and appeals process. At this time, because of the inherent lag in insurance companies responding to appeals, we are not yet able to assess the impact on denials overturned.

Our teams benefit from getting the key information from denial letters extracted and highlighted in the insurance outcome notification and gaining additional insights from LabGC review. This may not be possible in all clinical practices. Nevertheless, the core principles of identifying the denial reason and tailoring an appeals letter to specifically address it still apply. These insights about the denials and appeals process should help clinical teams be more efficient and effective. ■

References

1. Mathias PC, Conta JH, Konnick EQ, et al. Preventing genetic testing order errors with a laboratory utilization management program. *Am J Clin Pathol* 2016;146:221–6.
2. Washington State. Office of the Insurance Commissioner. Common reasons for a denial and examples of appeal letters. <https://www.insurance.wa.gov/common-reasons-denial-and-examples-appeal-letters> (Accessed May 2022).

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Regulatory Roundup

FDA Grants EUA to Labcorp's Seasonal Respiratory Virus Test

The Food and Drug Administration (FDA) has given emergency use authorization (EUA) to Labcorp's Seasonal Respiratory Virus RT-PCR DTC test. This direct-to-consumer test detects and differentiates RNA from SARS-CoV-2, influenza A, influenza B, and respiratory syncytial virus (RSV) in patients with respiratory viral infection symptoms aligning with COVID-19. Consumers may use the Pixel by Labcorp COVID-19+Flu+RSV test home collection kit to collect anterior nasal swab specimens. Users should then follow Pixel's instructions to mail specimens to authorized laboratories for analysis with the Seasonal Respiratory Virus test. This testing is limited to

Labcorp-designated laboratories that are certified under CLIA to perform high complexity tests.

Under the terms of FDA's EUA for the product, people age 18 years or older can use the test themselves, people age 14 years or older can test themselves under adult supervision, and people age 2 years or older can test with adult assistance. Patients receive their test results through an online portal. If a patient receives positive results, a healthcare provider will contact the person and determine if self-isolation or quarantine is appropriate.



FDA CLEARS ABBOTT'S FREESTYLE LIBRE 3

Abbott has received Food and Drug Administration clearance for the Freestyle Libre 3, a 14-day continuous glucose monitor (CGM) that is the smallest in the world, according to the company. With this clearance, people 4 years and older who have diabetes may use this CGM system. It has a 7.9% overall mean absolute relative difference (MARD), making it the first CGM to feature a MARD under 8%. Alongside its high accuracy, the system is the size of two stacked U.S. pennies and comes with a one-piece applicator that makes it easy to apply. The Freestyle Libre 3

also includes an iOS and Android app that provides real-time glucose tracking and alerts users to the onset of serious medical events.

Freestyle Libre 3 will be available at pharmacies later this year and will be sold for the same price as previous Freestyle Libre models.

FDA APPROVES HOLOGIC'S APTIMA CMV QUANT ASSAY

The Food and Drug Administration (FDA) has approved Hologic's Aptima CMV Quant assay, which quantifies cytomegalovirus (CMV) in patients who have had solid organ or stem cell transplants. Performed on plasma

samples, it uses real-time transcription-mediated amplification and targets the *UL56* gene, with a time-to-result of < 3 hours. It is the first test that Hologic has introduced in the U.S. for post-transplant pathogen detection and monitoring on the company's fully automated Panther system. This system also features tests for HIV-1, hepatitis C, and hepatitis B.

In addition to being approved by FDA, the Aptima CMV Quant assay is CE-marked for diagnostic and viral load monitoring use in Europe. For the future, Hologic also hopes to pursue regulatory approvals for other transplant assays that are currently in development for the BK virus and Epstein-Barr virus.



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HEALTH CANADA APPROVES PANEL FOR RAPID MOLECULAR BLOODSTREAM INFECTION IDENTIFICATION

BioMérieux's Biofire Blood Culture Identification 2 (BCID2) panel has received Health Canada's approval for identifying bloodstream pathogens, antimicrobial resistance genes, and other targets. The test is designed to accelerate sepsis diagnosis, which in turn will help clinicians to identify appropriate therapy for patients faster. According to Jessica Blavignac, director of Scientific and Medical Affairs of bioMérieux Canada, the new panel identifies pathogens up to 70% faster than other bloodstream infection tests. Additionally, it decreases optimal therapy initiation by 33.5 hours.

Biofire BCID2 tests for 43 bloodstream infection targets, including both gram-negative and gram-positive bacteria, yeast, and 10 different antimicrobial resistance genes. The test identifies all these targets from one sample, with results yielding in about an hour from positive blood culture. According to bioMérieux, the new panel has one of the broadest menus available today for a highly multiplexed syndromic panel, as it also covers respiratory, meningitis/encephalitis, and gastrointestinal syndromes.

ANGLE EARNS FDA CLEARANCE FOR PARSORTIX SYSTEM

The Food and Drug Administration (FDA) has cleared Angle's Parsortix system, a liquid biopsy for breast cancer patients. The test analyzes circulating tumor cells, in contrast to standard liquid biopsies, which analyze circulating tumor DNA. This enables the Parsortix system to provide a more complete picture of a patient's cancer development, one that doesn't just examine DNA, but also RNA, protein expression, and the cytology and morphology of the actual cancer cells. This also means that Parsortix results closely approximate the information obtained from metastatic tissue biopsies, and that the test can be used for repeat noninvasive biopsies to assess cancer status.

Angle worked for 6 years to achieve FDA clearance for this test. Over that time, the company conducted validation studies on 300 metastatic breast cancer patients and several thousand healthy volunteer donors.

BD GETS CE MARK FOR SARS-COV-2 AND INFLUENZA A/B TEST

The BD SARS-CoV-2/Flu assay from Becton, Dickinson, and Company (BD) has been CE marked, making it the second test available on the BD Cor PX/MX system to receive this regulatory authorization. This new test is an automated, multiplexed real-time PCR assay that detects and differentiates SARS-CoV-2, influenza A, and influenza B from a single sample. It is intended for use in both symptomatic and asymptomatic patients.

The BD Cor PX instrument prepares samples for the BD SARS-CoV-2/Flu assay by performing the appropriate pre-analytical processing steps and automatically delivering the samples to the BD Cor MX instrument for molecular analysis. The BD Cor MX instrument then performs the extraction, amplification, and detection steps of the test.

Additionally, the BD Cor MX/PX system allows up to 1,700 specimens to be loaded at a time. It has an onboard capacity for reagents and samples that provides more than 6 hours of unimpeded system processing and up to 1,000 sample results in 24 hours.

Pandemic Sparks Fast-Track Innovation through Lab Automation

In response to the COVID-19 pandemic, Pandemic Response Lab (PRL) launched in 2020 to significantly increase testing capabilities in New York City. PRL integrates its parent company's (Opentrons Labworks) laboratory automation equipment with world-renowned scientific expertise from NYU Langone to innovate the PCR process so that samples are analyzed rapidly and reliably at 1/3 market cost. PRL's automated pipeline and operational efficiency enable the capacity to process 100,000+

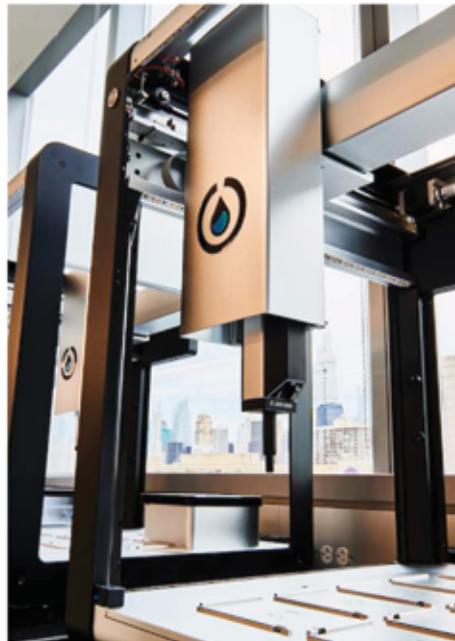
tests per day, delivering 99 percent of results within 24 hours. In under two years, PRL has opened three CLIA-certified labs and recently launched a syndromic respiratory panel, with additional infectious disease and routine tests for general health in the pipeline.

Read the testimonial of how lab automation and scalability helped one of PRL's customers in maintaining a safe work environment for their clients.

COVID Testing Needs for the Production Industry

Kameo Health, whose mission is to keep studio productions stay safe in the era of COVID-19, offers clients a suite of comprehensive tools through its testing management platform and provides efficient onsite testing services with fast results. Kameo has supported more than 375 productions and has administered over 300,000 COVID-19 tests for clients including Netflix, Disney, Sony Pictures, HBO and more.

According to Chief Operating Officer Sebastian Hayto, Kameo strives to meet the high demands of the entertainment production industry by providing excellent customer service, working with efficient labs and hiring from within the industry. In each of Kameo's 12 production hubs, they partner with a primary lab and a backup lab, and it is essential that each lab partner is contracted on <12-hour turnaround times to help mitigate outbreaks on set.



Lab Partner with Next-Level Automation

Pandemic Response Lab is one of Kameo's primary lab partners in both New York and Los Angeles, two of their largest regions. PRL's testing capacity and focus on automation are what initially attracted Kameo to form the partnership.

"Our goal is to deliver consistent, quality results at a competitive price with fast turnaround time, and PRL's automation allows for that," Sebastian stated. "PRL then went a step further and did two things – one is build out a team that would accommodate our needs. We've got a great intercompany communication channel set up with PRL. The second thing is they were willing to integrate with us very quickly."

Seamless Integration

PRL was the first lab Kameo fully integrated with, and it involved about 10 engineers from each team collaborating on how to push through the integration. According to Greg Gillam, Kameo Sr. Director of Lab Operations, the process went seamlessly.

"I've been in the lab space for quite a while, and historically, it's an industry that moves slowly," Greg said. "Knowing that PRL is so automated and future-thinking about how they want to operate and set up their systems is ideal for us."



Proven Results

Since integrating with PRL, Kameo has been able to reduce their turnaround time for customers and is averaging roughly six hours from the time of sample drop-off to the time of result.

"Due to the level of automation that PRL offers, their rates are very competitive, allowing us to pass significant value to our clients," Greg stated. "If we are able to get a lower cost for the same or better-quality PCR testing, we can offer a more competitive price to productions and increase our overall presence."

With new innovations on the horizon, PRL and Kameo look forward to aligning their initiatives and growing their partnership to offer expanded diagnostic services to a broader audience.

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D Industry Playbook

PrecisionLife and Sano Genetics Partner to Accelerate Understanding of Long COVID

PrecisionLife and Sano Genetics plan to develop a better understanding of the long-term effects of SARS-CoV-2 infections for those who experienced mild cases. PrecisionLife's combinatorial analytics can provide users with patient stratification biomarkers that may lead to new treatments to aid long COVID diagnoses, the companies said.

Under the terms of the agreement, Sano Genetics will provide PrecisionLife with data from 3,000 U.K. adults diagnosed with long COVID. PrecisionLife will then analyze this data to identify risk factors and potential drug targets

within long COVID patients. The companies are working to ensure that the results are accurate and representative of the population demographics in the U.K. Innovate UK, a U.K. government funding body, provided financial support to Sano Genetics that enabled the company to collect the patient data used in this partnership.

Previously, PrecisionLife used its analytics solution to identify 68 genes associated with serious disease and hospitalization in SARS-CoV-2 patients. Additionally, PrecisionLife revealed opportunities for 29 approved drugs that target the identified genes and that could be repurposed as COVID-19 treatments.



■ BABSON DIAGNOSTICS AND BD EXPAND STRATEGIC PARTNERSHIP

Babson Diagnostics and BD announced their partnerships' expansion to advance diagnostic blood collection in new care settings. The two companies have collaborated to create small-volume capillary blood collection devices for retail settings since 2019. Plans under the new agreement include continuing research and development to create at-home self-collection devices and accompanying mobile services. Additionally, both companies aim to broaden the different types of blood tests possible through small-volume blood collection beyond care-oriented tests.

Babson Diagnostics CEO David Stein said that this partnership is "critical" for today's healthcare environment, and that Babson aims to

expand convenient blood testing to a global scale. Stein also noted that retail convenience is important for consumers today.

Brooke Story, president of Integrated Diagnostics Solutions for BD, added that, because capillary blood collection is less invasive than the venous blood draw method, the two companies' self-collection devices may lead to better compliance among patients for routine blood tests.

■ QLUCORE COLLABORATES WITH LUND UNIVERSITY TO DEVELOP BETTER BLADDER CANCER DIAGNOSTICS

Qlucore has teamed with scientists from Lund University to develop improved bladder cancer diagnostics. Qlucore will use its expertise in bioinformatic software to

analyze Lund University's cancer diagnostics data. Advancements from both parties will be used in Qlucore Diagnostics, a machine learning-based software that features user-friendly 3D visualizations of patient results.

Professors from Lund University developed "the Lund Taxonomy" to classify patients into molecular subtypes with clinical values based on RNA expression analysis. RNA-based analysis allows for classification based on gene fusions and gene expression signatures. Meanwhile, DNA expression analysis reflects the dynamics of an already developing cancer.

The two collaborators aim for the Qlucore Diagnostics solution to fill a missing element in the clinical precision diagnostic workflow and to improve prediction of patients' responses to treatment. Through the partnership, Qlucore will sell



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Qlucore Diagnostics and related products to hospitals, clinics, and diagnostic laboratories in the United States and Canada.

■ STAGEZERO LIFE SCIENCES PARTNERS WITH DIAGNOSEATHOME TO OFFER MULTICANCER BLOOD TEST

StageZero Life Sciences has joined forces with DiagnoseAtHome to create a multicancer blood test in the United States and Canada. According to the companies, the test, Aristotle, is the first-ever mRNA panel that screens for multiple cancers from one blood sample.

Aristotle interrogates mRNA from a sample and detects gene expression profiles that indicate specific cancers, including breast, ovarian, endometrial, colorectal, liver, stomach, and prostate cancers. mRNA gene expression technology from StageZero lays the foundation for this new test, while DiagnoseAtHome offers accessible at-home health and lab testing solutions as convenient alternatives for patients, the companies said.

The partnership with DiagnoseAtHome will allow for greater accessibility for both existing clients and new ones, said StageZero CEO James Howard-Tripp. The two companies also plan on further developing a test to diagnose different cancers in the early stages.

■ NICOYA ACQUIRES LSK TECHNOLOGIES, EXPANDING DIGITAL PLATFORM INTO MOLECULAR TESTING

Nicoya Lifesciences, a company focused on digital proteomics solutions, has bought LSK Technologies, a University of Toronto startup that is working to decentralize laboratory testing with their high-throughput lab-in-a-box platform. Nicoya has continued to build upon its novel method of viral detection since 2021, incorporating the company's digital microfluidic and nanoplasmonic

biosensor technology into a portable device for rapid antigen testing. With the integration of LSK's amplification technology and associated intellectual property, Nicoya will further broaden the applicability of their platform across a variety of testing and diagnostic applications, while maintaining affordability and ease of use.

CEO and co-founder of Nicoya, Ryan Denomme, said collaborating with LSK Technologies strengthens the company's foundation in point-of-need testing while simultaneously expanding Nicoya's portfolio. Meanwhile, CEO and cofounder of LSK Technologies, Seray Cicek, said that the new deal will make progress towards making testing more accessible and affordable.

With the new acquisition, Nicoya will continue to support LSK's existing customers while also offering LSK products under the Nicoya brand.

■ BIODESIX TEAMS WITH MEMORIAL SLOAN KETTERING TO DEVELOP MINIMAL RESIDUAL DISEASE TEST

Biodesix announced that they developed a master sponsored research agreement with the Memorial Sloan Kettering Cancer Center (MSK) to develop a novel minimal residual disease (MRD) test. The test will be a highly sensitive molecular test designed to run on the Bio-Rad QX600 ddPCR system and will launch later this year. As part of the partnership, Biodesix also plans to develop and commercialize oncology biomarker assays based on their array of genomics, proteomics, artificial intelligence, and machine learning capabilities.

"The initiation of this research program with MSK is a significant milestone for Biodesix," said Biodesix CEO Scott Hutton. "While the initial focus will be on developing a novel MRD test for solid tumors as an addition to our pipeline, Biodesix hopes to codevelop and validate a number of new test concepts under the agreement."

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Ask The Expert

Focus on FibroTest



EXPERT

By Nikola A. Baumann, PhD

What is the intended use of the FibroTest-ActiTest and NASH-FibroTest?

A: FibroTest-ActiTest and NASH-FibroTest are proprietary algorithms developed and patented by BioPredictive. These algorithms utilize the patient's age and sex, along with measurement of serum biomarkers, to estimate liver fibrosis/cirrhosis, necro-inflammatory activity, steatosis, and nonalcoholic steatohepatitis (NASH).

FibroTest-ActiTest measures gamma-glutamyltransferase (GGT)

activity, total bilirubin, alpha-2-macroglobulin, apolipoprotein A1, haptoglobin, and alanine aminotransferase (ALT) activity in the patient's serum. The BioPredictive algorithm then calculates a fibrosis score between 0–1 that corresponds to a fibrosis stage (F0–F4) and an activity score between 0–1 that translates to an activity or inflammatory stage (A0–A4). On the FibroTest relative scale, F0=no fibrosis and F4=severe fibrosis (cirrhosis). FibroTest is useful for diagnosing fibrosis in carriers of chronic hepatitis B, patients with chronic hepatitis C, and patients with metabolic conditions such as nonalcoholic fatty liver disease (NAFLD) or alcoholic liver disease.

NASH-FibroTest includes the components of FibroTest-ActiTest and the following additional serum/plasma tests: aspartate aminotransferase (AST) activity, cholesterol, triglycerides, and fasting glucose. In addition to FibroTest for estimating liver fibrosis, NASH-FibroTest includes SteatoTest2 to assess hepatic steatosis and NashTest2 to evaluate the level of necro-inflammatory activity caused by NASH. Steatosis is reported relative to a scale ranging from S0–S2S3 (S0=no steatosis (<5%), S1=mild steatosis (5–33%), S2/S3=moderate/severe steatosis (34–100%)). A stage of S1 or S2S3 is considered clinically significant. NashTest 2 is reported relative to a scale ranging from N0–N3 (N0=no NASH, N3=severe NASH).

How does FibroTest compare to other noninvasive tests and liver biopsy for diagnosing liver fibrosis?

There are several noninvasive methods for assessing liver fibrosis, and each has its strengths and weaknesses. Numerous serum biomarker panels exist. Tests such as the AST-to-platelet ratio index (APRI) and FIB4 score (calculated from age, AST, ALT, and platelet count) are widely available as they utilize common lab tests and can be easily calculated by the healthcare provider using a calculator or app. A few other proprietary testing algorithms exist as well.

Imaging techniques include ultrasound-based transient elastography (TE) and magnetic resonance

elastography (MRE) among others. TE assesses the "stiffness" of the liver and has been widely evaluated, but it requires high-cost equipment, proper calibration, and trained operators. MRE has sufficient accuracy for staging liver fibrosis, but it's costly, requires the use of two contrast agents, and its availability is limited to select advanced tertiary care centers.

There are more than 300 peer-reviewed publications evaluating FibroTest in various patient populations. Houot and colleagues published a systematic review with meta-analysis that directly compared common biomarker panels (APRI and FIB4), FibroTest, and TE with biopsy for the diagnosis of fibrosis in chronic hepatitis C and B patients (Ailment Pharmacol Ther 2016;43:16–29). FibroTest performed slightly better than TE and APRI for identifying advanced fibrosis (F2–F4) and was comparable to TE and FIB4 for identifying cirrhosis. The general consensus in the literature is that noninvasive methods, including FibroTest, are very good for detecting severe liver fibrosis and cirrhosis and for ruling out fibrosis.

How do reference labs offer this testing?

BioPredictive holds an international patent for FibroTest-ActiTest and NASH-FibroTest. However, because the serum analytes used in the company's proprietary algorithms are readily available Food and Drug Administration-cleared lab tests, labs can enter into a licensing agreement with BioPredictive and offer the testing to their laboratory clients. The clinical laboratory must adhere to BioPredictive's technical recommendations for the assays, which include specifications for methodology, specimen requirements, calibration, and assay imprecision. Test results and patient age and sex are securely transmitted to BioPredictive, the algorithm is applied, and scores and stages are returned to the performing laboratory.

Nikola A. Baumann, PhD, is co-director of the Central Clinical Laboratory and Central Processing at the Mayo Clinic in Rochester, Minnesota.

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ENHANCING HEART
FAILURE OUTCOMES

48%

Increase in patients getting
specialized care

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Simple Changes Lead to Outsized Improvements in Healthcare

BY KIMBERLY SCOTT

Sometimes seemingly the simplest change can lead to significant improvements in patient care. Such is the case with the winners of the 2021 UNIVANTS of Healthcare Excellence Awards, reinforcing that healthcare improvements don't necessarily have to be overly complicated to create meaningful and impactful results. From changing the time patient specimens are collected to implementing opt-out screening for HIV to flagging patients at risk for heart failure, these top-ranked integrated clinical care initiatives share one thing in common that is perhaps the most difficult to achieve: Simplicity.

Another commonality that these three winning initiatives share is that they all rely on insights from high quality clinical laboratory testing to improve patient care. Laboratorians were intimately involved on the interdisciplinary teams, developing process improvements that have been recognized by UNIVANTS. The UNIVANTS of Healthcare Excellence award program are prestigious global honors created by Abbott in partnership with AACC and other leading healthcare organizations.



The awards recognize teams that collaborate across disciplines to transform healthcare delivery, and ultimately, patient lives. Below we explore the unique achievements of the top winning teams recognized in 2021 as UNIVANTS of Healthcare Excellence winners.

IMPROVING TIMELINESS OF LABORATORY TEST RESULTS

The COVID-19 pandemic has not only affected patient acuity and case load in the acute care setting, but it also has sparked a movement referred to as “The Great Resignation.”

Combined, these two factors have had a negative impact on patient care.

Across the globe, clinical laboratories have seen a significant increase in test volumes while staffing challenges have worsened.

In early October, nursing departments at Banner Health and Laboratory Sciences experienced challenges with balancing the demands of a community COVID-19 surge with nursing and laboratory staffing shortages. They quickly realized that morning routine laboratory tests were increasingly re-ordered as STAT or Timed Study to escalate priority. A re-direction of resource utilization was necessary for the phlebotomy services of the clinical laboratory to keep up with the

high demand during the pandemic crisis. Additionally, a house-wide communication plan for resolving day-to-day challenges was needed to help nursing teams, ensuring that patient results were reported for morning rounds, explained Kimm Wuestenberg, MHI, MLS(ASCP) cm, LBBP, CPHQ, associate director, quality improvement at Banner.

“This happened in early October, and I had just attended a National Association for Healthcare Quality seminar that focused on the laboratory’s involvement in quality improvement,” she said. “I happen to be a laboratorian and ended up in hospital quality, so the two fit together nicely.”

Rapidly Improving Timeliness of Laboratory Test Results

35.8%

Improvement in timeliness
of patient discharge
before 1 p.m.

72%

Decrease in STAT orders
resulting from completion of
tests results by 7 a.m.

1.6%

Decrease in overall
patient length of stay



For this situation, the team needed a rapid cycle process improvement plan that considered the needs of the laboratory staff, nursing staff, physicians, patients, and payers. A small workgroup comprised of representatives from several different departments – clinical laboratory, medical-surgical, clinical care operations, and quality improvement – formed to work on solutions using an integrated process improvement methodology. They targeted each key stakeholder with the goal of driving change in the short term, while they vetted long-term solutions.

The team chose to optimize an existing process based on the principles of Lean Six Sigma by applying fast and flexible sprint sessions in a small group (Scrum) of department leaders to improve productivity while reducing bottlenecks (Kanban). They also incorporated Design Thinking into the rapid cycle process improvement through innovation with the generation and testing of new ideas. They found that the innovations associated with this project were due not only to the development of an enhanced process, but also in the integration of multiple process improvement methodologies for a successful targeted rapid cycle process improvement project, Wuestenberg explained.

“We changed the specimen collection schedule so that the med/surg results would be ready for morning rounds,” she said. “Instead of collecting specimens in the middle of the night, we had them collected between 10 and 11 the prior evening. Moving it earlier really helped everyone out, and it was great for the patients, too.”

As a result of the process improvement, morning routine laboratory test results were completed by 7 a.m., resulting in early discharges. In fact, discharges before 1 p.m. improved by 35.8%. This is significant because earlier discharge reduces the risk of hospital acquired infections and improves patient satisfaction. The process improvement also led to a 1.6% decrease in overall patient length of stay.

“Instead of collecting specimens in the middle of the night, we had them collected between ten and eleven the prior evening.”

—Kimm Wuestenberg

“It seems so simple, but sometimes you just have to go back to basics,” Wuestenberg said. “This helped with the laboratory workflow, it helped the physicians and the nurses, and it was better for the patients.”

Collecting specimens the night before also resulted in a 33% decrease in time studies (TS) and a 72% decrease in STAT orders in the early morning hours. “Earlier test results available to physicians reduced repetitive test orders, specimen collections, and testing duplication,” Wuestenberg said.

As part of the initiative, clinical staff held meetings each day at 3 a.m. to determine if there were any barriers to getting specimens the night before. If there were, nurse leaders ensured that specimens were collected in time for results to be ready for morning rounds. This daily communication between the clinical laboratory and clinical care operations about specimen collection barriers allowed for better resource allocation, according to Wuestenberg.

This initiative, “Utilizing an Innovative Approach to Process Improvement in the Era of a Global Pandemic and The Great Resignation: Rapidly Improving Timeliness of Laboratory Test Results for Multidisciplinary Rounds in an Acute Care Setting,” used various integrative process improvement methodologies, including Six Sigma, Scrum, Kanban, Lean and Design Thinking. The clinical care initiative is highly scalable, Wuestenberg said, noting that this process improvement methodology mix can be used

in various circumstances where a temporary solution is needed while leaders work on long-term solutions.

“This is a data-driven process improvement project with laboratory test result timing as the primary focus,” she explained. “This affects physician decision making, patient continuum of care, operations utilization, and payer reimbursement.”

Timothy Hersom, MBA, MT(ASCP), the administrative director of the clinical laboratory, concurred. “The phlebotomy labor shortage and increased number of draws have stretched this finite resource to its limits,” he said. “From the lab’s perspective, the change has given the phlebotomists an opportunity to complete med/surg routine draws first, ensuring that these results are available by 6 a.m. This has a positive domino effect on the turnaround times of lab draws on other units.”

GETTING TO ZERO AIDS

In the United Kingdom, 1 in 14 people living with HIV are unaware of their diagnosis. Croydon, a large town in South London, has an extremely high HIV prevalence area (more than 5 infected per 1,000 people), with more than 46% of those infected diagnosed late in the disease.

In Croydon, 65% of HIV patients are Black African, 50% are female, and 75% are heterosexual, all groups who tend to be diagnosed late.

The marker of late HIV diagnosis is a CD4 count of less than 350 cells/mm³. Individuals with a late diagnosis are estimated to have been unaware of their infection for at least 3-5 years, increasing the

likelihood of ill health, premature death, and onward transmission. Early diagnosis allows initiation of highly effective treatment.

Prior to 2020, many emergency departments (EDs) used opt-in testing for HIV, but it was difficult because doctors were uncomfortable asking patients if they wanted to be tested, and most patients do not believe themselves to be at risk or need testing.

In 2020, the British HIV Association (BHIVA) recommended that opt-out HIV testing be implemented in EDs across the UK as a means of diagnosing HIV infection earlier and reducing mortality. In May 2020, a multi-disciplinary team at Croydon University Hospital

implemented opt-out HIV testing in its ED. Since implementation of the initiative, at least 97% of all ED patients who had a blood test have been screened for HIV, and the number of new HIV diagnoses has tripled, said Ian Cormack, MD, clinical lead for HIV medicine in the hospital's HIV Health Clinic.

Posters in the ED explain that HIV screening will be done automatically unless a patient opts out. If a screening test comes back positive, the patient will be brought back to the hospital for additional testing and will be linked to the appropriate care and treatment.

"This has allowed us to pick up on people with HIV early in the disease progression, before they become

ill," Cormack explained. "HIV can easily be mistaken for many other diseases. It can present itself in so many different ways."

Prior to implementation of the HIV screening initiative, patients typically were tested only if they were already ill, with a significant number ending up in intensive care and/or dying. Since implementation of the HIV screening initiative in May 2020, more than 80,000 people have been screened. Mortality among inpatients who were newly diagnosed with HIV dropped from 23% per year in 2017-2019 to 0% in 2020-2021. AIDS-defining illness (ADI), which occurs when patients' immune systems can no longer protect them from life-threatening

Getting to Zero AIDS

0%

Percent of inpatients newly diagnosed with HIV who died during 200-2021 (compared to 23% per year from 2017 to 2019)

78% to 4%

Reduction in newly diagnosed patients presenting with AIDS defining illnesses

60%

Percent of complex, hard-to-reach patients with HIV who were successfully re-engaged in HIV care



infections and cancer, decreased from 78% (2005-2010) and 46% (2017-2019) to 4% (2020-2021).

The rate of ADI in newly diagnosed hospitalized HIV patients is now 4%, with 0% mortality and 0% intensive care admissions. The readmission rate in these patients has dropped from 31% (2005-2010) to 0% (2020-2021).

In addition, the average length of inpatient stay has dropped from 35 days (2017-2019) to only 2.4 days (202-2021), thereby freeing up valuable NHS resources during the COVID-19 pandemic. In one year, there were 815 fewer inpatient hospital days for 25 new HIV inpatient admissions, which at £400 per day equates to £326,000. A reduction in readmission rates resulted in additional cost savings of £75,000 per year.

“HIV is straightforward to treat with antiretroviral medication, but patients with unrecognized or undiagnosed HIV can present with dangerous and complex AIDS defining illness,” Cormack said. “These usually have a high mortality rate and carry a significant risk of permanent disability. Starting the correct treatment of these opportunistic infections promptly and ideally within 48 hours dramatically improves outcomes.”

Detecting HIV infection early in someone’s hospital admission dramatically reduces clinical risk and inappropriate investigations or procedures, Cormack added, noting that HIV can affect any body system and can be easily missed or mistaken for another disorder. “For example, people with advanced HIV infection will commonly have weight loss and diarrhea,” he explained. “Without effective HIV testing, they are often referred for colonoscopy and bowel biopsy, which is not necessary. We have witnessed unnecessary colonoscopies being cancelled at our gastroenterology unit as a result of our testing program as the patient’s symptoms got better on starting HIV treatment.”

As a result of the testing program, staff in the HIV health clinic receives a daily list of all HIV-positive patients in the hospital. This allows the HIV team to be

“Patients with unrecognized or undiagnosed HIV can present with dangerous and complex AIDS defining-illness.”

—Ian Cormack

involved with their care whatever the reason for their admission. This has improved the quality of their care by allowing healthcare staff to spot any potential drug-drug interactions with anti-retroviral medication (ARV) and any new treatment that has been prescribed, Cormack said, noting that such a negative drug interaction has been prevented at least once a week since the initiative began.

This reduction in ADI presentations has led to a dramatic reduction in hospitalization and HIV deaths, and more than 20 HIV transmissions have been prevented, saving the National Health Service more than £7 million in avoided lifetime healthcare costs. All partners of newly diagnosed patients have remained HIV negative using post and pre-exposure prophylaxis, reducing transmissions to zero. Opt-out HIV testing is now performed in all EDs in extremely high prevalence areas in the UK, and Cormack believes it has the potential to finally get to zero AIDS.

“We did this without any additional resources,” Cormack said. “After two years we finally have some additional resources to make it sustainable and to expand in some other areas as well,” such as primary care physician offices or other medical departments.

An added benefit of the HIV screening is a re-engagement rate of more than 60% of people previously diagnosed with HIV who had stopped receiving care. Prompt, correct management of

HIV-related conditions and re-engagement with an HIV service has led to a decrease in mortality among this population from 25% to 16% per year.

“These patients have always had the worst prognosis, as they have a high level of mental health problems, alcohol and substance addiction, and a reluctance or inability to engage with HIV services,” Cormack said. “They often present severely unwell with a high rate of sepsis or cancer diagnosis. We have successfully re-engaged well over 60% of these complex and sometimes hard to reach patients.”

This initiative, “Sustained 97% Opt-Out HIV Testing in the Emergency Department: Getting to Zero AIDS,” could well help the UK eliminate HIV infections entire by 2030, Cormack believes.

ENHANCING PERSONALIZED CARE FOR HEART FAILURE PATIENTS

Heart failure is a chronic disease and a leading cause of hospitalization and 30-day readmissions in the United States. Acute and post-acute patient management pathways have been well documented for improved and enhanced patient care.

To improve care of heart-failure patients, a multidisciplinary clinical care team at Prisma Health, Greenville Memorial Hospital, created an initiative focused on identifying heart failure patients earlier, improving access to and utilization of limited resources, and reducing the overall cost of care.

This was accomplished through a patient identification and workflow program that used inherent capabilities of the electronic medical record (EMR) and integrated IT systems to identify and improve access for patients with increasing risk and advanced risk for heart failure.

Under this new program, heart failure patients are risk-stratified with deployment of real-time, point-of-care decision support and workflow, enabling improvement to care coordination and helping ensure the right provider sees at-risk heart failure patients at the right time.

The risk-score model uses laboratory results and is updated on an ongoing basis so that risk profiles used by clinicians are current.

Implementation of this EMR registry risk score resulted in a reduction in overall mortality, reduced length of stay, increased rates of high severity patients seen by the advanced heart failure specialty clinic, improved collaboration of clinicians for management of heart failure inpatients, and improved patient and family referrals, said Sandi Stoudenmire, director of cardiovascular services at Prisma Health.

“Broad adoption of this methodology demonstrated significant impact in the care of heart failure patients at our facility and can become a powerful tool for other disease states in the future,” she said.

The use of risk scoring in the electronic medical record yielded

a 48% increase in the number of high-risk patients actively receiving care from an advanced heart failure specialist. Access to these specialists is limited by the number of available appointments, and the population of heart failure admissions in the facility increased 18% between 2020 and 2021. By matching resources to risk score, the most vulnerable patients have access to the specialty, Stoudenmire noted.

Prisma Health also saw a 12% improvement in overall mortality for all registry patients with heart failure. The post-registry mortality rate for high-risk registry patients is now approximately half that of patients with heart failure who during the same timeframe (September

Enhancing Personalized Care for Heart Failure

116%

Increase in follow-up within 7 days with high-risk heart patients

14.84%

Increase in revenue resulting from a 67% increase in overall heart failure clinic volume

59%

Reduction in emergency and urgent care visits, with a cost savings of \$866 per visit



2020 through August 2021) were not triaged and treated in accordance with the registry. In addition, use of risk scoring led to a 200% increase in referrals for palliative care and a 40% increase in hospice care referrals.

Since implementation of the heart failure registry, there is increased frequency of follow-up in patients of high severity, specifically a 116% increase in patient follow-up within 7 days. This improved post-discharge care of heart failure patients helps reduce readmissions, according to Stoudenmire.

Improved use of the EMR risk score to drive appropriate referrals at discharge also resulted in a 67% increase in overall heart failure clinic volume, which also increased revenues by almost 15%. In addition, a 59% reduction in average emergency and urgent care visits resulted in cost savings of about \$866 per visit.

The initiative, which Stoudenmire describes as highly unique, was only moderately difficult to implement. “The development of the heart failure registry and addition of the patient risk-score within the provider’s daily work involved a small group with a passion to improve care through the enhancement of patient identification and personalization,” she said. “This work included automated referrals to the advanced heart failure team at the appropriate phase of a patient’s care, both acute and post-acute, in addition to referrals to the palliative care team and hospice and referrals for low- to medium-risk patients to the transitions clinic at discharge.”

The initiative, “Enhancing Personalized Care for Heart Failure Patients: A Risk-Scoring EMR Model,” is also highly scalable, Stoudenmire said, noting that it is serving as a model for other complex disease states in the development of the EMR.

MAKING A DIFFERENCE IN PATIENTS’ LIVES

Detecting disease and chronic conditions early enough to have a significant effect on patient outcomes is essential to improving the health of populations. These interdisciplinary initiatives, though relatively simply in nature, have had a demonstrable

“Broad adoption of this methodology demonstrated significant impact in the care of heart failure patients ... and can become a powerful tool for other disease states in the future.”

—Sandi Stoudenmire

impact on patient care and outcomes, from prompt treatment for HIV to earlier discharge from the hospital to personalized care for patients at risk for heart failure.

These are just a few of the projects in which integrated care teams including the clinical laboratories are transforming healthcare

delivery. To learn about other initiatives recognized through the UNIVANTS of Healthcare Excellence program, go to www.univantshce.com.

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Univants 2021 Teams Recognized In This Issue

Utilizing an Innovative Approach to Process Improvement in the Era of a Global Pandemic and The Great Resignation: Rapidly Improving Timeliness of Laboratory Test Results for Multidisciplinary Rounds in an Acute Care Setting
Banner Health and Laboratory Sciences of Arizona, Sun City West, Arizona, United States

Kimm Wuestenberg
Connie Morena
Timothy Hersom
Kevin Cruz
Teri Dahn

Enhancing personalized care for Heart Failure Patients: a Risk-Scoring EMR model
Prisma Health Greenville Memorial Hospital, Greenville, South Carolina, United States

Beth Wehlitz
Jason Guichard
Stephanie Flippin
Beverly Jameson
Sandi Stoudenmire

Sustained 97% Opt-Out HIV Testing in the Emergency Department: Getting to zero AIDS
Croydon University Hospital, Croydon, Surrey, United Kingdom

Andrew Widdowson
Mike Bell
Leslie Parry
Ian Cormack
Sarah Horne
Linda Cheyenne Vaccari

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Banner Health and Laboratory Sciences of Arizona

Utilizing an Innovative Approach to
Process Improvement in the Era of a Global
Pandemic and the Great Resignation:
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Croydon University Hospital

Sustained 97% Opt-Out HIV testing
in the Emergency Department:
Getting to Zero AIDS

Prisma Health Greenville Memorial Hospital

Enhancing Personalized Care for
Heart Failure Patients: A Risk-Scoring
EMR Model



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