

March 2021

C L N

Clinical
Laboratory
News

DETECTING
HEART TRANSPLANT
REJECTION

81% 19.6%

vs

Sensitivity of
% donor-derived
cell-free DNA

Sensitivity of
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PAGE 7

An AACC Publication | Volume 47, Number 2

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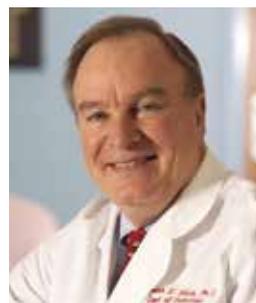
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Early middleware technologies were not designed to handle the highly diverse and emerging connectivity challenges of point-of-care testing.
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Federal Insider

AACC Warns of Continuing Supply Chain Problems

Even as public attention has focused on COVID-19 vaccines, new data from AACC's ongoing clinical laboratory survey on SARS-CoV-2 testing finds that supply shortages for testing have not let up, prompting the association to call on Congress to act.

AACC's data from December 2020 to January 2021 show that 60% of responding laboratories continue to encounter problems obtaining supplies needed to perform SARS-CoV-2 testing. In fact, the percentage of laboratories able to procure sufficient test kits has worsened over the past few months. In May 2020, 48% of responding laboratories said they were unable to obtain test kits. This figure now stands at 58%, with 50% reporting trouble obtaining reagents.

Importantly, the supply problem is undermining other types of diagnostic testing, too. Now 58% of laboratories say they cannot perform all their non-COVID-19 related tests due to supply shortages. AACC is calling on Congress to work with federal agencies and the healthcare community to develop a clear, transparent plan for ensuring that officials at the national level are aware of essential laboratory supply needs and a distribution process is put in place to more efficiently produce and allocate supplies.

Meanwhile, federal help might be on the way from the executive branch, but as yet, there are few specifics. President Biden issued an executive order in January directing the heads of government agencies to work with the administration's COVID-19 Response Coordinator and use the defense production act to close gaps for testing materials. That 1950 law allows the president to force private companies to prioritize orders from the federal government.



DEFENSE, HEALTH DEPARTMENTS PAY UP FOR HOME SARS-COV-2 TESTS

The Department of Defense, in coordination with the Department of Health and Human Services, announced a \$231.8 million agreement with Australian diagnostic test company Ellume to onshore production capacity of its COVID-19 Home Test. The test is the first rapid self-test for SARS-CoV-2 detection authorized by the Food and Drug Administration for both asymptomatic and symptomatic use without a prescription. The test can be performed in about 15 minutes from a nasal swab specimen with results reported on a dedicated smartphone app.

Under the agreement, Ellume's U.S.-based manufacturing facility will deliver 8.5 million home tests. The expansion is also expected to allow the company to keep producing even

more units. Once at full capacity, the U.S. facility will be able to produce up to 19 million tests per month. Development of Ellume's COVID-19 Home Test was supported by the National Institutes of Health Rapid Acceleration of Diagnostics initiative program.

BIDEN ADMINISTRATION SO FAR SILENT ON LDT REGULATION

Department of Health and Human Services officials in the previous administration surprised the lab community in 2020 by officially stating that the Food and Drug Administration (FDA) did not have authority to regulate laboratory-developed tests (LDT) without formal rulemaking. At the time, even officials within FDA made the case that the agency should be able to oversee LDTs.

Now some observers, including FDA's former acting chief scientist

Luciana Boria, MD, are calling on the Biden administration to reverse course. Boria made the case in testimony before a House Energy and Commerce health subcommittee hearing on February 3. "There is tremendous confusion about the approach FDA is taking to facilitate access to appropriate tests, while ensuring that tests perform to a minimal standard," Boria said. "The last administration hurt the American public when it declared that FDA did not have the authority to regulate laboratory-developed tests."

So far Congress's efforts to deal with LDT oversight have failed. Sen. Rand Paul (R-Ky.) introduced in 2020 the Verified Innovative Testing in American Laboratories (VITAL) Act, which would codify federal oversight of LDTs under CLIA. AACC has endorsed the VITAL Act and has long held that LDTs are already regulated under CLIA and do not need an additional layer of oversight from FDA.

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Managing Supply Chain Disruptions During the COVID-19 Pandemic

Let's be honest. The emergency disaster relief policies that labs had in place at the start of 2020 were high level placeholders required by our accrediting agencies. Very few—if any—of us had plans for responding to a global pandemic that seriously disrupted supply chains worldwide. Instead of strategizing and planning, we found ourselves primarily responding, trying to maintain our operations and serve our customers.

Like most everyone, Loyola Medicine, a three-hospital system based in the Chicago suburb of Maywood, Illinois, struggled with these issues. We started in-house SARS-CoV-2 testing on March 19, 2020, and by the end of the year had performed 120,000 polymerase chain reaction (PCR) tests using six testing platforms. We performed another 6,300 antibody tests, including on 4,000 colleagues. We've learned many valuable lessons this past year and, in this article, describe some of our key takeaways.

Just-in-time inventory doesn't work for pandemics, but stockpiling has its limitations beyond essential personal protective equipment (PPE). We've had to balance between these extremes to support patient care activities. We wanted at least 4 weeks' inventory to offset vendor disruptions. A key aspect of this involved tracking daily fluctuations in our test volume. Armed with this data, we were more adept in establishing pandemic par levels for reagents, kits, and collection supplies.

Cutting personnel in response to low test volumes is short-sighted. Early in the pandemic, as it became evident that supply shortages were coming, our microbiology lab redeployed two technologists to assist in sourcing critical sample collection and PPE supplies. They identified and placed multiple small orders across several vendors to obtain materials, which we validated to maintain par inventory levels.

Keep training staff. Our lab couldn't completely cease training and competency evaluations during the pandemic. Even in this uncertain time, we've had turnover and filled vacant positions. Additionally, several associates assumed

roles they weren't hired to perform, but having met the qualifications, were trained to perform and assessed for competency. For example, our point-of-care (POC) coordinators trained for and began performing POC SARS-CoV-2 testing.

Fear of modifying a method, thereby making it a laboratory developed test (LDT), shouldn't automatically rule out this option. The commercial interleukin-6 (IL-6) assay we validated to support management of patients hospitalized with COVID-19 was previously available for research use only. This necessitated a more extensive clinical evaluation to establish the assay's utility in these patients. We enlisted several pathology residents to undertake thorough chart reviews and follow the medical history of approximately 100 hospitalized patients who had serial IL-6 measurements. The lab completed a comprehensive method validation to satisfy LDT requirements. Although this assay received an emergency use authorization (EUA) within 3 months of our validation, initial lack of this regulatory approval didn't dissuade us from validating and making this assay available as a valuable clinical tool.

Vendor loyalty might bring products into a lab, but when that company experiences supply disruptions, not having relationships with multiple vendors could prove problematic. Initially, SARS-CoV-2 antibody assays entered the market extensively and rapidly, unlike anything we've seen in our collective 50+ years' experience. Options were plentiful, but EUAs were not, at least on automated immunoassay systems. Many laboratories with vendor loyalty found themselves without options amid rapidly escalating demand. Those with more than one system had options for the types of antibodies they could detect and type of results they could render (quantitative versus qualitative).

Build supplier redundancies. Having redundancy in essential and emergent testing not only provides



Jack A. Maggiore, PhD, MT(ASCP)



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an operational safety net, but also facilitates a competitive marketplace. Few of us have had the luxury of evaluating secondary and tertiary methods or products, but as we emerge from the pandemic, we all will do well to establish lists of evaluated products that meet our needs.

Recognize when it's time to execute backup. Notifications from vendors about backorders or delayed deliveries signal the need to seek alternate sources and/or prepare to implement established backups. We recommend that labs work with their logistics specialists to find emergency suppliers. Establish these relationships now for future needs by occasionally ordering and evaluating new items and building a surplus inventory. Laboratories that already have backup procedures should build semiannual events into their quality calendars to perform comparison testing and document compliance.

Develop systems for outsourcing nonessential testing. SARS-CoV-2 testing often has been our lab's highest priority. This at times means instrumentation that typically runs 5-7 different infectious diseases tests runs only SARS-CoV-2 tests. While our volumes dropped significantly for many tests, they didn't zero-out. This meant relying on our reference labs, first by confirming that a lab was accepting specimens for each test in question. Next, we communicated to providers that a test was being outsourced, which in turn would affect turnaround times. Finally, we updated order test codes to reflect these changes in our electronic medical record and laboratory information system.

Look hard at all primary and essential methods to determine if a sound, validated backup exists, and detail the logistics required to implement this solution. Our lab established redundancy for our COVID-19-related diagnostic testing, and we already had redundancy for key tests that supported COVID-19 patients' care, like blood gases, electrolytes, and coagulation testing. As demand for these assays grew nationwide, we maintained a steady reagent and instrument part supply inventory for our primary and backup platforms.

Audit and revise labs' pandemic response plans. We expect to revise our business continuity plan by updating required staffing levels and interactions and supply inventory management steps for critical PPE and routine, high-use consumables like plastic transfer pipettes and pipette tips. We're still exploring how we'll audit this revised plan.

As the pandemic wears on, laboratories continue to lean on each other for ideas, support, and solutions. In our lab, we've had successes while still learning and adapting. We long for the days when we could pull a disaster plan off the shelf to guide us in evaluating options and executing solutions. In reality, we're actively writing our plan for the future as we experience this (hopefully) once in a lifetime event.

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The Sample

Mitochondrial DNA is Early Marker of Severe COVID-19 Illness

Mitochondrial DNA (MT-DNA) levels assessed within a day of patients' hospitalization for COVID-19 were highly elevated in those who ultimately died, required intensive care, intubation, or vasopressor or renal replacement therapy in comparison to those without these complications (JCI Insight 2021;jci.me/143299/pdf). After further validation, this testing, performed in about an hour using standard reverse transcription-polymerase chain reaction (rt-PCR) but without a DNA purification step, could give doctors a tool to know better when to implement treatments such as monoclonal antibodies, according to co-senior author Andrew Gelman, PhD.

Viral infections can trigger cellular necrosis, which releases MT-DNA and other MT-damage associated molecular patterns known to cause acute lung injury and systemic inflammation. With these pathologies found in COVID-19, the authors questioned whether elevated levels of circulating MT-DNA might be a risk factor for severe disease.

The blood samples of 97 patients with laboratory-confirmed SARS-CoV-2 infection admitted to Barnes-Jewish Hospital in St. Louis underwent two rounds of centrifugation to generate platelet poor plasma. The investigators then performed rt-PCR using a BioRad CFX-Connect instrument to measure MT-DNA levels.

The researchers found that MT-DNA levels were about 10-times higher in those who developed acute respiratory failure or eventually died. After multivariate analysis adjusting for age, sex, and comorbidities, MT-DNA remained an independent risk factor for mortality (2.24 adjusted odds ratio (OR); 1.28–4.16 95% confidence interval (CI); p value 0.015), intensive care admission (3.97 adjusted OR; 1.83–10.34 CI; p value 0.002), and intubation (8.48 adjusted OR; 3.48–27.33 CI; <0.0001 p value).

In comparison to other markers of inflammation typically measured in COVID-19 patients, including C-reactive protein, ferritin, lactate dehydrogenase, and D-dimer, MT-DNA levels yielded similar or improved area under the receiver operator characteristic (AUROC) for key outcomes (mortality and intensive care, similar AUROC of 0.68 and 0.75, respectively; intubation, superior AUROC at 0.86%).

The authors intend to continue assessing MT-DNA in a larger multicenter trial of patients hospitalized with COVID-19.

2021 ADA STANDARDS OF CARE HIGHLIGHT GLUCOSE METER ANALYTICS

In the *American Diabetes Association Standards of Medical Care in Diabetes–2021*, the association (ADA) clarified its guidance about using point-of-care tests (POCT) to diagnose diabetes,

expanded descriptions of glycemic measures beyond A1c, and emphasized analytical considerations with glucose meters (Diab Care 2021;44:S1).

In the section on diagnosing diabetes, ADA underscored that while POCT might have NGSP-certification and Food and Drug Administration (FDA) clearance

for monitoring glycemic control in patients with diabetes, in both CLIA-regulated and CLIA-waived settings, only POCT cleared by FDA for diagnosing the disease should be deployed for that purpose, and only in the settings for which they have clearance.

In addition, the A1C testing subsection has been renamed to

“Glycemic Assessment” and the recommendations for assessing A1C changed to “Assess glycemic status (A1C or other glycemic measurement).” The 2021 document also removed the prior 6.3 recommendation, “Point-of-care testing for A1C provides the opportunity for more timely treatment changes.”

ADA strengthened the recommendation on assessing hypoglycemia (6.9) to state that patients should not only be asked about any hypoglycemic episodes, but also that these episodes should be investigated as indicated. The prior recommendation did not stress the need for investigating these incidents.



In the section on diabetes technology, ADA made more prominent the recommendation that providers should be aware of differences in glucose meter accuracy, moving it to 7.3 from 7.7. The document also placed comments on meter standards earlier in the discussion. In addition, the authors changed a prior subsection labeled “Glucose Meter Accuracy” to “Glucose Meter Inaccuracy.”

The technology section also reflects changes to recommendation 27, which previously noted patients might be using glucose monitoring systems not approved by FDA to stating that “patients using diabetes devices should be allowed to use them in an inpatient setting when proper supervision is

available.” The discussion around this recommendation notes FDA’s recent policy change in light of the COVID-19 pandemic to support hospitalized patients’ using their continuous glucose monitors.

■ PERCENTAGE DONOR-DERIVED CELL-FREE DNA BESTS ENDOMYOCARDIAL BIOPSY IN DETECTING EARLY HEART TRANSPLANT REJECTION

Levels of donor-derived cell-free DNA (ddcfDNA) detect acute rejection (AR) after heart transplant and avert about 80% of invasive tissue biopsies used to detect rejection (Circulation 2021; 10.1161/CIRCULATIONAHA.120.049098).

The Genomic Research Alliance for Transplantation study involved 171 patients who underwent heart allografts at five hospitals in the metropolitan Washington, D.C. area. These individuals had surveillance monitoring at pre-specified times after their transplants, including endomyocardial biopsy (EMBx) and donor specific antibody and cytomegalovirus testing, along with assessment of immunosuppression trough levels. Before the transplants, the researchers also genotyped DNA from whole blood samples via shotgun sequencing of both transplant donors and recipients to identify single nucleotide polymorphisms for each donor-recipient pair.

The subjects, followed for a median of 17.7 months, had 1,392 EMBx and 1,834 ddcfDNA measurements. Median %ddcfDNA levels declined after surgery to 0.13% by 28 days. In patients with AR, %ddcfDNA rose again compared to those without rejection, 0.38 versus 0.03, and was detected 2 weeks to 3.2 months before a histopathology diagnosis from EMBx. The maximum %ddcfDNA area under the receiver operator characteristics curve (AUROC) for detecting AR (0.92) occurred at day 28 after transplant. %ddcfDNA $\geq 0.25\%$ had a sensitivity, specificity, positive predictive value, and negative predictive value (NPV) of 81%, 85%, 19.6%, and 99.2%, respectively. In contrast, the

sensitivity of EMBx to detect AR when %ddcfDNA ≥ 25 was 19.6%, with a specificity of 99.2% and NPV of 85%.

The researchers also found several notable differences in %ddcfDNA levels in patients who experienced antibody-mediated rejection (AMR) versus acute cellular rejection (ACR). %ddcfDNA levels were significantly higher in AMR than ACR, overall and at all grades of rejection. %ddcfDNA elevations also occurred earlier in AMR than in ACR, and the AUROC for AMR was higher than for ACR. Discerning AMR from ACR matters because the initial treatment strategies and long-term implications of rejection are quite different, according to the researchers.

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Beyond Test Results

Defining the Role of Clinical Laboratories in Value-Based Population Health Equity

Clinical laboratories are reinventing their place in healthcare delivery by investing in strategic restructuring to meet ever-changing needs in their communities.

BY MONIQUE DODD, PHARM.D., PHC, MLS(ASCP)^{CM}, RICK VANNESS, MS, AND DAVID GRENACHE, PH.D., DABCC, FAACC

Clinical laboratories figure prominently in the continuum of care by delivering timely and accurate results to clinicians. As the U.S. health-care system evolves into a value-based care model, laboratories are moving from transactional interactions to approaches that support integrated services and proactive population health (1). This means they are actively evaluating the strength of their data and capitalizing on their domain knowledge to develop actionable insights from longitudinal trends within the data (2).

This domain knowledge is key. Clinical expertise and information technology advancements are just two essential ingredients for this innovative multidisciplinary approach (2). Together, a data infrastructure modeled to stratify risks and a strategy to close care gaps are the building blocks for delivering better healthcare information to providers, payors, and patients.

TriCore Reference Laboratories, an independent, not-for-profit clinical laboratory serving the state of New Mexico



since 1998, has been collaborating with other stakeholders in the state to build a value-based care model. New Mexico is considered rural and has one of the most ethnically diverse populations of all U.S. states, with nearly 50% Hispanic residents, 11% American Indian and Alaska Native, 2% Black or African American, and 1% Asian (3). Nearly one-third of New Mexico's 2.1 million inhabitants reside in rural communities (4). Even as access to healthcare generally keeps expanding in these areas, many residents still face barriers to care. These social determinants of health factor significantly in whether people seek access to healthcare services and are becoming a critical component of population health initiatives across the state.

Social determinants of health ... are becoming a critical component of population health initiatives across the state.

Health insurance coverage is only one determinant of whether a person will pursue healthcare services. Uninsured individuals face unaffordable healthcare and pay more out-of-pocket expenses, and the elderly generally access healthcare services more than their younger counterparts and are at higher risk of complications from chronic diseases. This results in higher healthcare expenses for the elderly who also become vulnerable to insurance claim denials.

In New Mexico, 9% of the population lacks insurance; this burden falls disproportionately on American Indians and Alaskan Natives (16.2%) and Hispanics 11.9% (5). The state's rural areas have the highest proportion of people age 65 or older, who compose about 18% of the state's population, and have an uninsured rate of 6.5% (3,5,6). At the end of 2019, approximately 10.5% of people younger than age 65 lacked health insurance (7). Of those who were eligible for Medicaid and market subsidies, 6.1% and 29% were uninsured, respectively (5).

By stratifying risk and identifying care gaps, clinical laboratories have leading roles in understanding these populations and supporting proactive approaches to health equity (1,2). Recognizing the strength of its data, a laboratory can help clinical partners achieve the highest standard of care for all individuals. This change occurs by reducing health disparities and modifying determinants of health to realize health equity across all communities (8,9).

VALUE OF LABORATORY DATA IN HEALTH EQUITY

Across the continuum of care, laboratories serve as clinical informants for healthcare partners, highlighting risks and care gaps within a population. By evaluating trends and developing guideline-derived algorithms to identify and manage health conditions, laboratories create descriptive and proactive models to support clinical decisions.

Hepatitis C Virus

Hepatitis C virus (HCV) causes acute and chronic infection of the liver, which can progress to hepatocellular carcinoma if not diagnosed early and

treated effectively (10). Most individuals go years without symptoms, and HCV infection remains grossly undiagnosed. Individuals at high risk for HCV infection include current or past injected-drug users, children born to HCV-infected women, and those infected with HIV (11). No vaccine prevents HCV, but newer direct-acting antiviral drugs show a cure rate of greater than 99% (12). Clinical guidelines on treating and managing HCV call for all diagnosed individuals to be treated—with few exceptions (11,12).

On December 15, 2017, the New Mexico Human Services Department (NMHSD) declared that denial of treatment for HCV infection should not be influenced by any degree of liver damage, and that access to treatment only requires a diagnosis of HCV (13). This declaration specifically imposed changes in contracts of the state's Medicaid program with managed care organizations (MCO) to improve access to treatment for Medicaid members across the state (14). Under this order, health plans have absorbed more HCV treatment costs among their enrolled members, which was met with a per member per month subsidy from NMHSD (15). As more individuals seek treatment—with a 12-week course of first-line medications costing between \$39,600 and \$94,500—payors are designing strategies to help manage and effectively distribute costs associated with chronic HCV infection (16, 17). These strategies are noble and essential as NMHSD's subsidy to payors was also met with a penalty of up to 0.3% of their entire capitated payment if the payor did not treat at least 90% of their members with an HCV claim. Laboratories are thus positioned uniquely to help their payor partners achieve these aims, both of which advance value-based care and improve equal access to healthcare throughout their shared communities.

Clinical laboratories can identify potential health inequities within the population of HCV infected individuals by using data such as age, insurance status, and address, and by developing clinical insights from these factors in combination with laboratory results indicative

 Join Us for an Important Critical Care Webinar

Resurgence of the BUN/Creatinine Ratio in Severe Illness: COVID-19, Sepsis, and Trauma

Urea and creatinine have been key indicators of kidney function for years and can be measured easily and quickly with currently available whole blood point of care analyzers. While newer tests for assessing renal function may hold promise for the future, they currently lack the history and clinical familiarity of urea, creatinine, and their ratio. In addition, the BUN/Creatinine ratio has significant value in selected patient populations, particularly critically ill patients, COVID-19 patients, and trauma patients. This webinar will describe the biochemistry of urea and creatinine production, and the physiology and handling of these metabolites by the kidneys as a lead-in to a discussion of the BUN/Creatinine ratio. New clinical studies will be summarized that describe the novel use of the BUN/Creatinine ratio — not just as a marker of kidney function, but also as a rapid, easy-to-obtain parameter to gauge the severity of the illness and the likelihood of survival in COVID-19, sepsis, and trauma patients.



Primary Presenter

John Toffaletti, PhD, Professor of Pathology
Director of ABG and CPED Labs
Duke University Medical Center

Learning Objectives

- Describe the physiology of urea and creatinine production and handling of these metabolites by the kidney
- Understand physiology of the kidneys and how kidney handling of urea and creatinine change with disease severity
- Apply and interpret the BUN/Creatinine ratio in critical illness



BUN/Creatinine Ratio Not Only a Marker of Kidney Function, but a Prognostic Indicator in Critical Illness

Presenter

Dennis Begos, MD, FACS, FACRS
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1.1%

of New Mexicans have a detectable HCV viral load

14%

are older than 65

13.5%

are insured through Medicaid.

of chronic health conditions, such as a detectable HCV viral load. Laboratories can pinpoint populations that need screening based on clinical guideline recommendations and also individuals who potentially need treatment.

According to TriCore's data repository, an estimated 1.1% of New Mexicans have a detectable HCV viral load, indicating a need for treatment. About 14% of these individuals are older than age 65, and 13.5% are insured through Medicaid. Losing both these populations to follow-up when individuals elect not to pursue additional medical treatment remains a concern of providers. Understanding social determinants of health that would influence an individual's reasoning for not seeking care when diagnosed with HCV is valuable to improving health equity.

Laboratory data algorithms can be configured into clinical analytical tools to help care coordinators provide targeted patient outreach and close care gaps. Partnering with Blue Cross Blue Shield of New Mexico (BCBSNM) in this effort, TriCore found that 28% of BCBSNM members covered by Medicaid had a reactive HCV antibody screening test but no follow-up confirmatory viral load test. Additionally, of the 1.4% of BCBSNM Medicaid members with a detectable viral load within the past year, nearly 15% had their first detectable viral load. For care coordinators, this information conveys a new HCV diagnosis and prompts them to work with providers to evaluate a patient's readiness for treatment. This supports the need for partnerships between laboratories, payors, and providers to break

down barriers to healthcare and create an environment supportive of health equity opportunities.

Pregnancy

In 2016, New Mexico ranked 48th in the U.S. for live births to women who received prenatal care before the third trimester (18), with only 63.4% of women having a healthcare visit in their first trimester (national average, 77.2%) (19). That same year, the March of Dimes gave New Mexico a "C" rating owing to its 9.5% preterm delivery rate (national ranking, 30th overall) (20). Studies have tied coordinated care in pregnancy to a reduction in preterm deliveries among women enrolled in Medicaid (21, 22, 23). To improve New Mexico's performance in prenatal care and birth outcomes, NMHSD required MCOs providing coverage to Medicaid recipients to track, report, and better their prenatal and postpartum care quality measures. Additionally, NMHSD financially incentivized continual progress with these measures, as a means of improving outcomes for Medicaid beneficiaries (21).

To meet NMHSD's requirements, MCOs utilize medical claims data, communications from healthcare providers, prescription records, and member self-reporting to identify pregnancies, coordinate prenatal care needs, and detect births. However, most prenatal care claims are not filed until after infants are delivered, resulting in latent data (24, 25). Also, rural patients might lack awareness of or access to obstetric services, thereby potentially seeking routine care in emergency settings, not receiving ongoing prenatal care, and not accessing healthcare services until they go into labor.

In prenatal care, clinical laboratories provide more reliable and timely data than insurance claims (26, 27, 28). By combining patient results across providers and locations, laboratories create a longitudinal picture of prenatal care gaps to facilitate timely obstetric care. While not all prenatal visits include laboratory testing, the American College of Obstetricians and Gynecologists (ACOG) recommends laboratory testing milestones according to specific gestational age (29); this

enables laboratories to verify the presence or absence of routine prenatal care. Additionally, a patient's longitudinal history of laboratory testing indicative of high risk (e.g., diabetes, urinary tract infection, age, etc.) furthers a laboratory's ability to innovatively enhance the value of a single prenatal test.

TriCore created a prenatal algorithm over an 11-month period, testing its ability to enhance care coordination provided by a New Mexico MCO, BCBSNM. Our study indicated that of the 1,355 BCBSNM Medicaid members identified as pregnant:

- More than 65% identified for needing prenatal care were not reflected in BCBSNM claims data;
- 77% were in their first trimester;
- 64% received at least 80% of ACOG's recommended medical laboratory testing; and
- Women who received regular prenatal care:
 - Used emergency care 25% less;
 - Had fewer births requiring a NICU admission; and
 - Had fewer preterm deliveries.

These results indicate that clinical laboratory data-driven algorithms provide real-time and longitudinal insights; using these laboratory generated insights, BCBSNM was able to identify more pregnant members, increase the number of women receiving early prenatal care, monitor ongoing prenatal care, and affect the likelihood of an uncomplicated gestation. *The American Journal of Managed Care* recently published this study (30).

Diabetes

Diabetes is a growing epidemic in the United States with an estimated annual cost in 2017 of \$327 billion, including \$237 billion in direct medical costs and \$90 billion in reduced productivity (31). To help prevent or delay the progression of diabetes mellitus complications, the American Diabetes Association (ADA) sets forth annual care guidelines (32). One recommendation calls for patients with diabetes who are meeting treatment goals to receive a hemoglobin A1c (HbA1c) test twice annually, and

those not meeting glycemic management targets to undergo quarterly testing. Additionally, ADA recommends a random urine albumin-to-creatinine ratio (uACR) at least annually to monitor microvascular kidney complications. Organizations that assess the quality of healthcare adopt these guidelines, and similar to prenatal care, NMHSD incentivizes the annual improvement of these measures among MCOs that provide health insurance to Medicaid recipients.

Health plans work to improve these annual measurements each year through a variety of mechanisms. A popular method involves contacting eligible members and assisting in their

members with diabetes (36). Further, the report describes how this insight allowed BCBSNM's diabetes care management team to achieve higher completion rates with recommended annual HbA1c and uACR testing in the study group. In 2017, BCBSNM's HbA1c compliance rate within Medicaid was 82% (36), which led to development of an algebraic forecast for the study group's year-end completion rate. With an estimated 89% annual completion rate, the study demonstrated that collaboration between BCBSNM and TriCore could achieve a 7% higher rate of compliance with HbA1c testing among eligible diabetic patients. This higher rate of

DISCUSSION

As these examples demonstrate, clinical laboratories have access to valuable and actionable insights, derived from their data warehouses, that can be used to improve both individual and population health. This is particularly relevant for communities that experience barriers to care. Notably, a laboratory does not need to serve an entire state in order to make a difference. Strategies like those described here can be applied on a smaller scale.

Clinical laboratories leverage their value most effectively in partnership with others. Clinicians, educators, payors, care coordinators, and, of course, patients themselves are all

Clinical laboratories leverage their value most effectively in partnership with others.

diabetes management by educating them, coordinating visits among their providers, and focusing on preventative services to reduce costly complications. This process, commonly referred to as care management (33), assesses the needs of each member by utilizing a variety of data elements such as medical claims data, communications from providers, prescription records, and member self-reporting. Some of these data sources (e.g., diagnosis data) might contain errors (34,35), which could limit the effectiveness of care management operations. By delivering accurate and timely clinical results laboratories have the potential to identify and track patients who need diabetes care management. To prove this concept, TriCore again collaborated with BCBSNM by providing patient-focused analytics. For nearly 4 months, both organizations aimed to determine if our laboratory could better identify BCBSNM Medicaid members with diabetes and whether BCBSNM care management could improve their diabetes quality measures.

The study, published in *The Journal of Applied Laboratory Medicine*, demonstrated that TriCore's insights could accurately identify BCBSNM's

compliance would assist BCBSNM in exceeding its contractual obligations with NMHSD and avoid the monetary penalty associated with HbA1c testing for members with diabetes.

After assessing the impact of this collaboration, TriCore then calculated the financial incentives NMHSD assigned to these diabetes quality measures. TriCore determined that NMHSD assigned \$3,693,000 per measure, parsed among MCOs based on the number of Medicaid enrollees. Dividing the total NMHSD incentive by the total number of Medicaid members with diabetes indicated that each Medicaid recipient with diabetes is worth \$55.10 for each quality measure (38). New Mexico's reimbursement rate for an HbA1c test (based on the CMS Clinical Lab Fee Schedule) was \$11.27 in 2018 and lowered to \$9.13 in 2020 (39). When comparing the HbA1c reimbursable test rate against the NMHSD quality incentive rate, we found that an HbA1c test in New Mexico is worth less than one-fifth the value per patient. This indicates NMHSD's strong desire to ensure all Medicaid recipients are integrated into care and creates an opportunity for laboratories to assist in this effort.



necessary ingredients for success. Laboratory partners have so much to gain from positioning themselves as leaders in value-based healthcare among these diverse teams and from making their voices heard and contributions recognized. This makes sense, given the large amount of information and decision-making derived from laboratory data.

However, laboratory professionals also possess the domain knowledge required to effectively translate these data into actionable insights. Measuring the value of clinical

laboratories beyond lab-focused metrics is no simple matter and will take time, energy, and resources to realize. Nonetheless this goal can be realized, and the process of doing so has already begun. ■

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AACC Disruptive Technology Award finalists

show how IVD innovators are bringing to life the latest advances in biotechnology and artificial intelligence.

A

s in other disciplines, disruptive technology in laboratory medicine is

often the brainchild of necessity. The focus on patient care drives both clinical laboratorians' obsession with quality and their passion for ingenuity and invention.

Figuring out how to do something better often takes complete reimagining of a process to open space for the next generation of technology. The companies that participated in the AACC Disruptive Technology Award program at the 2020 AACC Annual Scientific Meeting in December illustrated this type of quest.

From designing diagnostic tests for babies instead of co-opting adult-ready assays, to using artificial intelligence to identify biomarkers for psychiatric disorders, to making tests for something as common as strep throat as easy and inexpensive as a pregnancy dipstick, Disruptive Technology Award finalists showed they are disrupting lab medicine for good.

Testing Babies at Baby Scale

Baebies impressed both the judges and AACC Annual Scientific Meeting attendees, winning the top prize in the competition as well as the Audience Choice Award, which was determined by audience voting.

The problem for patients the company wants to fix is common and simple: Babies need clinical laboratory testing as much as adults, but these tiny patients just don't have a lot of blood, especially those born prematurely. Typically, babies have transfusions to make up for the volume of blood depleted through testing, but this raises the risk of infection and complications.

Digital microfluidics move discrete droplets of fluid by electrical control of surface tension, or electrowetting, to perform bioassay protocols.



“Right now all devices that are being used for diagnostic testing for babies are typically intended for adults,” said Rama Sista, PhD, senior director of point-of-care products at Baebies. “Babies are not tiny adults. There’s just no platform out there that focuses on babies only.”

Baebies’ FINDER is an all-in-one diagnostic kit that tackles a common problem in treating the smallest patients. It uses digital microfluidics to move discrete droplets of fluid by electrical control of surface tension, or electrowetting, to perform bioassay protocols. This means the kit needs just 50 μ L of blood to work. FINDER “has access to discrete droplets and can do pretty much anything you typically do in a laboratory,” said Sista. The platform works with multi-functional assay methods, including molecular, immunoassay, and chemistry, on the same cartridge. Results take 15 minutes.



The size of FINDER is a key part of the technology, too: It’s about 8 inches wide with a tablet interface, and is designed to be a bedside tool without requiring specialized laboratory knowledge or skills.

Sista said that the company’s priority is making testing easier for babies, but recognizes that FINDER also has utility in adult patients. The company plans to apply to the Food and Drug Administration (FDA) for an Emergency Use Authorization for a SARS-CoV-2 reverse transcription polymerase chain reaction test that provides results in 14 to 17 minutes. “We’re not inventing new assays,” said Sista. “All we’re doing is miniaturizing everything because of the capabilities of the technology.”

Molecular Testing, At Home

While the need for at-home SARS-CoV-2 testing has been a pressing focus of the IVD community, Sherlock Biosciences has been working to make more ordinary tests needed in non-pandemic times easier, cheaper, and feasible for patients to perform at home, similar to at-home pregnancy tests.

Sherlock’s INSPECTR platform, a finalist for the AACC Disruptive Technology Award, “enables molecular testing at the simplicity of use and price point of a simple dipstick immunoassay,” said William J. Blake, PhD, the

company’s chief technology officer. The technology “combines the features of antigen tests that are low cost and simple with the accurate high specificity of sensitive molecular testing,” he added.

INSPECTR is a CRISPR-based diagnostic platform that combines nucleic acid preamplification with CRISPR-Cas enzymology for specific recognition of desired DNA or RNA sequences. This allows for multiplexed, portable, and ultra-sensitive detection of RNA or DNA from clinically relevant samples. Another unique aspect of the system is its use of freeze-dried synthetic gene networks.

Precision Diagnostics for Psychiatry

Right now, it's not easy for psychiatrists to differentiate between bipolar disorder and depression because the symptoms are so similar. Patients typically go 7 years before getting an appropriate diagnosis of bipolar disorder, said Marianne Morini, business development manager at Alcediag. Moreover, 69% of those with the disease are initially misdiagnosed.

The results of a misdiagnosis can be catastrophic. Bipolar disorder is one of the 10 most disabling diseases, according to the World Health Organization. Being prescribed the wrong medication after a misdiagnosis could pose disastrous side effects. Bipolar disorder also presents a financial burden, both to patients seeking treatment and to society, with care costing \$24 billion a year in the U.S. alone.

"We have treatments for bipolar disorder and depression, and people can be stabilized if they have the right diagnosis," Morini said.

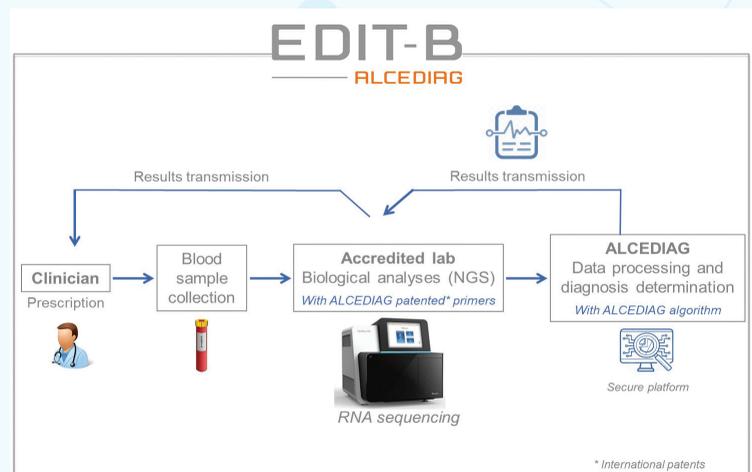
Alcediag's EDIT-B, a finalist for the AACCC Disruptive Technology Award,

is the first blood-based diagnostic test for bipolar disorder—and for any psychiatric disease. The platform uses RNA sequencing and artificial intelligence to look at epigenetic biomarkers, specifically RNA site mutations, to determine "which combinations of those mutations on different sites of different biomarkers are significant characteristics of bipolar disorder," Morini said.

EDIT-B sequences the DNA and calculates the level of editing in RNA; then an algorithm takes the sequencing data and creates a score that determines how likely the depressed person is to suffer from bipolar disorder. So far, the company says studies show EDIT-B is 87% accurate in this diagnosis.

Alcediag is currently in talks with U.S.-based laboratories to "put the test in a clinical laboratory setting,"

said Morini, a step toward FDA authorization and broader dissemination. She knows those regulatory roads are long, but she's optimistic about what EDIT-B can do, not just in diagnosing bipolar disorder but also other psychiatric conditions. Morini also believes that the technology could be used in other fields of medicine, including oncology. "We are at the beginning of the story," she said.



The company is deploying the platform for SARS-CoV-2 testing. Sherlock has an FDA-authorized SARS-CoV-2 self-testing kit using the INSPECTR platform that returns results in about an hour. In December, the Bill & Melinda Gates Foundation awarded Sherlock a \$5 million grant to advance the INSPECTR platform for SARS-CoV-2 testing, and the company plans to launch a home-based test by mid-2021.

Sherlock's overall goal remains to make routine molecular testing simpler. Blake uses the example of a child who might have strep throat.

Instead of a parent taking off from work and pulling the child out of school, a clinician could prescribe a test performed "in the comfort of the patient's home with a technology that is as accurate as the most accurate molecular tests today," he said. The INSPECTR technology is truly disruptive, Blake stressed, because the goal is to be "low cost and accessible to the individual, and not require instrumentation." ■





COLORECTAL CANCER

and the Problem of Youth

The quest is on to understand the distinct clinical and molecular traits of this disease and identify early diagnostic biomarkers.

BY DEBORAH LEVENSON

Colorectal cancer (CRC) is the third-most common type of malignancy in the U.S., and the second-leading cause of cancer deaths. CRC mostly affects older adults and has been declining in this population due to better prevention and early detection. However, CRC is on the rise in adults under age 50, with incidence rates more than doubling in the U.S. since the 1990s. Several other countries have seen similar increases. Typically, this early-onset CRC (EOCRC) is diagnosed at more advanced stages and is more aggressive than CRC diagnosed in older people.

"It's only in the most recent 10 years that more urgent attention has turned toward early-onset disease," said Yi-Qian Nancy You, MD, associate professor of colorectal surgical oncology and associate medical director of the clinical cancer genetics program at University of Texas MD Anderson Cancer Center in Houston.

Robust research efforts aim to understand what's driving the rise in EOCRC, its specific clinical and molecular features, and the best ways to diagnose and prevent this disease. In response to their findings, the U.S. Preventive Services Task Force in October 2020 issued draft guidance that calls for CRC screening in the general population to

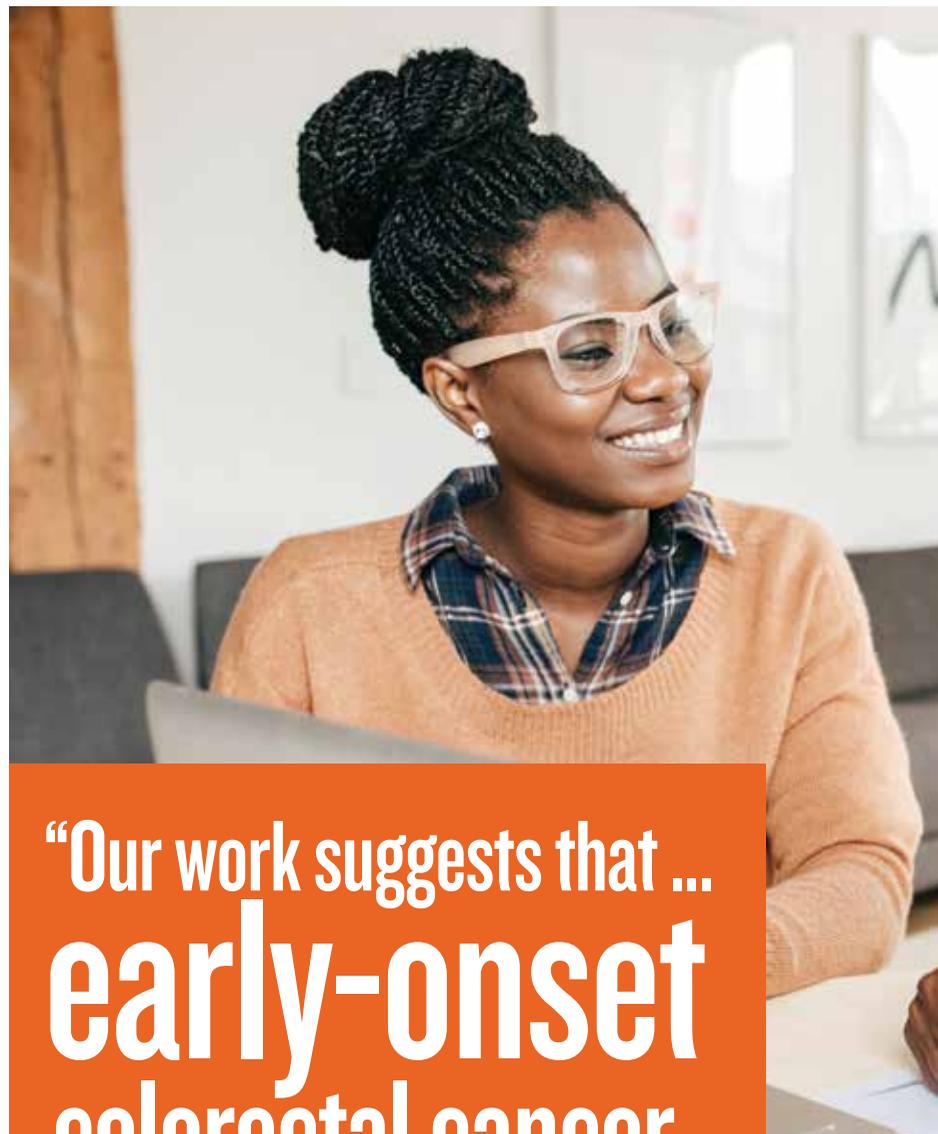
begin at age 45 rather than 50. But because a research focus on EOCRC is still relatively new, “there’s a great open field for novel applications, tests, and techniques” to detect the disease, You noted.

DIET AND MORE

A slew of recent papers has identified possible culprits behind the rise in EOCRC, particularly poor diet. For instance, researchers at Washington University in St. Louis and the Harvard T.H. Chan School of Public Health showed an association between poor diet quality and risk for early-onset, high-risk distal and rectal adenomas (J Natl Cancer Inst 2020; 10.1093/jnci/djaa164). This analysis of the prospective Nurses’ Health Study II cohort compared associations of a Western diet and recommended healthier eating approaches with early-onset colorectal adenomas—which usually turn into cancer—and those of high malignant potential as surrogate endpoints. The authors found that a Western diet was associated with increased early-onset adenoma risk, whereas healthier diets had an inverse association with adenomas.

This research is among the latest in a series on risk factors for EOCRC by senior author Yin Cao, ScD, associate professor of surgery at Washington University in St. Louis. Her team and collaborators have also found evidence implicating obesity, sedentary behavior, and metabolic syndrome as risk factors, she noted. “Our work suggests that similar to later-onset CRC, EOCRC is a multifactorial disease. Identification of the set of risk factors that contribute to the rising incidence is a priority,” said Cao.

An editorial accompanying Cao’s recent paper calls for stepping up efforts to identify preventable EOCRC risk factors. The authors note that her team looked at adenomas because existing prospective studies have too few cases in younger people to properly investigate risk factors. To address this dearth of EOCRC research subjects, the editorial authors—Neil Murphy, PhD, Peter Campbell, PhD, and Marc Gunter, PhD—recently established the Colorectal Cancer Pooling



“Our work suggests that ...
**early-onset
 colorectal cancer**
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**Identification of
 the set of risk factors that contribute
 to the rising incidence
 is a priority.”**

—Yin Cao, ScD



Project (C2P2), an international effort of more than 25 prospective cohort studies.

C2P2 will comprehensively examine potential risk factors and biomarkers for CRC diagnosed in people in different age groups and provide an infrastructure for unraveling the etiology of EOCRC. C2P2 also plans to study potential biomarkers that might be intermediates of established lifestyle risk factors related to metabolic health and gut dysbiosis, or microbial imbalance. Investigations will begin with a population of EOCRC cases and controls and later expand to older patients for comparison, said editorial co-author and C2P2 co-founder Campbell, scientific director of population science at the American Cancer Society.

THE GUT MICROBIOME

A recent review identified several possible EOCRC risk factors, including a Western diet, with heavy intake of red and processed meats, high-fructose corn syrup, synthetic dyes, and monosodium glutamate, as well as stress, antibiotic use, and sedentary behavior (Nat Rev Gastroenterol Hepatol 2020;17:352-64). The paper calls inflammation and the gut microbiome “guardians of the colon.” First author Lorne J. Hofseth, PhD, a professor of pharmacy and director of the Center for Clinical Colon Cancer Research at University of South Carolina, emphasized the outsized influence of diet: “We have much to learn about the role of diet. But its role in prevention is clear.

The low-hanging fruit is to change your freaking diet.”

Among many others, Georgetown University researchers also have noted evidence that the human gut microbiome might play a role in cancer pathogenesis (Curr Oncol Rep 2019;21:3). They describe epidemiologic shifts in CRC incidence and mortality across age groups and differences between younger and older patients in clinicopathologic, molecular, treatment, and survival characteristics. More studies of the microbiome might elucidate bacterial causes of CRC in younger individuals, they note.

MOLECULAR FEATURES

Other research suggests EOCRC has distinct clinical and molecular features in particular age groups, a finding that might warrant more consideration of patient age in testing and in managing the disease (Cancer 2019;125:2002-10). This review of more than 36,000 CRC patients showed that compared with older patients, those with early onset disease were more likely to have microsatellite instability (MSI), although an earlier paper reported that EOCRC is less likely to involve MSI (JAMA Oncol 2017;3:464-71). The *Cancer* paper also found that in comparison to older patients those with EOCRC were more likely to have primary tumors in the distal colon and rectum, and fewer *BRAF V600* mutations. In patients younger than 40, consensus molecular subtype (CMS)1 was the most common, whereas CMS3 and CMS4 were rare.

The review published in *Cancer* also suggests greater use of genetic testing and whole genome sequencing (WGS), especially for high-risk patients and family members of patients with EOCRC.

Hofseth noted that WGS and other genetic tests might identify molecular changes in several genes already well-associated with early disease, such as *KRAS* and *P53*. These genes, as well as *LINE-1* hypomethylation, are very common in nonhereditary cancers and might also serve as EOCRC biomarkers.

Other studies have noted more genetic variations associated with EOCRC. One that observed a higher

rate of hereditary cancer syndromes in EOCRC patients found pathogenic variations in cancer genes not previously associated with CRC, such as *BRCA1* and *BRCA2* (JAMA Oncol 2017;3:464-71). The Ohio Colorectal Cancer Prevention Initiative examined variations in 450 patients who were prospectively recruited at 51 of the state's hospitals. Among EOCRC patients, 16% had a pathogenic variant in at least one cancer susceptibility gene. Of these, about half had Lynch syndrome, the most common cause of hereditary CRC, while the other half did not. Of those without Lynch syndrome, about a third had pathogenic variants in genes not previously associated with CRC. Senior author Heather Hampel, MS, CGC, a clinical professor of human genetics at The Ohio State University, said that a forthcoming paper on 3,310

individuals involved in the initiative shows similar results.

National Comprehensive Cancer Network guidelines recommend that all CRC patients under 50 get genetic evaluations, Hampel pointed out. In light of this, her hospital has a liaison between the pathology and genetics departments who identifies EOCRC patients and navigates them to genetics consults.

DNA AND STOOL-BASED TESTS

Many groups are developing less invasive CRC methods that rely on circulating tumor cell (ct) DNA for screening, diagnosing, and monitoring treatment for the disease. Most patients—especially younger people—find them easier to accept than colonoscopies. Hofseth noted that fecal samples can reveal changes in the genome, metabolome,

microbiome, and inflammation that point to disease, and stool-based DNA tests can find mutations associated with CRC.

But ctDNA and stool tests have downsides, including being less sensitive for detecting adenomas. ctDNA has been used successfully to monitor metastatic disease, but detecting minimal residual disease (MRD), early-stage cancer, or small premalignant, molecular changes has been more challenging. “All of the tests have detection limits. Ongoing efforts aim to improve sensitivity while maintaining specificity,” said You, who is a co-leader in MD Anderson's Colorectal Cancer Moon Shot Program.

The plethora of ctDNA testing platforms and methods used in symptomatic CRC patients was an impetus for a recent National Cancer Institute Colon and Rectal-Anal Task Force meeting on integrating ctDNA technology in clinical care. You co-authored a white paper based on the proceedings, which notes that ctDNA has potential to detect MRD, monitor responses to therapy, and track clonal dynamics in response to targeted therapies and other systemic treatments. But first, the field must establish optimal assay characteristics for various clinical scenarios, standardize assay quality control and reference materials, and ensure reliable pre-analytical variables. Related clinical trials should be collaborative and benefit from new platforms that help research groups share data and collaborate, the paper adds (Nat Rev Clin Oncol 2020;17:757-70).

In the meantime, “the message remains that early-onset disease remains insufficiently understood and tends to have distinct clinical behavior,” said You. The field is trying to understand underlying molecular differences at various levels, such as DNA and RNA, tumor epigenetics, and the microenvironment including the tissue cellular matrix and microbiome. You emphasized, “Although there has not been a big breakthrough yet, there is a lot of very active ongoing research.” ■

“Early-onset disease remains insufficiently understood and tends to have distinct clinical behavior.”

—Yi-Qian Nancy You, MD

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** <https://www.fda.gov/news-events/press-announcements/fda-issues-alert-regarding-sars-cov-2-viral-mutation-health-care-providers-and-clinical-laboratory>

FDA Issues Alert About Tests Affected by Emerging SARS-CoV-2 Variants

As of January 2021, the Food and Drug Administration (FDA) has identified three emergency use authorized molecular tests for SARS-CoV-2 that could give false-negative results when testing SARS-CoV-2 genetic variants. In an alert, the agency stated that these three tests are Mesa Biotech's Accula SARS-CoV-2 test, Thermo Fisher Scientific's TaqPath COVID-19 Combo kit, and Applied DNA Sciences' Linea COVID-19 assay kit.

The performance of Mesa Biotech's test may be impacted when testing SARS-CoV-2 patient samples that have a genetic variant at position 28881 (GGG to AAC). Meanwhile, the tests from Thermo Fisher and Applied DNA Sciences have shown reduced sensitivity for the virus's S gene when certain mutations are present, including one of the mutations in the B.1.1.7 SARS-CoV-2 variant that was first identified in the U.K.

FDA notes that the overall impact of variants on these three tests does not appear to be significant—especially for the Thermo Fisher and Applied DNA Sciences tests, which detect multiple genetic targets. However, out of an abundance of caution, the agency still thought it best to alert healthcare professionals about this potential issue. Additionally, FDA wants labs that are using the Thermo Fisher and Applied DNA Sciences tests to be aware of the pattern of detection when certain mutations are present. This might help with early identification of new variants in patients, which in turn could help to further reduce the spread of infection.

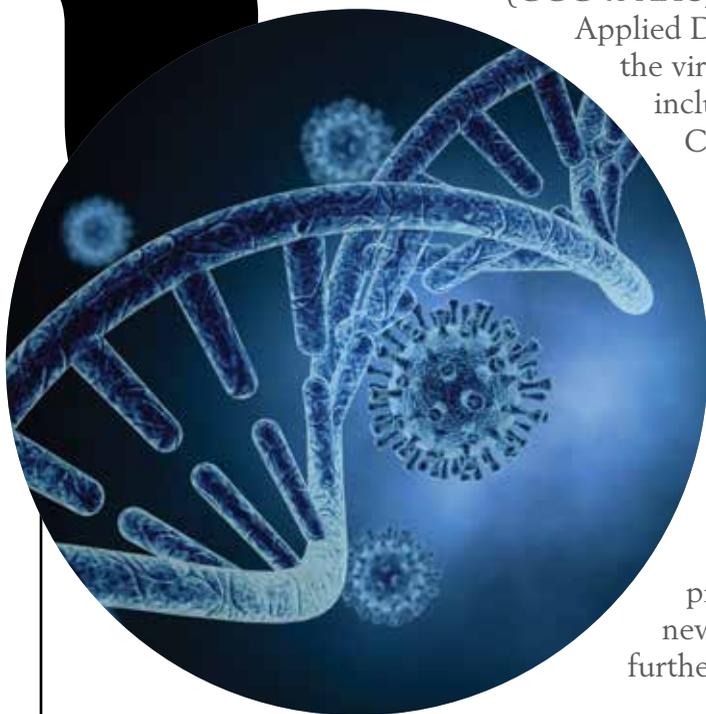
FDA AIMS TO INCREASE COVID-19 PATIENT ACCESS TO VISCOELASTIC COAGULATION TESTING

The Food and Drug Administration (FDA) has issued new guidance in order to expand the availability and capability of viscoelastic coagulation analyzers for use in COVID-19 patients. Currently, FDA has not cleared or approved any coagulation systems for measurement of whole blood viscoelastic properties in hospital patient healthcare settings. However, as the pandemic has continued, it has become clear that these devices are needed to test for and manage

coagulopathies in hospitalized COVID-19 patients, who are at an abnormally increased risk for blood clotting. With this guidance, FDA intends to foster the continued availability of safe and effective medical devices while being flexible regarding certain modifications made to viscoelastic coagulation systems so that they can be used in COVID-19 patients. Specifically, the agency does not intend to object to limited modifications to the indications, functionality, hardware, and/or software of viscoelastic coagulation analyzers that are within the scope of this guidance, even if the manufacturer does not submit a new 510(k) submission to FDA.

ABBOTT RECEIVES FDA AUTHORIZATION FOR PRESCRIPTION HOME SARS-COV-2 ANTIGEN TEST

The Food and Drug Administration has issued a new emergency use authorization (EUA) for Abbott's BinaxNOW COVID-19 Ag Card test. This SARS-CoV-2 antigen test first received an EUA in August 2020 for use in healthcare settings. With this new EUA, patients can now use the test at home with a prescription if their healthcare provider suspects that they have COVID-19. The test should be used within the first 7 days of symptom onset and is authorized



for use with self-collected nasal swab samples from individuals ages 15 years or older and with adult-collected nasal swab samples from individuals 4 years or older. Abbott will offer the test in partnership with a telehealth service that will take users step-by-step through the sample collection process and provide assistance in reading and understanding the results. The telehealth provider will also report all test results to the relevant public health authorities in accordance with local, state, and federal requirements.

■ **FDA OKS SIEMENS TEST THAT HELPS PREDICT COVID-19 CYTOKINE STORM**

Siemens Healthineers has received an emergency use authorization from the Food and Drug Administration for its laboratory-based IL-6 assay that measures the presence of interleukin-6 (IL-6) in human serum or plasma. IL-6 is an indicator of potential severe inflammatory response in patients

with confirmed SARS-CoV-2 infection. In conjunction with clinical findings and the results of other laboratory testing, this assay could help clinicians to identify COVID-19 patients who are at risk of cytokine storm and need intubation with mechanical ventilation. The test could also help clinicians start timely interventions with IL-6 activity blockers such as tocilizumab and sarilumab. Siemens' IL-6 assay is currently available across the U.S. on the Advia Centaur Immunoassay systems with a time-to-result of 18 minutes. The test is also CE marked for use outside the U.S. on the Advia Centaur systems, Atellica IM analyzer, and Immulite systems.

■ **FDA GRANTS EUA FOR ELLUME'S OVER-THE-COUNTER SARS-COV-2 HOME ANTIGEN TEST**

The digital diagnostics company Ellume has earned Food and Drug Administration emergency use authorization (EUA) for its rapid,

direct-to-consumer SARS-CoV-2 antigen test, the Ellume COVID-19 home test. The test will be available for non-prescription home use in adults and children aged 2 years or older with or without symptoms. It works in conjunction with a smartphone application that provides step-by-step instructions for the user. All analysis is performed by the test's electronic analyzer, which then uses Bluetooth connectivity to display the test result on the user's smartphone in 15 minutes or less.

In a simulated home-setting clinical study of 198 subjects, the Ellume COVID-19 home test demonstrated an overall sensitivity of 95% and specificity of 97% when compared to an EUA polymerase chain reaction SARS-CoV-2 laboratory test. This same study showed that in individuals presenting with COVID-19 symptoms, Ellume's test demonstrated 96% sensitivity and 100% specificity, while in asymptomatic individuals, the test demonstrated 91% sensitivity and 96% specificity.

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Industry Playbook

Mammoth, MRI Global Sign Contract for CRISPR-Based Technology

Mammoth Mammoth Biosciences has secured a four-year contract with the U.S. Department of Defense's (DOD) Defense Advanced Research Projects Agency (DARPA) with MRI Global as the prime contractor. Under the agreement, the company will spearhead the Detect It with Gene Editing Technologies (DIGET) program to develop CRISPR-based diagnostics for the DOD. The contract comes as a result of the COVID-19 global pandemic that left many healthcare facilities unprepared. It aims to meet the needs of any future pandemic or disease threats.

Through DIGET, the parties plan to use CRISPR to develop a point-of-care (POC) device with the ability to detect 10 pathogens at once. Also in the works

is a massively multiplexed detection (MMD) platform that screens more than 1,000 samples simultaneously. According to the companies, the POC device will improve the speed and efficiency of treatment for the military and public health in even the most restricted environments. Additionally, the MMD platform will detect early threats and characterize known and emergent pathogens. The technologies are said to detect pathogens in areas such as respiratory illnesses, febrile illnesses, vector-borne illnesses, gastrointestinal illnesses, and sepsis.

Under the terms of the contract, MRI Global has received \$12.7 million with a potential of up to \$36 million.

EMEDGENE AND ILLUMINA PARTNER FOR AI GENOME INTERPRETATION

Emedgene and Illumina announced an exclusive partnership to advance automated data interpretation in genetic testing using artificial intelligence (AI) technology. Under the terms of the collaboration, the companies will integrate Emedgene's AI-powered Clinical Rare Disease application with Illumina's TruSight Software Suite to provide rapid genomic interpretation.

According to the partners, Emedgene's Cognitive Genomics Intelligence solution automatically analyzes genome data compiled

from Illumina's TruSight products without long hours of manual review. Specifically, the AI technology will be able to read phenotypes associated with rare diseases. Through the partnership, the parties expect to accelerate the analysis process and provide new insights to improve diagnosis and treatment of patients with rare genetic disorders.

"In the future, patients will have access to the \$100 genome, making it as ubiquitous as a blood test," said Einat Metzer, co-founder and CEO of Emedgene. "This genomic data will be attached to an electronic medical record, and inform clinical decision-making throughout our lives. Billions of patients across disease areas will benefit from faster diagnosis and better treatment."

BAYER AND VERACYTE TEAM FOR THYROID CANCER THERAPIES

Bayer and Veracyte have joined forces for the Precision Oncology Patient Identification Program, which will focus on patients who have advanced or metastatic radioactive iodine refractory thyroid cancer and could benefit from biomarker-driven therapies.

As part of the collaboration and program, Veracyte will offer its Afirma Xpression Atlas (XA) test that identifies underlying genes in patients' tumors, including neurotrophic tyrosine kinase (*NTRK*) gene fusions that drive tumor growth. Through RNA whole-transcriptome sequencing, the Afirma XA detects 905 DNA variants





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and 235 RNA fusions in 593 genes on needle samples taken from thyroid nodules or lymph nodes.

Bayer plans to offer testing at no cost to eligible patients when a physician orders a test. Additionally, Bayer will alert physicians when test results detect *NTRK* gene fusions.

"Patients whose thyroid cancer contains actionable alterations and no longer responds to traditional radioactive iodine therapy now have targeted treatment options available to them. Our goal is to identify such patients so physicians can make more informed treatment decisions for their patients," said Bhavesh Ashar, senior vice president and head of U.S. Oncology at Bayer.

ONCOCYTE EXPANDS DETERMARX TO CHINA'S BURNING ROCK

Oncocyte Corporation has signed an exclusive agreement to license its DetermaRx test to Burning Rock Biotech, one of the largest companies in China's next-generation sequencing-based cancer therapy



selection market. The DetermaRx assists in identifying high-risk, early-stage lung cancer patients who need treatment to improve their five-year survival. Through analysis of molecular signatures from tumor tissue, DetermaRx helps physicians determine the best treatment options for patients.

The agreement is the fifth licensing agreement for Oncocyte and will achieve the company's goal to commercialize DetermaRx in all major markets across the globe within one year of the product launch.

"Combining DetermaRx with our products for genetic testing and minimal residual disease detection, we can provide a comprehensive testing strategy for oncologists to ultimately benefit Chinese early-stage non-small cell lung cancer patients by improving their survival and quality of life," said Yusheng Han, founder and CEO of Burning Rock.

Oncocyte will receive cash payments after installation of DetermaRx as well as ongoing royalties for each patient tested.

HOLOGIC INKS \$230 MILLION DEAL FOR BIOTHERANOSTICS

Hologic announced a \$230 million deal in which it will acquire

Biotheranostics, a private company that provides molecular diagnostic tests for breast and metastatic cancers. Through the purchase, Hologic aims to enhance its current work in the field of oncology with more personalized treatment and better outcomes for women.

Biotheranostics will provide Hologic with its two polymerase chain reaction (PCR) tests, Breast Cancer Index (BCI) and CancerTYPE ID. Biotheranostics' BCI test compiles tissue from a biopsy test to help doctors and patients determine the risk of recurrence and whether anti-estrogen therapy is needed to reduce the risk. In addition, the CancerTYPE ID test allows medical experts to identify a specific type of cancer by comparing genetic information from a patient's tumor to a database of more than 2,000 tumors. Both PCR tests have gone through extensive validation and are well established across the United States.

Hologic was able to acquire Biotheranostics after seeing a growth in revenue from COVID-19 testing in 2020.

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Ask The Expert

The Search for Reliable Instrument Interface Connectivity



EXPERT

By Kenneth E. Blick, PhD, ABCC, ACS

How did the use of middleware in the lab first arise?

A: Fifty years ago or more, automated instruments for the clinical laboratory had primitive software capabilities. These instruments were directly cabled to a laboratory information system or laboratory information management system (LIS/LIMS) port

and used vendors' custom-designed software on the instrument and LIS/LIMS (also known as a vendor-specific interface) to enable connectivity. Usually, this software transmitted test orders from the LIS/LIMS to the automated instrument while also transmitting interfaced laboratory results from the instrument back to the LIS/LIMS, all with no middleware software involved whatsoever.

In those days, it was very expensive and time-consuming to get a working and reliable interface, mostly because of the variety of different instrument and LIS/LIMS vendors involved. Also, there were essentially no uniform standards for communication between various instruments and LIS/LIMS computers for data transmission protocols, data record formats, and the like.

AACC's Informatics Division was formed in part to address this connectivity challenge. As chairman and founder of the division, I was involved early on in writing the first prototype specification for the now universally accepted ASTM interface standard for medical laboratory instrument interfaces. Shortly after we developed this standard, several vendors began to provide flexible middleware solutions to make the ASTM instrument-LIS/LIMS connectivity less vendor-specific and more flexible. This was essential because many LIS/LIMS vendors were quick to embrace ASTM connectivity standards while instrument vendors lagged far behind, with many older, non-ASTM compliant instruments still deployed in clinical laboratories.

However, these early middleware technologies were not designed to handle the highly diverse and emerging connectivity challenges of point-of-care testing (POCT).

Why do we need middleware designed specifically for POCT interfaces?

When the use of bedside POCT first took off, interface challenges for this service rapidly became a major problem. This was due to several factors, including: 1) the large number of hand-held devices being deployed, 2) compliance issues with training and

quality control for the large number of nonlaboratory personnel performing POCT, 3) support issues involved in remotely monitoring devices, testing personnel, quality control, and patient results in real-time, 5) specific and unique POC CLIA compliance issues and monitoring, and 6) billing and other resource management issues.

Additionally, the need for interfaced POC patient demographic information prior to testing made the ASTM interface standard a poor option for POCT. Fortunately, this particular issue at least was solved early on by conforming POC interface protocols to the HL7 interface standards instead.

As for all of the other connectivity challenges associated with POCT, vendors of POC devices initially addressed these issues with vendor-specific interface solutions. However, these soon became a significant problem in their own right as laboratories deployed different POC vendor solutions throughout the hospital.

It was middleware vendors who came to the rescue by developing hospital-wide interface solutions with an open system approach. This enabled: 1) multiple vendor POC solutions to be interfaced and managed with a standard middleware turnkey solution, 2) speedier deployment of best-of-breed POC devices, since laboratories were no longer locked into particular vendor solutions, and 3) better overall control and compliance of the entire POCT program throughout the hospital using a lean-management approach.

These days, middleware dominates as the preferred connectivity solution for the clinical laboratory. Even though connectivity standards exist, subtle connectivity issues remain between different instruments and LIS/LIMS vendors. Middleware's flexibility enables it to handle these issues effectively and reliably, thus providing a stable interface connectivity solution.

Kenneth E. Blick, PhD, ABCC, ACS, is an emeritus professor of pathology at the University of Oklahoma Health Sciences Center.

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