May 2020

CLN Clinical Laboratory News

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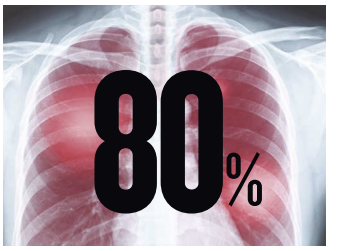
PREDICTING ACUTE RESPIRATORY DISTRESS SYNDROME



Accuracy of a prototype AI model for COVID-19

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A New Point-of-Care Testing Menu

COVID-19 Lab Preparedness

Gut Microbiome Matters

AACC Better health through laboratory medicine.

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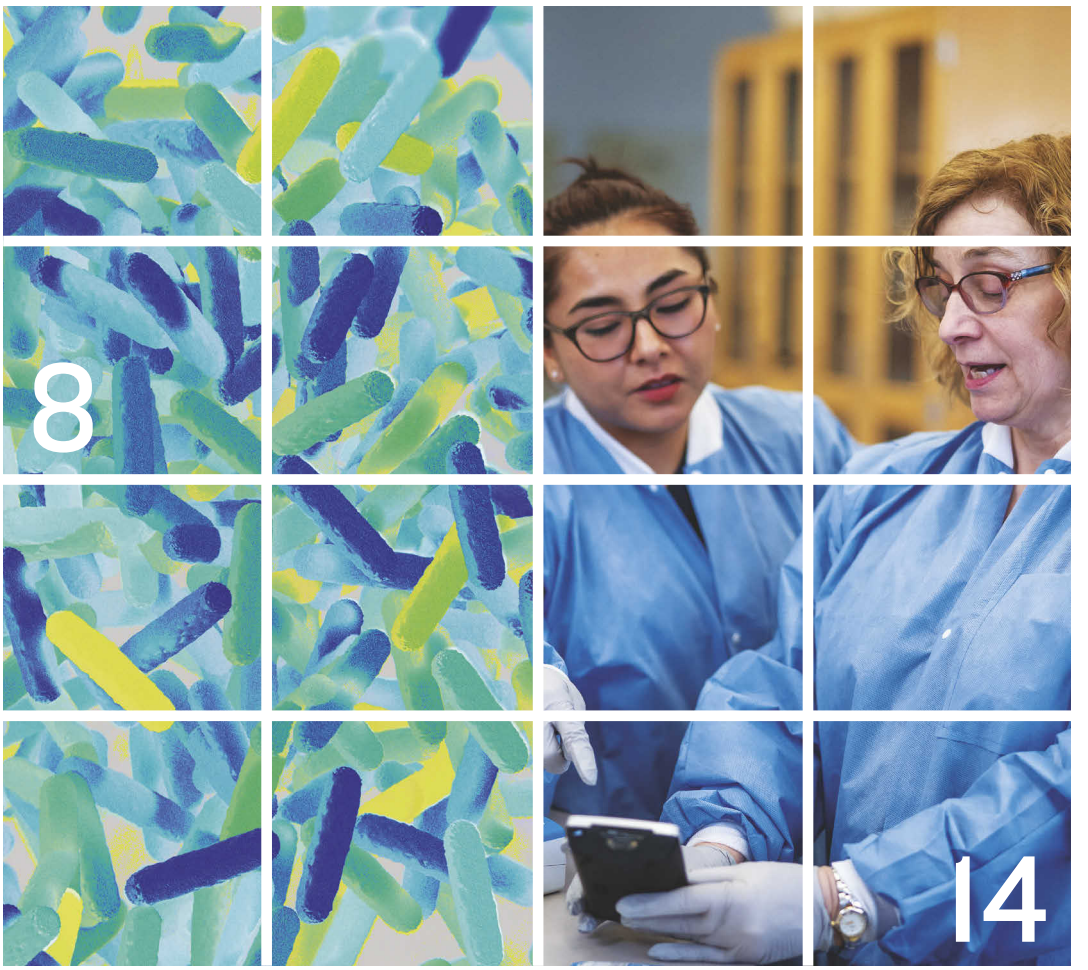
Features



Departments

In the past decade, label-free technologies have advanced into the era of dip-in-solution sensing probes. The resulting label-free immunoassays are open access, making them similar to plate-format assays without complicated sample delivery or fluidics.
p24

Federal Insider

AACC Endorses Verified Innovative Testing in American Laboratories Act

AACC endorsed the Verified Innovative Testing in American Laboratories (VITAL) Act, which would clarify the law around laboratory-develop tests (LDT) and definitively locate LDTs oversight solely within CLIA administered by the Centers for Medicare and Medicaid Services (CMS). This effort pushes back against other moves from Congress and the Food and Drug Administration (FDA) to move LDTs further under FDA's purview, creating a cumbersome and duplicative regulatory structure.

In a letter to the VITAL Act's sponsor, Senator Rand Paul, R-Ky., AACC wrote that it agrees "that the increase in the number and complexity of LDTs may warrant a fresh assessment of the regulatory and professional oversight for these tests." However, while "some adjustments may be necessary," the association believes CLIA oversight is sufficient.

"The FDA regulatory structure is designed for medical device manufacturers, not clinical laboratories. Laboratories occasionally modify FDA-cleared or approved tests or develop new in-house tests to meet specific clinical needs," AACC wrote. "To add FDA requirements to clinical laboratories utilizing these tests will stifle innovation and hinder patient access to testing, as occurred recently when the FDA became involved in LDT oversight during the outset of the COVID-19 public health emergency." The VITAL Act would prevent such delays in developing needed tests in the future, the association added.

AACC URGES CORONAVIRUS TASKFORCE TO BOLSTER LAB ACCESS TO TESTING SUPPLIES

In a letter to the administration's Coronavirus Task Force, AACC called on the White House to tackle the critical needs clinical laboratories face around sample collection, analytical test components, and personal protective equipment.

New guidelines released by the White House call for an extensive testing scheme that states are expected to rely on to reopen their economies.

Guidelines recommend that states first ensure they have the ability to quickly set up safe and efficient screening and testing sites for individuals with symptoms of COVID-19, the illness caused by SARS-CoV-2. These guidelines also recommend that states test syndromic and influenza-like illness-indicated persons for COVID-19, ensure sentinel surveillance sites are screening for asymptomatic cases, and trace contacts for all SARS-CoV-2 positive results.

"AACC's members, as laboratory professionals, are on the front lines combating this disease," AACC wrote in the letter. "While the capacity for performing COVID-19 testing has increased significantly in recent weeks, our ability to perform tests is still limited. There is a shortage of necessary supplies, including sample collection and test components … Unless and until these supply chain issues are resolved, the nation's laboratories will remain stymied in their attempts to maximize their testing capacity. At this point, the biggest barrier to testing is not capacity, but access to vital supplies."

The letter encourages the Coronavirus Task Force to communicate "directly and regularly" with the clinical laboratory community to address barriers to testing.

PHARMACISTS MAY ADMINISTER COVID-19 TESTING

The Department of Health and Human Services (HHS) issued new guidance under the Public Readiness and Emergency Preparedness Act authorizing licensed pharmacists to "order and administer" SARS-CoV-2 testing that has been authored by the Food and Drug Administration (FDA). The guidance specifically notes that this can include serology tests.

According to the HHS guidance, pharmacists are "well positioned to aid COVID-19 testing expansion." The guidance also notes that the majority of Americans live close to a retail or independent community-based pharmacy.

Some pharmacies maintain a CLIA certificate of waiver that allows them to perform certain tests termed CLIA waived. In the case of the novel coronavirus, FDA has said that any test with an emergency use authorization (EUA) indicating it is appropriate for point-of-care use should be considered CLIA waived. At *CLN* press time, these waived EUAs included the Abbott ID NOW, Mesa Biotech Accula, and Cepheid Xpert Xpress.

simpson33 / Getty Images

Join Us for an Important COVID-19 Webinar

COVID-19 Bedside Glucose Management

Risk of Ascorbic Acid and Hematocrit Interference

Interest in the antioxidant properties of ascorbic acid use in critically ill patients is growing, especially during the COVID-19 pandemic.[1,2] For these critically ill patients, severe anemia is also a common underlying condition. This webinar examines the risk of inaccurate glucose meter results due to interference from ascorbic acid and anemia. The only glucose meter that measures and corrects for these interferences will also be described.

Learning Objectives

- The use of adjunctive therapies such as ascorbic acid with COVID-19 patients
- The risk of glucose meter error due to ascorbic acid and anemia interferences
- How hospitals can protect their COVID-19 patients from glucose meter interferences

Intended Audience

- Point of Care Coordinators
- Lab Managers
- Critical Care Clinicians

Presenter

Charbel Abou-Diwan, PhD
Director, Medical
and Scientific Affairs
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- Approved by the American Society for Clinical Laboratory Science for 1.0 contact hours for P.A.C.E. continuing education credits.
- Approved by the American Association of Critical-Care Nurses (AACN) for 1.0 CERPs, Synergy CERP Category A, File Number 23158. Approval refers to recognition of continuing education only and does not imply AACN approval or endorsement of the content of this educational activity, or the products mentioned.

Two Webinar Times are Available

Thursday, May 28th, 1 PM Eastern Daylight Time
Thursday, June 18th, 4 PM Eastern Daylight Time

Register Now at:

novabiomedical.com/poc/glu/covid

1. Fowler AA, 3rd, et al., Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: the CITRIS-ALI Randomized clinical trial. *JAMA*. 2019;322:1261-1270.
2. Arabi YM et al., Critical care management of adults with community-acquired severe respiratory viral infection. *Intensive Care Medicine*. 2020;46:315-328.

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Bench Matters

Lab Preparedness During the COVID-19 Pandemic

Strategies for curtailing test menus, implementing social distancing, and supporting staff morale in response to a surge in testing and staffing shortages

Jonathan Hoyne, PhD, DABCC, FAACC

The past few months have been a whirlwind of news about, and activities in response to, the emergence and spread of the novel coronavirus, SARS-CoV-2. As this pandemic unfolds, laboratory personnel are key to the efforts to halt the virus's spread and treat patients.

The consequences of the pandemic on laboratories are likely to go beyond those of more familiar emergencies, like floods or hurricanes. In addition to a possibly overwhelming surge in patients with COVID-19 illness, we might experience planned reductions in other patient populations, a changed patient mix to mostly or nearly all COVID-19 patients, supply shortages, and staff shortages as team members need to self-quarantine or stay home to care for family members.

A GOOD START

CLSI 36-A:2014, Planning for Laboratory Operations During a Disaster, is an essential document for laboratory emergency preparedness planning during the COVID-19 pandemic. Chapter 10, which deals with planning for pandemic influenza, easily can be adapted to our current situation.

To help prepare for the pandemic, laboratory leaders at Mayo Clinic in Florida utilized this document to aid us in adjusting our hurricane crisis plan to the current situation. Our plan involves closing outpatient clinics, decreasing inpatient census, and providing only the essential testing our patients need.

To consider what testing might be most useful for COVID-19 patients we looked at the literature, recommendations from the Centers for Disease Control and Prevention, and practice guidelines or useful internet tools. Finally, we considered how our testing menu would change along with fluctuations in workforce availability, with staffing levels at 60%, 30%, and 15% of normal.

Our tiered plan involves shutting down one of our two labs—keeping open the one that already serves inpatient needs—and operating only our main chemistry analyzer and immunoanalyzer line. We also will shut or slow down testing on platforms where turnaround time can be delayed and will have the option of sending to a reference laboratory testing that we would normally perform in-house. In the current crisis, we will prioritize essential COVID-19 testing, along with testing we would perform during our hurricane response.

By focusing our test menu, we're able to divert staff to our hospital laboratory, cover for absences, supplement our phlebotomy teams, and provide necessary rest to our staff.

To prepare for a limited menu offering, lab staff should be cross-trained between benches as much as possible. Analytes of specific or increased utility during our current crisis might be prioritized. In the extreme, lab staff might be asked to perform non-laboratory functions, or to supervise non-laboratory personnel assisting in the lab.

Greg Gibson

ATTENDING TO STAFF

We also have to implement social distancing, maintaining 6 feet between individuals whenever possible, holding

meetings via conference calls or in rooms large enough to accommodate all the attendees while keeping appropriate distance. Staff must remind one another, independent of hierarchical position, to maintain safe distancing. Reminders should be accepted with a spirit of gratitude that each team member is looking out for the entire team.

In addition, labs need to establish a clear line of authority beyond our usual supervisory structures. This way, if supervisors and leads are unable to work, we still will have a chain of authority for centralizing decision-making and prioritizing tasks. The entire lab staff needs to understand this structure going into the crisis.

In an ever-changing emergent situation with daily tasks and the workforce in flux, communicating effectively becomes more challenging. We need to speak precisely, avoiding the use of imprecise descriptors like he, she, there, and that to minimize confusion and inefficiency.

A good way to know if a message has been communicated effectively is to have the person receiving the information repeat it back, with the person giving the information asking questions about points that might be susceptible to misunderstanding. Taking the extra time to communicate effectively will pay off with the increased efficiency it affords in completing tasks.

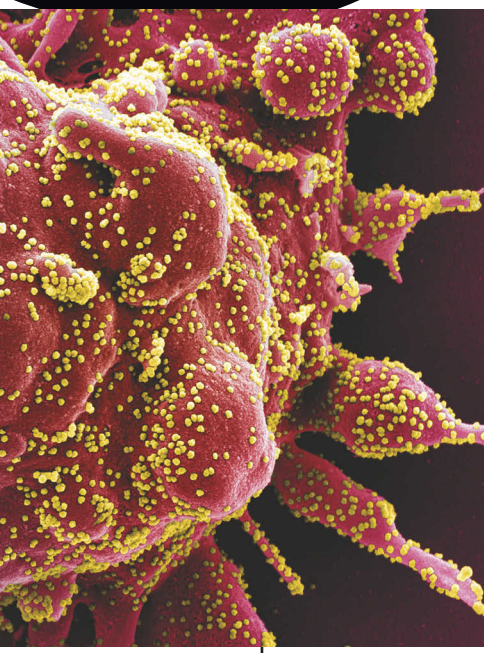
An overlooked aspect of emergency planning—addressed in the CLSI document—is the emotional impact over time that working in an emergency has on employees. Initially, people come together as a team to tackle an overwhelming problem. But as time moves on and staff continue to work under stressful conditions, ignoring personal needs becomes unsustainable. To make it successfully through an extended high-stress situation rest has to be programmed into the plan, and we need to proactively identify all non-essential tasks and defer or cease them until the emergency ends.

We will remember the events of the next weeks and months for the rest of our lives. Clinical laboratory professionals are essential members of the medical community upon which our society depends. We will rise to the occasion and make ourselves and our country proud. Take care of yourselves and each other.

Jonathan Hoyne, PhD, DABCC, FAACC, is director of clinical chemistry at Mayo Clinic in Jacksonville, Florida.
+EMAIL: Hoyne.Jonathan@mayo.edu

What measures has your lab taken in response to the COVID-19 pandemic? Join the conversation on the Artery, AACC's online community: artery.aacc.org/home

The Sample



Alanine Aminotransferase, Hemoglobin Levels 2 of 3 Features in Artificial Intelligence Tool That Most Predict Severe COVID-19 Outcomes

A prototype artificial intelligence (AI) tool showed that just three inputs had the most predictive power for discerning which patients with COVID-19, the illness caused by the novel coronavirus SARS-CoV-2, would likely develop acute respiratory distress syndrome (ARDS) (Comput Mater Con 2020;63:537-51). Based on data from 53 patients treated at two hospitals in China, this predictive analytics system found that elevations in alanine aminotransferase (ALT) and hemoglobin, along with patient-reported myalgia predicted risk of ARDS with up to 80% accuracy.

Surprisingly, many of the clinical features associated with COVID-19 such as ground glass opacities on chest computed tomography, fever, cough, lymphopenia, and dyspnea did not distinguish risk of disease progression and were not highly predictive. Patients' viral load (cycle threshold) also did not prove to be predictive.

Moreover, the patients' ALT and hemoglobin values were only modestly elevated. The median ALT value at the time of presentation at hospital was 24 U/L (range, 15-40.5 U/L; reference range, 9-50 U/L). The median hemoglobin level was 13.7 g/dL (range, 12.9-14.4 g/dL, reference range, 12.8-16.5 g/dL). Other features, including sex, temperature, age, and levels of sodium, potassium, and creatinine, and lymphocyte and white blood cell counts, added modestly to prediction.

"The model highlights that some pieces of clinical data may be underappreciated by clinicians," wrote the investigators in Wenzhou, China, and in New York City. They added that features don't have to be causal to be predictive.

In their feature engineering and statistical analysis, the researchers employed entropy, which measures how much information a feature encapsulates; information gain—the amount of information acquired after knowing the value of the feature; Gini index, a measure of the impurity of a dataset; and Chi-Squared statistics, indicating how dependent two variables are.

The authors speculated that myalgia "could represent generalized inflammatory and cytokine response not captured well by other indicators." The slightly elevated hemoglobin levels could be linked to smoking, which has been associated with increased hemoglobin values, or to male sex.

MAJOR GENETIC TESTING-GUIDED TRIAL FALLS JUST SHORT OF 1-YEAR EVENT END POINT

The much-anticipated TAILOR-PCI trial assessing genetic testing to guide antiplatelet therapy after percutaneous cardiovascular intervention failed to meet its primary end point of a 50% reduction in adverse cardiovascular events at 1 year. However, the largest trial to explore the clinical utility of detecting *CYP2C19 *2/*3* loss of function allele carriers prior to starting antiplatelet therapy showed a 34% reduction in a composite of major cardiovascular events at year 1. TAILOR-PCI also found a statistically significant 40% drop in the total number of events per patient who received genetically guided treatment compared with those who received standard therapy. These outcomes were presented at the virtual American College of Cardiology/World Congress of Cardiology meeting (20-LB-20309-ACC).

"Although these results fell short of the effect size that we predicted,

NIAID

they nevertheless provide a signal that offers support for the benefit of genetically guided therapy," said co-principal investigator Naveen Pereira, MD, professor of medicine at the Mayo Clinic in Rochester, Minnesota.

In a post hoc analysis, the researchers found a nearly 80% reduction in the rate of adverse events in the first 3 months of treatment in participants who received genetically guided care versus those who received standard care.

Subjects were randomized to receive either standard care—75 mg daily of clopidogrel—or genetic testing-guided care. Those who were determined through genetic testing to be *CYP2C19 *2/*3* carriers (35%) received 90 mg of ticagrelor twice daily; otherwise, participants in the genetic testing arm of the trial received clopidogrel. There were 1.6% major or minor bleeding events at the end of 1 year in participants in the standard care arm and 1.9% in carriers in the guided-treatment group.

LITTLE CONCORDANCE AMONG NONINVASIVE METHODS FOR IDENTIFYING NASH

Three noninvasive methods for identifying patients with nonalcoholic steatohepatitis (NASH) agree in only 18% of cases, under-scoring the need for better noninvasive means of recognizing this condition, according to an abstract accepted for the Endocrine Society's annual meeting (SUN-606).

The investigators used data from the National Health and Nutrition Examination Survey III (NHANES III) to compare three noninvasive methods of identifying NASH: the NASH liver fat score, the HAIR score, and the Gholam score.

The HAIR score incorporates the presence of hypertension, alanine transaminase (ALT) levels, and insulin resistance. The NASH liver fat score is based on the presence of metabolic syndrome, type 2 diabetes, and levels of serum insulin, ALT, and aspartate aminotransferase (AST), while the Gholam score uses AST and a diagnosis of type 2 diabetes.

The investigators identified NHANES III participants who had moderate to severe hepatic steatosis, as determined by ultrasound. In all 1,236 subjects were determined to have NASH by at least one noninvasive method, but the three methods all identified NASH in just 18% of cases. Two methods agreed in 20% of cases.

The three methods all identified significant risk factors for NASH as being overweight or obese, having elevated AST or ALT levels, and having raised C-peptide, serum glucose, or serum triglyceride levels. However, the methods disagreed on the significance of other risk factors.

Gut Micro

Next Frontier of

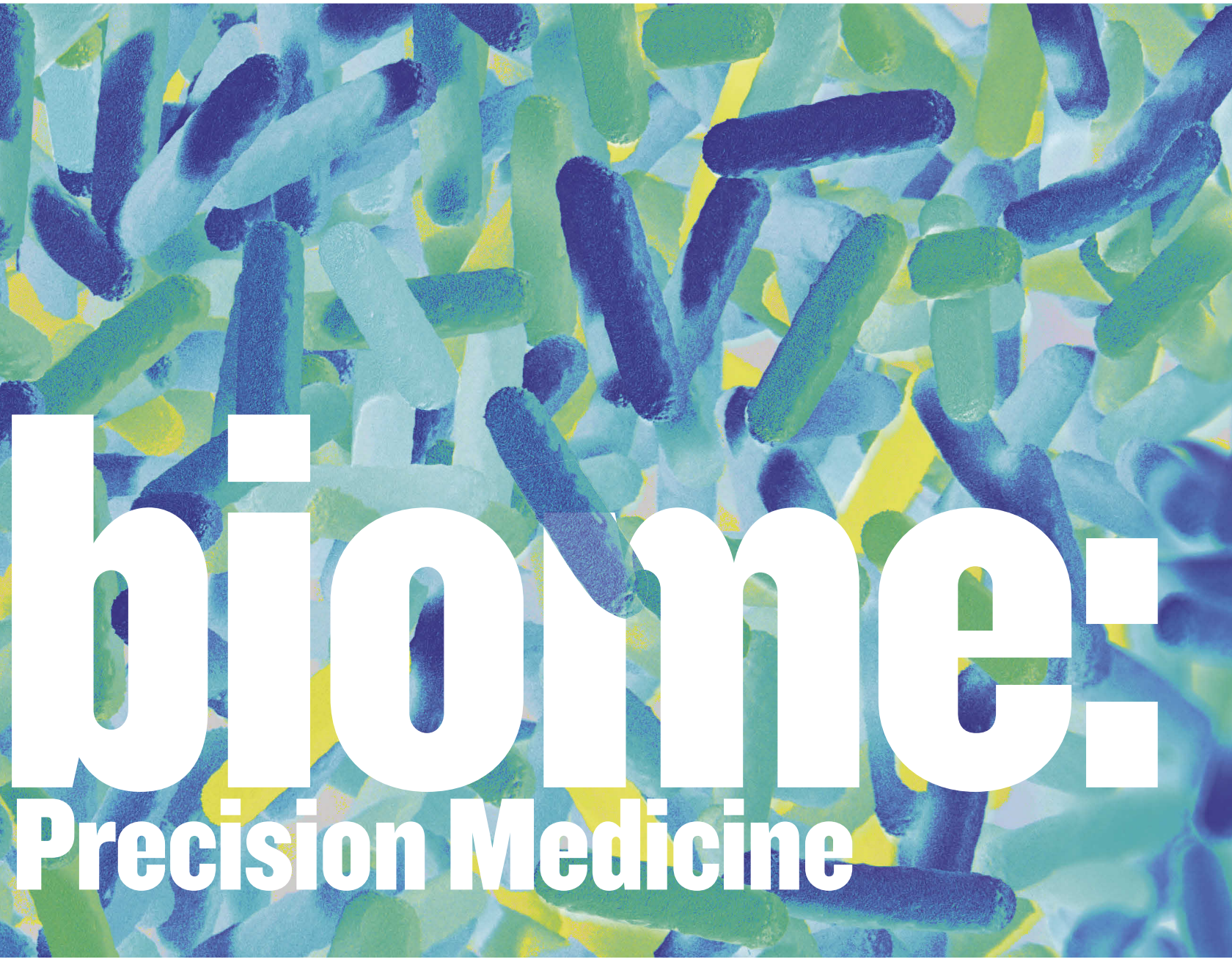
Research advances still a ways from clinical practice

BY PRANALI P. PATHARE, PHD

Tremendous advances in next-generation sequencing and omics technologies have catapulted microbiome science into an exciting new frontier in medicine. Emerging data suggest that the microbiome—the rich ecosystem of more than 100 trillion bacteria, fungi, and viruses in and on the human body—is integral in almost all aspects of human health and disease and that analysis of the microbiome one day could play an important role in clinical practice.

"The pendulum has swung from a focus on killing pathogenic bacteria to a focus on healthy, symbiotic, and commensal microbes," said Melissa Melby, PhD, co-director of the Humans and the Microbiome Program at the Canadian Institute for Advanced Research (CIFAR) in Toronto. "There has been a shift in clinical care as well as the popular consciousness with the realization that microbes are not all bad."

This deeper appreciation of the microbiome's power doesn't mean that clinical labs should expect to



biome: Precision Medicine

be performing omic analyses of the microbiome anytime soon, according to Robert Britton, PhD, professor of molecular virology and microbiology at Baylor College of Medicine in Houston. "I do believe that in five to ten years, we'll see microbiome-based therapies making it to clinics, but what that's going to be, who knows," he said. "We now must do the heavy lifting and find the functions behind … associations showing microbiotas have positive and negative effects on different types of diseases."

With more than 1 million genes—versus 23,000 in the human genome—the abundance and diversity of the microbiome is staggering; microbiome communities in different body sites have unique profiles, as does each individual, influenced by diet, medications, and other environmental factors.

A BURGEONING FIELD

Research into the complex and dynamic interactions between microorganisms and their human hosts has taken off in recent years. One of the most promising lines of investigation involves the gut microbiome. Initially thought to have a role limited to digesting complex carbohydrates and synthesizing vitamins and nutrients, this microbiome now is understood to be a structural and functional part of the body. Evidence shows that the gut microbiome globally governs host physiology by regulating metabolism, immunity, and even the gut-brain axis, via signaling of unique microbiome-generated bioactive metabolites.

Disturbances in normal gut microbial profiles have been associated with

a range of conditions from cancer to metabolic, inflammatory, cardiovascular, and even neurodegenerative diseases. "Amazing and incredibly large observational studies have shown very clear associations between features of the gut microbiome and clinical outcomes," said Jonathan Peled, MD, PhD, a medical oncologist at Memorial Sloan Kettering Cancer Center in New York City. "We and others have found associations between perturbations of the gut microbiome and complications of bone marrow transplant."

Peled and his team profiled fecal samples taken from a large cohort of cancer patients undergoing bone marrow transplants at four geographically distant transplant centers and found that patients with more diverse gut flora had better survival outcomes than those with lower diversity (N Engl J Med 2020;382:822-34). These findings imply that screening gut bacteria or providing interventions to balance the gut ecosystem prior to transplants might enhance patients' health.

A specific gut bacterial profile also has been reported in people with pulmonary arterial hypertension (PAH) (Hypertension 2020;119:14294). This signature predicted the presence of PAH with 83% accuracy. Although these data are correlative, they suggest that gut microbiome changes eventually could become a way to screen for the disease. However, changes in the microbial ecosystem are what drive changes in microbial function—not merely the presence or absence of specific microbial species, said W.H. Wilson Tang, MD, professor of medicine and research director of heart failure and transplant at the Cleveland Clinic Lerner College of Medicine.

"For a successful clinical transition, we have to go beyond a very pathway-specific manner of looking at things and instead look at how systems interact," he explained. His team and others have identified metabolites processed by gut microbes that drive the progression of several cardiovascular pathologies like atherosclerosis, hypertension, heart failure, and type 2 diabetes. "These findings suggest that the gut microbiome functions like an endocrine organ by generating bioactive metabolites that can directly or indirectly affect host physiology," wrote Tang in a recent review (Nat Rev Cardiol 2019;16:137-54).

PERSONALIZED NUTRITION THERAPY

In addition to its diagnostic potential, the human microbiome also represents an exciting new target for diet-based disease interventions. Recently, several pivotal studies have revealed new insights into how the diet influences the gut microbiome, with potential implications for disease modification and treatment.

Most notably, a team led by Eran Segal, PhD, professor of computer science and applied mathematics at the Weizmann Institute of Science in Rehovot, Israel, developed a machine-learning algorithm to integrate microbiome data and evaluate an individual's glycemic response to identical foods (Cell 2015;163:1079-94). The investigators discovered not only that each person's blood glucose levels were different even when they consumed the same food as others but also that microbiome rather than genetic data correctly predicted each person's blood glucose response to an identical food. Furthermore, the team's algorithm accurately predicted individual dietary interventions that successfully balanced glucose levels in pre-diabetic people—outperforming the standard-of-care diet.

These unexpected findings portend a whole new era of personalized nutrition in which specific diets based on an individual's gut microbiome composition could enhance a person's health outcomes. These findings also validate the idea that integrating microbiome readouts in combination with genetic data offers a more reliable and powerful approach to assessing disease risk. "Deep phenotyping of human cohorts, including the collection of microbiome data, could transform therapy development," opined Segal.

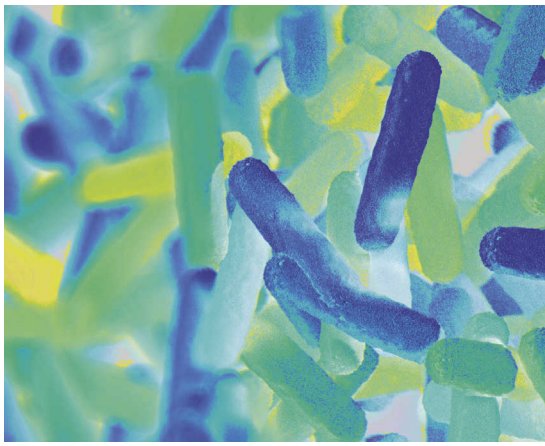
GUT OVER GENETICS

The Weizmann Institute team also showed that a host's genetics has only a "minor role" in the gut microbiome's composition, suggesting that individualized microbiome alterations aimed at improving clinical outcome can be carried out across people from diverse genetic backgrounds (Nature 2018;555:210-5).

"Understanding and integrating microbiome variability holds potential to promote personalized preventive and therapeutic approaches," said

"UNDERSTANDING AND INTEGRATING MICROBIOME VARIABILITY HOLDS POTENTIAL TO PROMOTE PERSONALIZED PREVENTIVE AND THERAPEUTIC APPROACHES."

— Eran Elinav, MD, PhD



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Eran Elinav, MD, PhD, co-author of both the *Cell* and *Nature* papers and a professor of immunology at the Weizmann Institute.

Based on Elinav's and others' findings, including his own, Melby's CIFAR colleague, Brett Finlay, PhD, recently put forth the provocative hypothesis that chronic diseases like obesity, heart disease, and diabetes might be transmissible akin to an infectious disease (Science 2020;367:250-1). "Data increasingly show that the microbiota is dysbiotic (altered) in individuals with various [noncommunicable diseases] NCDs … Therefore, we propose that some NCDs could have a microbial component and, if so, might be communicable via the microbiota," wrote Finlay, co-director of the CIFAR Humans and the Microbiome Program and professor of microbiology and immunology, biochemistry, and molecular biology at the University of British Columbia in Vancouver.

THE ROAD TO INTERVENTIONS

These emerging findings and theories have the microbiome poised to play an integral role in precision medicine. "We are at a point of inflection where we are transitioning from observational studies and some phenomenological mouse work to an era of deeper mechanistic analysis in animal models and to clinically actionable tests and interventions," said Peled.

The future armamentarium of microbiome diagnostics and therapeutics offers broad and deep possibilities for controlling and treating different diseases—personalized diets, prebiotics, postbiotics, microbiota transplantation, engineered bacteriophages, microbial metabolites, microbiota precision editing, and intestinal barrier modulation. So far, however, just one application has advanced clinically—fecal microbiota transplantation (FMT) to treat recurrent *Clostridioides difficile* infections. "That's the only example where it has really worked and where there has been actual progress that has been proven," asserted Peled. Published reports indicate that at least 10,000 FMT procedures take place annually, and FMT is also being investigated in at least 300 clinical trials.

Despite accumulating data about its efficacy, however, this treatment still faces hurdles. In mid-March the Food and Drug Administration issued a safety alert warning about the risk of serious, even life-threatening infections linked to FMT after six patients were infected with *Escherichia coli* following the procedure, the second such warning within a year.

As the challenges with FMT illustrate, progress is slow going from identifying associations to developing accurate and reliable methods for analyzing the gut microbiome and creating safe and effective clinical treatments.

"Although we are starting to tap into a lot of potential in the gut microbiome space, it is still a long and nebulous road to achieving true clinical impact," said Braden Tierney, a computational biologist and doctoral candidate at Harvard Medical School. His recent work posted on the preprint server bioRxiv found that the genetic signature of gut microbes was 20% better than their own genes at discriminating between healthy and diseased individuals. The microbiome also outperformed by 50% association studies predicting whether an individual had colorectal cancer.

"A big challenge is getting from correlation to causality and figuring out mechanisms for how microbes are actually affecting our health," he added.

Melby agreed that metabolomic and proteomic analyses of microbiome function will be key to making this research applicable to clinical settings. "Big data analysis and modeling is also going to be critical as it is not a particular organism or a particular metabolite, but a consortium of organisms that determine health or non-health," she noted.

Methodological variation poses another challenge. "There are so many different methods and approaches you can take to analyze data that if you put them side-by-side, you could end up with varying results," said Tierney. Since microbiome cohorts are relatively homogenous and limited in number, it is difficult to decide which observations are generalizable to larger patient populations across different geographical locations, he added.

Despite these hurdles, the promise of microbiome-based clinical tests in predicting, diagnosing, and treating diseases bodes well for the future of personalized medicine.

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WHAT'S NEXT on the POINT OF CARE TESTING MENU?

From SARS-CoV-2 to cardiac biomarkers, a steady stream of IVD innovation shows no signs of letting up

BY KIMBERLY SCOTT

While point-of-care (POC) testing in recent years has drastically altered how patients are treated for conditions such as diabetes, HIV, and cardiovascular disease, new advancements on the horizon are expected to vastly improve near-patient treatment for strokes, infectious diseases, and cancer, according to experts.

In vitro diagnostics (IVD) companies are working to improve specificity and sensitivity of devices so that testing can be done on smaller specimen samples, said Nick Collier, PhD, chief technology officer for Sagentia Medical, a contract research organization based in the U.K. "There is a lot of interest in reducing sample size—using capillary blood samples to do testing, for example."

At the same time, technology is getting smaller, cheaper, and more sophisticated. Lab-on-a-chip (LOC) devices, which require just a few drops of blood, already are in use and potentially could be more widely deployed, especially in areas with limited healthcare resources. In addition, diagnostics companies increasingly are combining different technologies into single platforms so users can perform multiple tests on one sample, Collier added.

Abbott's i-STAT 1 POC blood analyzer, for example, can run multiple tests on one cartridge, including tests for cardiac markers, coagulation, blood gases, chemistries, electrolytes, and hematology. Roche Diagnostics' cobas Liat PCR System also performs multiple tests, using polymerase chain reaction technology to test for influenza A/B, respiratory syncytial virus, and group A strep in about 20 minutes.

Roche is in the process of developing assays for other infectious diseases, said Corinne Fantz, PhD, director of Roche Scientific Affairs. "We have a goal to make molecular testing for sexually transmitted diseases [STDs] available at the point-of-care," she explained. "Having the ability to test for STDs in a doctor's office will have a big impact on treatment. The physician would be able to get the results before a patient leaves the office, which means they can have a discussion with the patient and decide on treatment."

"While there are more than 100 POC tests available in the U.S., not all are widely implemented, such as tests for proteins in blood used for cancer diagnosis."

— Kathleen David, MT(ASCP)

Also on the infectious diseases front, the COVID-19 pandemic has spurred development of POC tests for SARS-CoV-2, the virus that causes COVID-19. In the United States, Cepheid was first to market with a rapid, near-patient test that it says will give results in 45 minutes. The Food and Drug Administration (FDA) on March 21, 2020, issued an emergency use authorization (EUA) for Cepheid's Xpert Xpress SARS-VoV-2 test for use in high- and moderate-complexity CLIA labs. Mesa Biotech (San Diego) received an EUA March 24 for a test that gives results in 30 minutes, and Abbott Labs received an EUA March 27 for a POC test that can deliver positive results in as little as five minutes. Other companies seeking FDA approval for POC COVID-19 tests include Becton Dickinson, bioMerieux, Integrated DNA Technologies, LabCorp and Quest Diagnostics. In addition to molecular tests that analyze the viral RNA in patient throat/nasal swabs, other POC testing methods that are pending approval use immunoassays to detect COVID-19 antibodies in blood or serum.

Other companies seeking FDA approval for POC SARS-CoV-2 tests include Becton Dickinson, Bio-Rad, bioMérieux, Integrated DNA Technologies, LabCorp, and Quest Diagnostics. In addition to molecular tests that analyze the viral RNA in patient throat/nasal swabs, other POC testing methods that are pending approval use immunoassays to detect SARS-CoV-2 antibodies in blood or serum.

While there are more than 100 POC tests available in the U.S., not all are widely implemented, such as tests for proteins in blood used for cancer diagnosis, noted Kathleen David, MT(ASCP), POC testing manager for TriCore Reference Laboratories in Albuquerque, New Mexico. "Availability is one thing. Then there's acceptance and implementation," she said. "Some of these we will see in cutting-edge places in the next couple of years, but it will be longer before it filters down to POC in smaller hospitals or other settings."

What is on David's POC testing wish list? "Procalcitonin for sepsis, which would be useful in terms of curbing antibiotic resistance," she noted. "A fingerstick [complete blood count] test would also be wonderful. But one of the problems with POC testing is that if you want widespread adoption, you have to get a CLIA waiver. For doctors' offices and clinics, getting a waiver is relatively doable, but getting a certificate of compliance has more requirements and isn't always possible for most clinics."

"There is a lot of interest around sepsis diagnosis and treatment," agreed Collier, noting that only a few rapid tests for sepsis exist. An example is BioFire's BCID Panel that tests for 24 gram-positive, gram-negative, and yeast pathogens, as well as three antibiotic resistance genes associated with bloodstream infections. Abbott offers POC lactate testing that can be performed at a patient's bedside. While the BioFire test does speed up pathogen identification, it is not yet POC because it requires the blood to be cultured. Collier noted that there is significant interest in whether the blood culture step could be avoided, with molecular tests performed straight from blood to identify the pathogen and antimicrobial resistance genes.

Another likely trend in POC testing is use of high-sensitivity troponin I (hs-cTn) tests in emergency departments and urgent care centers to diagnose heart attacks more quickly, Collier predicted. These assays, which were first introduced in Europe in 2010, have only recently become available for clinical practice in the U.S. Hs-cTn T allows for detection of very low levels of troponin T, helping to diagnose heart attacks faster than testing sent to the central lab, which in turn speeds treatment and improves outcomes.

WHEN DOES IT MAKE SENSE TO OFFER POC?

Most physician office labs offer about five or six POC tests, often

Left and on previous page: Greg Gibson

for pregnancy, strep, and diabetes (glucose and hemoglobin A1C), said TriCore's David. Urgent care centers that do moderate-complexity testing typically offer additional testing, such as D-dimer tests, complete blood count, and flu testing. At hospitals, POC testing—from prothrombin time with international normalized ratio to blood gases—is performed in various units.

Before deciding whether to offer a POC test, a healthcare provider should consider several factors, experts say. First, how will the test benefit patient care? "If it means that treatment gets done faster or a patient gets a prescription right away, then that is a strong consideration for offering a test," David said. Second, can the site accommodate changes to workflow by offering a test—for example, drawing blood or having patients get swabbed before they even see a physician? Third, volume: Does the site have enough cases to warrant offering a test in-house? Fourth, what is the cost/benefit return? "A lot of the time a central laboratory can do testing cheaper than POC, but if you can free up a procedure room 30 minutes faster and that saves $2,000, that's a no-brainer," David said.

Determining the value of a POC test is critical to making decisions about whether to bring it in-house, commented Roche's Fantz. "A common test in the emergency department is POC creatinine to determine if patients have problems with their kidneys," she said. "It may be more expensive than sending to a lab but the value is in treating a patient faster to improve the throughput in crowded places like the emergency department."

Hospital department leaders should have a conversation with central laboratory leaders before deciding to offer POC tests, advised David, who said the laboratory might be able to improve workflow or communication to better suit the needs of staff. If the lab can't accommodate the changes needed, she suggested consulting with the hospital's POC manager or coordinator to determine which test would be appropriate for clinicians' needs.

Payment for POC also needs to be considered, Fantz added. "Increasingly, payors are looking for evidence that a POC test brings value over tests performed in a central lab. Test manufacturers typically generate this evidence, but times are changing, and the bar is getting higher every year."

POC testing will almost certainly increase in the coming months and years as technology continues to advance. As healthcare resources are stretched during the current global pandemic, near-patient testing will play an even greater role in helping patients get treatment quickly and efficiently.

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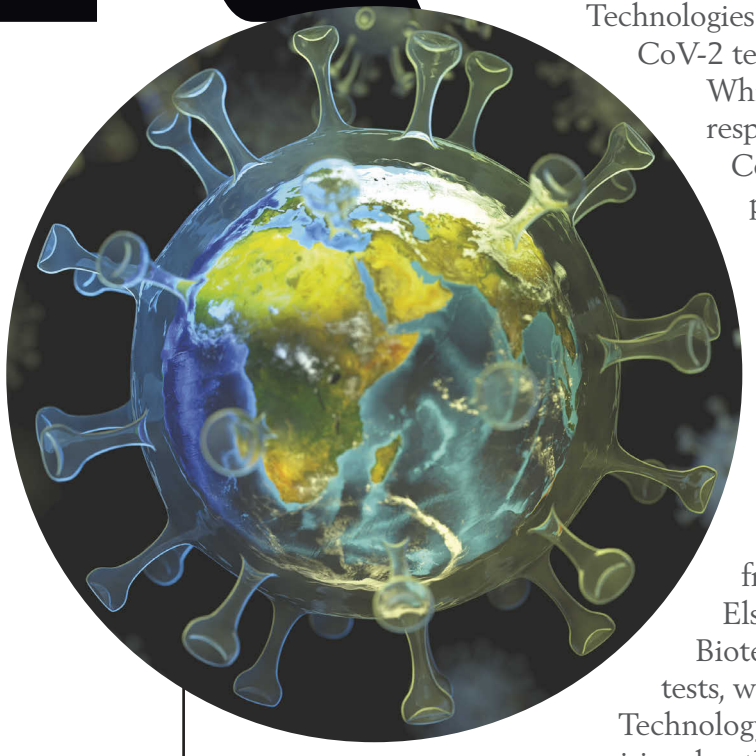
Regulatory Roundup

World Sees Explosion of Regulatory Authorizations for SARS-CoV-2 Tests

As the COVID-19 epidemic has intensified, diagnostic manufacturers have rushed to develop tests for SARS-CoV-2, leading to an unprecedented flood of diagnostic regulatory authorizations. In the U.S., Cepheid's Xpert Xpress SARS-CoV-2 test and Abbott's ID NOW COVID-19 test became two of the first rapid point-of-care tests for the virus to earn Food and Drug Administration (FDA) emergency use authorizations (EUA). Other companies that had received FDA EUAs for SARS-CoV-2 tests at the time *CLN* went to print include LabCorp, Quest, Hologic, bioMérieux, PerkinElmer, Luminex, Quidel, BGI Americas, Sentinel Diagnostics, Primerdesign, DiaSorin, GenMark, and Avellino Labs. Almost all of the tests that FDA has authorized so far are molecular assays, but serological tests are also starting to come to market, such as Diazyme's DZ-Lite SARS-CoV-2 IgG and SARS-CoV-2 IgM CLIA test kits. Additionally, the Centers for Disease Control and Prevention (CDC) qualified and approved primer and probe kits manufactured by LGC, Biosearch Technologies and Integrated DNA Technologies that are designed for labs implementing CDC's SARS-CoV-2 test.



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While an inability to test widely hamstrung the U.S.'s initial response to COVID-19, this sudden profusion of SARS-CoV-2 tests has not been without its drawbacks. In particular, FDA has needed to caution consumers against using unauthorized, fraudulent test kits that some companies are marketing as at-home tests for COVID-19.

Outside the U.S., Thermo Fisher, BGI, DiaCarta, AusDiagnostics, Bioneer, 3-Dmed, Genomica, Osang Healthcare, Co-Diagnostics, Vision Medicals, Credo Diagnostics, a collaboration between CerTest and BD, and SolGent have all received the CE mark for their SARS-CoV-2 tests. SolGent's test also received EUAs from Korean and Philippine regulatory authorities. Elsewhere in Asia, Fosun Long March and Rendu Biotechnology earned Chinese regulatory approval for their tests, while an assay developed by the Agency for Science, Technology, and Research and Tan Tock Seng Hospital gained provisional authorization from Singapore.

FDA RELEASES GUIDANCE TO AID MANUFACTURERS APPLYING FOR CLIA WAIVERS

The Food and Drug Administration (FDA) has finalized two guidance documents related to CLIA waiver submissions. The first guidance, "Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices," provides an update to FDA's 2008 guidance for manufacturers who are submitting CLIA waiver applications. Specifically, in compliance with the 21st Century Cures Act, FDA revised Section V of the 2008 CLIA Waiver Guidance to include the appropriate use of comparable performance between a waived user and a moderately complex laboratory user to demonstrate device accuracy.

The second new guidance, "Recommendations for Dual 510(k) and CLIA Waiver by Application Studies," includes recommendations for designing a single set of comparison and reproducibility studies that

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may support dual 510(k) clearance and CLIA waiver submissions. With this guidance, FDA hopes to increase use of the agency's Dual 510(k) and CLIA Waiver by Application pathway in order to expedite the process of bringing new in vitro diagnostic tests to CLIA-waived settings.

FDA APPROVES ROCHE TEST FOR TRIAGING HPV-POSITIVE SCREENING RESULTS

Roche has received Food and Drug Administration approval for the CINtec PLUS Cytology, making this the first commercially available biomarker-based triage test for women whose primary cervical cancer screening results are positive for the human papillomavirus (HPV) using Roche's cobas 4800 HPV test. While most HPV infections resolve on their own, some women who test positive for the virus or whose co-testing results are inconclusive—HPV-positive and Pap cytology-negative—develop pre-cancerous cervical lesions that, if left untreated, progress to cervical cancer. The CINtec PLUS Cytology test identifies those women whose HPV infections are most likely to progress in this manner and who would benefit from immediate referral to colposcopy versus repeat testing. The test detects the simultaneous presence within a single cell of the two biomarkers p16 and Ki-67, an abnormality that is associated with HPV infections that are transforming. Additionally, labs can perform the test using the same liquid sample that is used for HPV or Pap cytology testing.

CE MARK GIVEN TO RANDOX'S MULTIPLEX STI ASSAY

Randox Laboratories has earned the CE mark for its cartridge-based sexually transmitted infection (STI) assay, which tests for 10 of the most common STIs: *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, *Mycoplasma genitalium*, *Treponema pallidum* (syphilis), herpes simplex virus 1 and 2, *Haemophilus ducreyi*, *Mycoplasma hominis*, and *Ureaplasma urealyticum*. The test uses Randox's Biochip Array Technology, which enables simultaneous multi-analyte testing on one undivided sample by combining a panel of related assays on a single biochip with a single set of reagents, controls, and calibrators. The test is performed on the Vivalytic system, a point-of-care platform that Randox developed in partnership with the German technology company Bosch. Randox's STI test is also fully automated and provides a full molecular workflow, from extraction and polymerase chain reaction amplification through detection. Additionally, it does not require the use of additional peripheral equipment such as a laptop or keyboard, bar-code scanner, or filling stations.

DXTERITY GETS CE MARK FOR AT-HOME FINGERPRICK BLOOD COLLECTION DEVICE

The CE mark has been granted to DxTerity Diagnostics for the DxCollect MicroCollection Tube (MCD), which collects and preserves 100 µL of fingerstick blood for DNA- and RNA-based genomic testing. Unlike DNA testing, which can be performed from saliva or a cheek swab, RNA-based genomic testing usually requires a blood sample that is collected into specialized tubes and often shipped on dry ice. The DxCollect MCD stabilizes both DNA and RNA at room temperature, enabling specimens to be shipped under ambient conditions using standard mail. The device has been evaluated in large-scale, direct-to-patient clinical studies.

Following receipt of the CE mark, DxTerity is now focused on gaining Food and Drug Administration approval for the MCD in conjunction with the company's Modular Immune Profile assay, which is intended for home testing of systemic lupus erythematosus (SLE) patients. DxTerity hopes that regular monitoring of autoimmune patients using the MCD will enable physicians and patients to more effectively manage SLE by predicting potential flare-ups before they happen.

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References: 1. Kent HL. Epidemiology of vaginitis. Am J Obstet Gynecol. 1991 Oct;165(4 Pt 2):1168-76. **2.** Aptima BV Assay [package insert] #AW-18811, San Diego, CA; Hologic, Inc., 2019. **3.** Aptima CV/TV Assay [package insert] #AW-18812, San Diego, CA; Hologic, Inc., 2019.

Industry Playbook

Thermo Fisher to Acquire Qiagen for $11.5 Billion

Thermo Fisher Scientific announced it will acquire the molecular diagnostics-focused firm Qiagen for $11.5 billion.

Qiagen's specialization in molecular diagnostic services will allow Thermo Fisher to advance its work in precision medicine by increasing focus on infectious diseases, cancer, and genetic disorders, according to the companies. Specifically, Thermo Fisher plans to expand utilization of Qiagen's Quantiferon-TB Gold Plus latent tuberculosis detection test, the QiaSymphony platform for molecular diagnostics infectious disease testing, and the QiaStat-Dx syndromic testing system. These platforms add to Thermo Fisher's existing portfolio of quantitative polymerase chain reaction, next-generation sequencing, Sanger sequencing, and microarray technologies.

Thermo Fisher will also take advantage of Qiagen's sample prep technologies, assays, and bioinformatics solutions to expand its life sciences products, including existing reagents and consumables.

"This acquisition provides us with the opportunity to leverage our industry-leading capabilities and [research and development] expertise to accelerate innovation and address emerging healthcare needs," said Marc Casper, chairman, president, and CEO of Thermo Fisher Scientific. The deal is expected to be finalized in 2021.

Qiagen recently announced development of its QiaStat-Dx Respiratory SARS-CoV-2 Panel test for diagnosing patients with COVID-19. The Food and Drug Administration granted Qiagen an emergency use authorization for the test that can differentiate the SARS-CoV-2 coronavirus from 21 other respiratory pathogens in patients. Using nasopharyngeal swab samples, the test specifically targets two genes that help detect the COVID-19 pathogen.

BIODESIX, BIO-RAD SEEK EUA FOR COVID-19 TEST

Biodesix and Bio-Rad Laboratories have partnered on a droplet digital polymerase chain reaction (ddPCR) test for SARS-CoV-2. At *CLN* press time, the companies were hoping to gain Food and Drug Administration emergency use authorization (EUA) for this test.

Some laboratories have been using quantitative PCR (qPCR) tests for patients who show symptoms of COVID-19. However, two recent studies in China found that the ddPCR test can be significantly more sensitive in diagnosing patients before symptoms develop.

The studies showed that patients who underwent qPCR tests had the possibility of showing false negatives or false positives. The studies also saw a difference in accuracy with detection numbers increasing from 28.2% with qPCR tests to 87.4% with ddPCR tests. Though the studies have not been peer reviewed, both companies intend to begin offering this test in the U.S. once they receive EUA.

GRANT FUNDING GOES TO TUBERCULOSIS DETECTION ASSAY

Following an initial $500,000 grant from the Bill & Melinda Gates Foundation, Biological Dynamics announced a secondary grant of about $1 million from the foundation for a tuberculosis (TB) detection assay. The molecular

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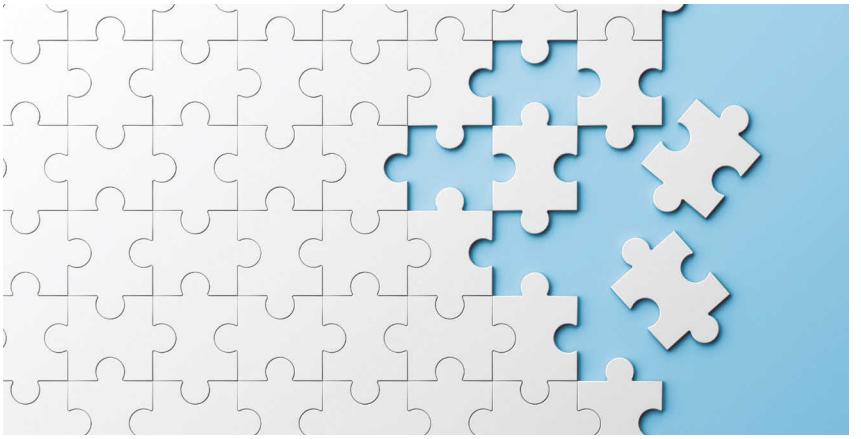

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diagnostics company previously began working on the TB assay to target countries with limited access to medical testing laboratories.

With Biological Dynamics' Verita lab-on-chip platform, experts are able to pinpoint nanoparticles and micro-molecules of a specific size in blood, plasma, or serum without interference from smaller or larger particles. The platform also eliminates complex and time-consuming processes. The company intends to offer the assay for early detection of TB with a strong focus on geographic areas that lack diagnostic resources.

Having raised $50 million in funding so far, Biological Dynamics also said its team of 38 employees is working on ways to improve rapid diagnoses of cancers and other diseases such as glioblastoma and Alzheimer's disease.

PERKINELMER, PUBLIC HEALTH ENGLAND PARTNER ON NEWBORN SCREENING

PerkinElmer and Public Health England have teamed to advance newborn screening for severe combined immunodeficiency (SCID). Public Health England has agreed to use PerkinElmer's VICTOR EnLite instrument, as well as the EnLite Neonatal TREC kit to evaluate newborns.

SCID can be severely debilitating, even causing death. However, if detected early enough in newborns, it can be treated through stem cell transplants from family members.

By using PerkinElmer technologies, Public Health England expects to improve efficiency in diagnosing SCID. The instrument and kit are capable of determining the T-cell receptor excision circle (TREC), a primary biomarker of SCID, and the TREC kit reduces typical laboratory steps involved in newborn screening.

COMPANIES COLLABORATE ON REMOTE SAMPLE COLLECTION

To reduce the need for patients to visit transplant centers during the COVID-19 pandemic, Transplant Genomics has announced a partnership with Eurofins Viracor to remotely collect samples from kidney transplant recipients. Along with Eurofins Viracor, Transplant Genomics has also formed relationships with Quest Diagnostics and other mobile collection providers to offer services to patients.

With remote sample collection, patients are still able to receive the same testing and analysis that they would by visiting labs. The companies are remotely providing testing services for Transplant's TruGraf blood test and Eurofins' TRAC liquid biopsy test. The TruGraf blood test allows surveillance to rule out silent rejection in stable kidney transplant recipients and also determines if patients are immune quiescent. Additionally, the TRAC test analyzes donor-derived cell-free DNA levels in blood to help rule out rejection.

Patients can directly contact either company to request remote sample collection services.

COLLABORATION TACKLES POINT-OF-CARE TESTING FOR COVID-19

Heat Biologics and the University of Miami have joined forces to develop a point-of-care (POC) diagnostic test for COVID-19 that the parties say will expand rapid testing compared to traditional methods. The partners also plan to develop the test as a less expensive alternative for both manufacturers and patients.

The POC test uses a pharyngeal throat swab and will show results on a paper strip in under 30 minutes, according to the University of Miami. This method will also use isothermal amplification technology to detect viral nucleic acids.

"Our lab has tremendous experience developing accurate and easily usable tests for infectious diseases such as human papillomavirus and Zika," said Sylvia Daunert, test co-developer and chair of biochemistry and molecular biology at the University of Miami Miller School of Medicine. "Our test is being developed to utilize molecular recognition and amplification of the target virus. This should allow for much earlier detection, providing critical and time-sensitive information to help curb the spread of the disease."

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Ask The Expert

Label-Free Detection of Therapeutic Monoclonal Antibody Interference

EXPERT
Yiqi Ruben Luo, PhD

What are label-free technologies?

A: Label-free technologies quantitate biomolecules by sensing a change in a physical parameter caused by biomolecular interactions. Typically, the physical parameter is refractive index, optical thickness, energy, or mass. Using this approach, immunoassays based on label-free technologies, i.e. label-free immunoassays (LFIAs), are able to measure antibody-antigen binding in real time, achieving immunometric quantitation without attaching a reporter molecule (enzyme, fluorophore, etc.) to the immunocomplex. Conventional label-free technologies include surface plasmon resonance, isothermal titration calorimetry, and quartz crystal microbalance to name a few.

What are the latest developments with label-free technologies?

In the past decade, label-free technologies have advanced into the era of dip-in-solution sensing probes. The resulting LFIAs are open access, making them similar to plate-format assays without complicated sample delivery or fluidics. This allows for simple experiment workflows and makes new LFIAs well-suited for clinical laboratory applications. A new technology of this kind is thin-film interferometry (TFI), which incorporates a thin glass rod as a sensing probe that transmits light to form thin-film interference on a sensing surface. When biomolecules bind to the sensing surface and change its optical thickness, the interference pattern also changes relative to the number of bound biomolecules. In this way, this method measures the quantity of bound biomolecules in real time.

How might label-free technologies improve detection of therapeutic monoclonal antibody (t-mAb) interference?

The ideal way to detect t-mAb interference in monoclonal gammopathy testing is to change the electrophoretic mobility of the t-mAb and shift it out of the gamma (γ)-region. However, only one product for immunofixation electrophoresis eliminates daratumumab (DARA) interference in this manner, and no product of this kind exists for use with serum protein electrophoresis (SPEP).

As an alternative, our lab conjectured that a clinical laboratory could employ an easy-to-use, rapid immunoassay to measure in serum samples the presence and quantity of t-mAbs known to cause interference with SPEP. This information could then enable labs to easily rule in or rule out interference from t-mAbs when interpreting SPEP results. Working off this hypothesis, we developed an LFIA based on TFI technology that quantitates DARA in serum samples (Clin Chim Acta 2020;502:128-32).

Using mass transport-controlled binding kinetics, this method quantitates DARA in only 10 minutes by measuring the initial binding rate between DARA and its target, CD38. To validate this assay, we measured 37 patient samples submitted for SPEP and found that the LFIA's positive and negative results agreed 100% with patients' history of DARA use as documented in their medical records. In addition, we found that the DARA band became visible on the gel between 250 and 500 µg/mL, which falls in the analytical measurement range of the LFIA (10-1,000 µg/mL). This means that the assay's quantitative results could help in judging the severity of DARA interference.

How can labs integrate a LFIA for t-mAbs into their SPEP workflow?

When we review SPEP results, if a sample has a band in the γ-region that we suspect is DARA, we will analyze the sample using our LFIA. We then use the LFIA result for the final SPEP interpretation. Alternatively, labs could also run the LFIA on all samples with a band in the γ-region, but for our own workflow, we decided this would likely be excessive since patient histories for individuals diagnosed with multiple myeloma are often available at the time of review. We found that the LFIA is most informative if a new band appears in the γ-region for established patients. We hope this workflow serves as a model for other labs trying to detect the interference of emerging t-mAbs with SPEP.

Yiqi Ruben Luo, PhD, is a clinical chemistry fellow at the University of California San Francisco. Prior to this fellowship, he worked with label-free technologies in the clinical diagnostic industry for 9 years.
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