May/June 2025

CLN Clinical Laboratory News

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RULING OUT DEMENTIA

>90%

Negative predictive values demonstrated by four blood biomarkers for 10-year all-cause dementia and Alzheimer's

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Closing the colorectal cancer screening gap

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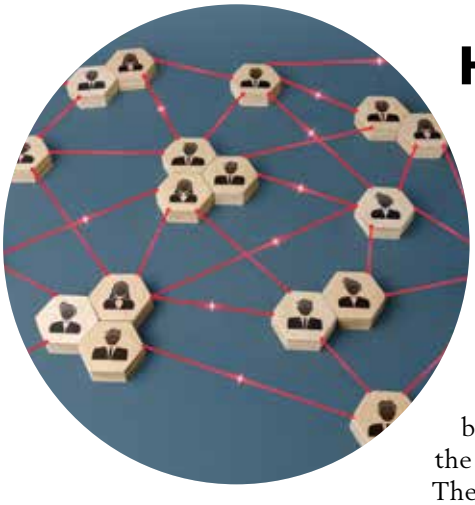

HHS proposes major FDA reorganization that would merge all product centers

The U.S. Department of Health & Human Services (HHS) is floating a seismic plan to reorganize the Food and Drug Administration (FDA) into five broad offices, with all its product review divisions merged into one. The proposal appears to fit in with HHS Secretary Robert F. Kennedy Jr.'s call for a new holistic approach to tackling chronic disease that looks beyond pharmaceuticals to include nutrition and dietary supplements.

The main focus of the proposal appears to be to separate the various functions of FDA's regulatory centers and to reorganize them as centralized offices. Each of these offices would be focused on one of the agency's broad functions and would presumably report directly to the FDA commissioner.

The reorganization plan includes combining FDA's review divisions into a new "Office of Product Evaluation and Regulation" that would serve as a "central hub for product review and regulatory decision-making across drugs, biologics, devices, tobacco, and foods." The office would be formed from the offices that review drugs, biologics, medical devices, tobacco products, human foods, and veterinary products. The HHS email on the proposed reorganization says the move "streamlines evaluation processes."

● ADLM LETTER PUSHES FOR REINSTATEMENT OF ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

The Association for Diagnostics & Laboratory Medicine (ADLM, formerly AACC), wrote to Robert Kennedy Jr., to urge the U.S. Department of Health & Human Services (HHS) Secretary to reinstate the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC). The ACHDNC plays an indispensable role in U.S. efforts to detect, diagnose, and treat asymptomatic babies with serious congenital conditions through newborn screening.

ADLM strongly recommended that Secretary Kennedy reinstate the ACHDNC to allow it to continue its work for parents and children. The letter went on to suggest that, if HHS decides not to restore the advisory panel, the agency should provide guidance on how new newborn screening tests will be evaluated for efficacy. The agency should also determine what process will be used to update the list of disorders that should be screened for.

● ADLM JOINS CDC COALITION STAKEHOLDERS ADVOCATING FOR ADDITIONAL FUNDING FOR AGENCY

The Association for Diagnostics & Laboratory Medicine (ADLM, formerly AACC) joined 218 members of the CDC Coalition and other supporting state, national, and academic organizations to urge the House Appropriations Subcommittee and the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies to include $11.581 billion in funding for the Centers for Disease Control and Prevention's (CDC) programs in the FY 2026 Labor, Health and Human Services, Education and Related Agencies appropriations bill.

In a letter addressed to the chairs and ranking members of these subcommittees, ADLM expressed serious concern for several recent actions by the administration that will significantly weaken CDC, the rest of the nation's public health system, and the efforts of organizations nationwide to combat many of the leading causes of death and disability in the nation. These actions include the claw back of more than $11 billion in previously appropriated funding to state and local health departments and an unworkable reorganization of the CDC that eliminates thousands of important positions and critical programs at the agency.

Texas district court strikes down FDA's LDTs final rule

In the wake of a major victory for clinical labs and patients, questions arise about whether the FDA could appeal the decision, about future laboratory developed tests legislation, and about areas where the impact of the court ruling isn't cut and dry. Read the full story at www.myadlm.org/cln.

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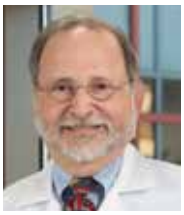
Bench Matters

A streamlined algorithm for better HIV testing

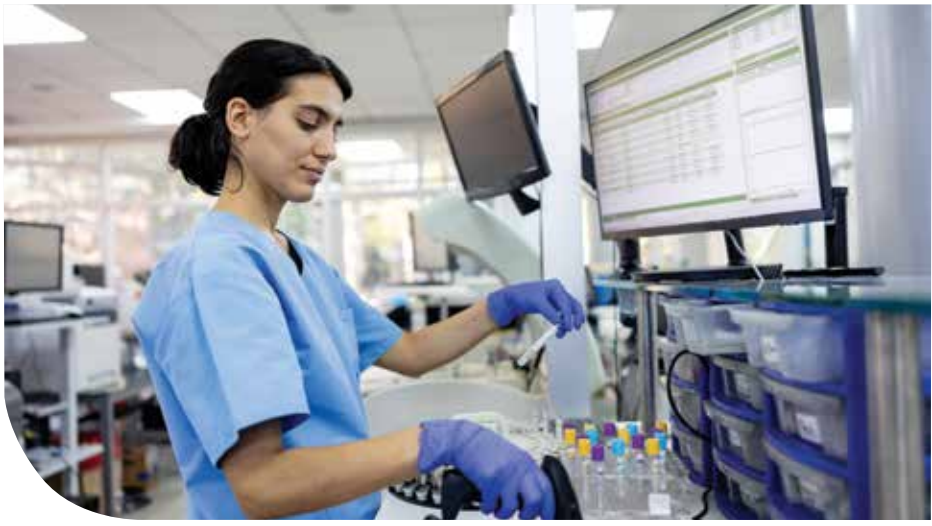
Nicole V. Tolan, PhD, DABCC

Nicholas Heger, PhD, NRCC



Gary L. Horowitz, MD

Clinicians and laboratorians face several practical challenges when following the laboratory HIV testing algorithm (Figure 1A, online) recommended by the Centers for Disease Control and Prevention (CDC), which we have observed results in longer wait times for diagnosis and treatment. We instead recommend a two-step algorithm that would be easier for labs to follow and would shorten time to diagnosis. This could help to ensure that patients are not lost to follow up, while also decreasing the risk that they might unknowingly transmit the disease.



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OVERVIEW OF THE CDC LABORATORY HIV TESTING ALGORITHM

The CDC's HIV testing algorithm, established in 2014, involves a three-step testing process that uses a highly sensitive fourth-generation HIV-1/2 antigen/antibody combination screening immunoassay (Ag/Ab-screen) with high negative predictive value. It allows for rapid determination of negative cases in low-prevalence populations (*1*). Fourth-generation Ag/Ab-screening assays detect not only IgG and IgM antibodies to HIV-1, HIV-2, and group O, but also the HIV-1 p24 antigen present in acute infection (*2*).

Ag/Ab-screen positive cases are then tested by a supplemental antibody immunoassay that differentiates HIV-1 from HIV-2 antibodies (Ab-differentiation). The Ab-differentiation assay can be performed using the same serum or plasma gel separator sample tube (SST/PST) for Ag/Ab-screening. Commonly, the Ab-differentiation is automatically reflexed for Ag/Ab-screen positive cases. Ab-differentiation positive results are conclusive for either HIV-1 or HIV-2 infection. However, the Ab-differentiation supplemental assays cannot confirm acute infection prior to seroconversion, when only the p24 antigen is detectable. Therefore, Ab-differentiation negative, indeterminate, or undifferentiated cases require HIV-1 and/or HIV-2 nucleic acid testing (NAT) to adjudicate between these two entirely divergent outcomes of acute infection or biologic false-positive Ag/Ab-screen results. Adding to the complexity, *HIV-2* indeterminate results by Ab-differentiation have a high likelihood of *HIV-1* infection requiring NAT, despite the results (*3*).

THE ALGORITHM'S PAIN POINTS

There are currently only three NAT methods approved for the diagnosis of HIV infection (*3*). However, many laboratories use methods with indications for use limitations that preclude their use for diagnosis, or to confirm HIV infection following results that are indeterminate or Ag/Ab-screen positive but Ab-differentiation negative (*4*). These methods are technically intended only to determine baseline viral load prior to and throughout antiretroviral therapy (ART). The limited sample types and processing requirements for NAT assays also preclude the use of the initial SST/PST sample. Thus, patients are either required to return for another sample collection, or laboratories must collect, process, and store a second sample upfront for NAT testing, despite the fact that the overwhelming majority of Ag/Ab-screening results will be negative in low-prevalence testing populations.

In most settings across the United States, laboratory testing for HIV infection is performed for routine screening in primary care,

obstetrics/gynecology, and infertility treatment where the pretest probability is low. Most inconclusive Ab-differentiation cases represent biologic false-positives. However, patients may not disclose high-risk behaviors that increase risk of infection, making it essential that NAT confirmation testing is performed so that the diagnosis and treatment of acute infection is not delayed. A reduced time to initiate ART has been shown to improve virologic suppression (*5*, *6*) and immune recovery (*7*), while reducing long-term comorbidities (*8*–*11*) and rates of transmission (*12*, *13*).

Unfortunately, this testing is commonly missed because of the complexity of the CDC testing algorithm and the inability of many laboratories to automatically reflex NAT. Internal studies at our respective institutions demonstrated that between 69%–84% of Ab-differentiation results are inconclusive in first-time Ag/Ab-screen positive patients, and 26%–29% of inconclusive Ab-differentiation results lack NAT confirmation. Additionally, we found that NAT confirmation can take more than 40 days on average due to the requirement for patients to return for a new specimen collection.

ELIMINATING AN UNNECESSARY STEP

With these factors in mind, we recommend a single-tube, two-step testing algorithm that reflexes all Ag/Ab-screen positive samples directly to NAT confirmation and that skips the Ab-differentiation step (Figure 1B). Regardless of the HIV-1/HIV-2 Ab differentiation results, NAT testing is required in all Ag/Ab-screen positive cases for diagnosis to confirm biologic false-positives or establish a baseline viral load prior to initiating ART (Table 1, online). Based on this and our experiences at our respective institutions, we have determined that this step delays final diagnosis and treatment without any significant benefits to offset this.

The most significant challenge clinical laboratories will face if they use our algorithm is the need to either collect a dedicated tube upfront for quantitative NAT; reflex the Ag/Ab-screen SST for *qualitative* NAT; or validate the off-label use of an alternative sample type, such as PST, as a laboratory developed test now subject to dual oversight from the Food and Drug Administration and CLIA (*14*).

HIV testing commonly is routinely performed with other sexually transmitted infection and hepatitis screening tests in an automation-friendly tube containing gel. We therefore performed an internal validation of PST and demonstrated excellent correlation of viral copy number to results obtained from pristine EDTA tubes. In light of this, we urge manufacturers to broaden the constraints of the indications for use and sample type restrictions to allow clinical laboratories to use PST for NAT assays and more efficiently provide rapid diagnosis of HIV infection.

Although rare (less than 1% of people have HIV), it is also important to determine if HIV controllers (*15*), with detectable antibodies but low viral copy numbers, will be detected by current NAT methods. Further, although the likelihood of a spontaneous viral load below the limit of NAT is estimated to occur in approximately only 25% of the HIV controller population, it is important to prospectively study the incidence of this occurring at the time of initial testing and the potential for missing nonviremic controllers when not performing the Ab-differentiation.

CONCLUSION

It is critically important for the HIV testing algorithm to be easy to follow and involve the automatic reflex of the initial sample collected to rapidly provide a final diagnosis. We believe this will play a critical role in achieving UNAIDS 95-95-95 targets to end the AIDS pandemic (*16*).

To view the references, figure, and table for this article, visit myadlm.org/cln.

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Capillary blood collection system shows promise

The BD MiniDraw, a blood collection option for non-traditional settings including pharmacies, is clinically equivalent to conventional capillary and venous collection for certain analytes and may expand access to laboratory testing (J Appl Lab Med 2025; doi: 10.1093/jalm/jfaf005).

Capillary blood sampling enables the collection of smaller volumes of blood and may benefit patients who require frequent disease monitoring. Technological advances in capillary blood collection can also be more convenient for patients. One of these capillary collection technologies — the BD MiniDraw Capillary Blood Collection System (BD MiniDraw) with the BD MiniDraw SST Capillary Blood Collection Tube (BD MiniDraw SST tube) — helps trained healthcare workers without phlebotomy experience to collect blood in non-traditional healthcare settings. In this scenario, dedicated phlebotomists or nursing professionals would be unnecessary, because pharmacists and pharmacy technicians working in retail pharmacies and patient service settings could draw blood. Specimen analysis occurs at a central laboratory.

To test the capillary collection method, three studies assessed systems and tubes in accordance with state laws. Studies one and two evaluated clinical equivalence for selected serum chemistry analytes in the BD MiniDraw, compared with currently marketed capillary and venous comparators. Study three evaluated in-tube stability for selected analytes up to 48 hours in BD MiniDraw SST tubes following storage at 2° to 8°C. For each study, the researchers prepared contrived specimens to cover medically relevant ranges and conducted testing on one general chemistry core laboratory analyzer. Biases and 95% limits within a predefined clinical acceptance limit at all medical decision levels and time points for stability demonstrated clinical equivalence.

The results also showed clinical equivalence for all analytes with BD MiniDraw versus capillary and venous comparators, except alanine aminotransferase and chloride for the venous comparator in study one. Both showed clinical equivalence at the upper limit of the reference range. The confidence interval exceeded the clinical acceptance limit at the lower limit. The studies showed in-tube stability in BD MiniDraw SST tubes up to 48 hours for all selected analytes.

POSSIBLE CAUSE OF DRUG-RESISTANT PNEUMONIA

The IncFIIK34 plasmid may be a key factor driving the global dissemination of carbapenem-resistant hypervirulent Klebsiella pneumoniae (CR-hvKp), underscoring the urgent need for better molecular surveillance of this emerging pathogen (The Lancet 2025; doi: 10.1016/j.ebiom.2025.105627). hvKp causes severe community-associated infections like liver abscesses and meningitis in otherwise healthy individuals, leading to high mortality rates. CR-hvKp shows resistance to most clinically available β-lactams, greatly limiting treatment options. The World Health Organization has reported a rising global incidence of CR-hvKp, particularly of sequence type 23. Inadequate laboratory capacity likely drives substantial underestimation of both hvKp's and CR-hvKp's global burden, the paper notes.

In response, the researchers analyzed CR-hvKp strains derived from canonical hvKp backgrounds and acquired a carbapenemase-encoding gene. The team identified these strains from 485 CRKp isolates in a Chinese cohort, 259 CRKp isolates from a multicenter study, and 67,631 genomes available in the GenBank sequence database. Next, the researchers selected clinical isolates harboring the IncFIIK34 KPC-2 plasmid for genome sequencing, RNA-Seq, conjugation assays, in vivo, ex vivo, and in vitro phenotypic characterization.

Analysis of clinical CR-hvKp isolates and the 414 genomes from 24 countries available in GenBank identified an IncFIIK34 KPC-2 plasmid as the prevalent KPC plasmid, detected in 25% of KPC-producing CR-hvKp across 33 countries. Compared with the epidemic IncFIIK2 KPC-2 plasmid, the IncFIIK34 KPC-2 plasmid exhibited a 100- to 1,000-fold increase in conjugation frequency and an in vitro growth advantage under meropenem challenge, likely due to the overexpression of conjugation-related genes and an increased blaKPC copy number and expression. CR-hvKp isolates and hvKp transconjugants carrying this plasmid often exhibited reduced mucoviscosity, while retaining hypervirulence in both murine models and human neutrophil assays.

The findings build upon prior evidence and underscore the emergence and prevalence of an IncFIIK34 KPC-2 plasmid in CR-hvKp. The noteworthy characteristics of this plasmid, including its high conjugation rate and elevated carbapenem resistance, highlight the critical importance of global surveillance of the IncFIIK34 KPC-2 plasmids and CR-hvKp strains.

Evidence on the clinical validity of blood biomarkers of Alzheimer's disease (AD) in the general population is lacking.

BIOMARKERS MAY HELP RULE OUT DEMENTIA

Recent research suggests that a specific group of biomarkers has the potential to rule out impending dementia in community settings (Nature Medicine 2025; doi: 10.1038/s41591-025-03605-x). Evidence on the clinical validity of blood biomarkers of Alzheimer's disease (AD) in the general population is lacking. In response, researchers estimated the hazard and predictive performance of six AD blood biomarkers for incident all-cause and AD dementia in a cohort of 2,148 dementia-free older adults from Sweden, who were followed for up to 16 years. The biomarkers included the ratio of amyloid-β 42 to amyloid-β 40, levels of tau phosphorylated at T217 (p-tau217), tau phosphorylated at T181 (p-tau181), total tau, neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP).

In multiadjusted Cox regression models, elevated baseline levels of p-tau181, p-tau217, NfL, and GFAP were associated with a significantly increased hazard for all-cause and AD dementia, displaying a nonlinear dose-response relationship. Elevated concentrations of p-tau181, p-tau217, NfL, and GFAP demonstrated strong predictive performance (area under the curve ranging from 70.9% to 82.6%) for 10-year all-cause and AD dementia, with negative predictive values exceeding 90% and low positive predictive values (PPVs). Combining p-tau217 with NfL or GFAP further improved prediction, with PPVs reaching 43%.

These findings suggest the biomarkers may need to be combined with other biological or clinical markers to be used as screening tools, the researchers noted.

The new screening option may appeal to patients who avoid colonoscopy or stool tests — but experts urge careful consideration of these tests' performance.

BY KAREN BLUM

CAN A BLOOD TEST HELP CLOSE THE COLORECTAL CANCER SCREENING GAP?

Last July, when the Food and Drug Administration (FDA) approved a blood-based test for colorectal cancer screening, the test joined the ranks of growing options available — from traditional colonoscopy to stool-based testing — to try to detect these cancers and their precursors. While the test's sensitivity lags behind some other screening options, it could prove to be a more attractive option for people not currently engaging in screening, experts say.

Guardant Health's Shield test, designed to detect fragments of DNA released by colorectal tumors into the blood (known as cell-free or cfDNA), was approved following publication of the ECLIPSE (Evaluation of the ctDNA LUNAR Test in Average Patient Screening Episode) trial (N Engl J Med 2024; doi: 10.1056/NEJMoa2304714). The clinical validation study of 7,861 people found a sensitivity of 83.1% for detection of colorectal cancers, including an 87.5% sensitivity for stage I, II, or III colorectal cancers and a 13.2% sensitivity for advanced precancerous lesions. Medicare and the U.S. Department of Veterans Affairs now cover the test for people at average risk for developing colorectal cancer with no personal or family history of the disease.

For years, colonoscopy has been the gold standard as the most sensitive test for cancers and precancers, said gastroenterologist John Kisiel, MD, a professor of medicine at the Mayo Clinic College of Medicine in Rochester, Minnesota, "but that requires that the colonoscopy be done very well. We know from countless studies that clinicians' colonoscopy performance varies. When a colonoscopy is done to evaluate a patient with a positive stool-based test, detection rates are much higher, and we assume that's probably due to some differences in endoscopist behavior when they know that the patient is being referred in."

HOW DO THE TESTS STACK UP?

The Shield test has the same sensitivity for colon cancer as the fecal immunochemical test (FIT), said gastroenterologist and molecular biologist William "Bill" Grady, MD, senior author of the *New England Journal of Medicine* (NEJM) study and a professor in the translational science and therapeutics division of the Fred Hutchinson Cancer Center in Seattle. "In fact, it's probably a little bit better. But it's not as good as the Cologuard [at-home] stool test or colonoscopy." Cologuard has a sensitivity of 92%.

Sensitivity for advanced cancers across all the tests "is quite high," Kisiel said, including 100% for stage II–IV cancers in the Shield study. "But that's not what matters, because advanced cancers are not what we want to find in a screening program. What we really want to find, ideally, are stage one or two cancers, which are considered curable. Even more important is finding advanced precancers."

Detecting precancers is still a challenge for blood-based testing, however, as the amount of mutated DNA shed by tumors circulating in peripheral blood is extremely small, said gastroenterologist Aasma Shaukat, MD, MPH, the Robert M. and Mary H. Glickman Professor of Medicine at New York University's Grossman School of Medicine.

When targeting advanced polyps, colonoscopy will miss 5–10 out of 100 times, Grady explained, whereas Cologuard will miss about 55 out of 100 times and Shield will miss 87 times out of 100. "So, it's clear that colonoscopy is much better than Cologuard or the FIT or Shield tests."

WEIGHING BLOOD TESTS' LIMITATIONS

If the Shield test is not as accurate as colonoscopy or a stool-based test, why use it? "Right now, anywhere from 25%–35% of people who should be doing colon cancer screening are not doing it," Grady said. As people are more likely to agree to a blood test than those other tests, it presents a potentially compelling option.

Uptake for the blood-based test by patients and providers is still "largely unknown," Shaukat noted. However, there was a "pretty high" uptake for tests that screen for prostate cancer by measuring prostate-specific antigen, she said. In studies where patients have been called or interviewed to ask if they would complete blood tests if they were available to screen for cancer, "the answer is largely yes," she said.

"The enthusiasm for a blood-based test is higher than for colonoscopy or for stool-based tests, the reason being colonoscopy is a very invasive test, there's prep involved, time off, and there's risk of complications," Shaukat said. While stool tests are convenient and can be done at home, some patients don't like handling stool, she added. Others may take the test home and forget to do it or misplace it.

"With a blood test, the potential is that it can be coupled with other blood draws that patients are used to getting for cholesterol or other routine things," Shaukat said. "It can be a convenient option, because as a physician, if I tell a patient to do it, then I can send them to the lab right away. I don't

Previous page ad right: gremlin / iStock

lose momentum by their taking it home and forgetting about it."

However, Grady said he worries that because the blood test is easy to order and complete, more people will opt for that as their first choice, rather than going to more accurate tests. "That we don't want to have happen … because more people would die from colon cancer than if we stick with our current program of people not getting any colon cancer screening. We don't want to completely replace it. We want that 30% of people who aren't doing anything to do something."

NEW GUIDELINES COULD BE NEXT

Whether physicians and guideline authors will embrace this option also remains to be seen, he said. The Shield test is not yet readily available at a lot of hospitals, and Grady has heard from people who say their doctor isn't aware of the test, which he said is typical with anything new.

The NEJM study is definitive enough for guidelines organizations such as the U.S. Preventive Services Task Force to potentially include in its recommendations, according to Grady. "I think they'll include it," he said, "but I think it's going to be probably a tier two option, where if you're going to do screening, the tier one options are going to be FIT testing, colonoscopy, or Cologuard, and then tier two would be the blood test."

For now, test results for blood and stool tests are returned solely as positive or negative, "and the FDA wants it that way," Shaukat said. "The FDA gets very nervous when there's interpretation involved, because they don't want the consumer or the patient trying to do that." Manufacturers of some

COLORECTAL CANCER SCREENING OPTIONS

Recommendations for individuals at average risk include:

- traditional colonoscopy every 10 years
- virtual colonoscopy every 5 years
- fecal immunochemical test, every 3 years
- sigmoidoscopy every 5 years
- Cologuard stool-based test every 3 years
- Epi proColon (now known as ColoHealth) blood test, which looks for the biomarker mSEPT9 in plasma samples, annually
- ColoVantage blood test to look for mSEPT9, which is not Food and Drug Administration-approved but is offered by laboratories including Quest Diagnostics and Ulta Lab Tests. ColoVantage also has a home test that allows people to sample their toilet water following a bowel movement, apply it to a test card, and mail it back to a lab.

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blood tests in development are looking to see if they could provide a range of risk and interpretation around that range, she said.

Going forward, next-generation sequencing could be incorporated into these tests, Shaukat said, as could technology to detect signals coming from the stromal and immune cells surrounding tumor cells to help identify preneoplastic lesions.

Meanwhile, other manufacturers also are aiming to get into the game. Freenome in 2024 announced results from the PREEMPT clinical study of its blood test for colorectal cancer, which demonstrated a nearly 80% sensitivity in detecting colorectal cancer and a 92% specificity for nonadvanced colorectal neoplasia. Universal Diagnostics initiated a clinical validation study of its own blood test for colorectal cancer, called Signal-C. Exact Sciences (manufacturer of Cologuard and other tests) and CellMaxLife also are developing blood-based screening tests for colorectal cancers.

MULTI-CANCER TESTS ALSO ON THE RISE

Beyond colon cancer, companies are adapting blood-based tests toward detection of multiple cancers, Kisiel said. Screening tests are available for breast, cervical, colon, prostate, and lung cancers, he said, but not for ovarian or pancreatic cancer, "which are much less common, but when people get them, they're highly fatal." Multicancer early detection testing could assure that while someone is getting blood drawn to screen for colon cancer, laboratories also could study the blood for presence of these other malignancies. "That's a rapidly exploding field that 5 to 10 years ago was science fiction, and is now being commercialized," he said.

For example, GRAIL's Galleri test screens the blood for cell-free methylated DNA from more than 50 types of cancer. The test is not approved by the FDA but is available from CLIA-certified labs as a laboratory developed test. However, it has shown an overall sensitivity of only 27.5% for earlier stage 1 and 2 cancers (Lancet 2024; doi: 10.1016/S0140-6736(23)02830-1).

"I don't think they're quite ready yet," said Grady, but clinical trials are evaluating blood-based multicancer tests to see if they are good enough for use in the clinic. The National Institutes of Health in February 2024 launched the Cancer Screening Research Network to evaluate these types of trials, he said. "We need to see what those trials show before we figure out whether these tests really should be used in the clinic … but if it turned out we had a test that could screen for 15 cancers at once in a blood test? Wow, that would be amazing."

Kisiel is an inventor of the Cologuard at-home stool screening test and receives royalties from sales of the product outside of the Mayo Clinic. Grady is a member of the scientific advisory board for Guardant Health, manufacturer of the Shield blood-based screening test, has consulted for Freenome, and consults for Karius.

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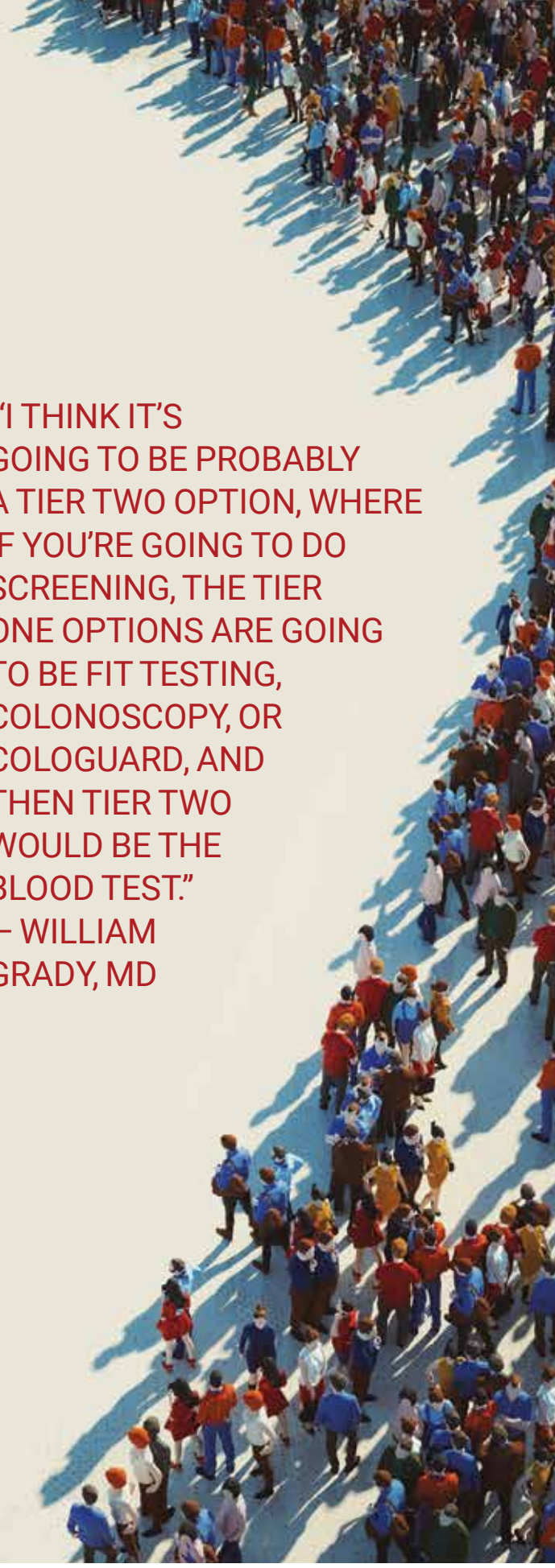

"I THINK IT'S GOING TO BE PROBABLY A TIER TWO OPTION, WHERE IF YOU'RE GOING TO DO SCREENING, THE TIER ONE OPTIONS ARE GOING TO BE FIT TESTING, COLONOSCOPY, OR COLOGUARD, AND THEN TIER TWO WOULD BE THE BLOOD TEST." — WILLIAM GRADY, MD

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MAKING AST FAST

A new generation of tests could optimize antibiotic stewardship by combining speed with specificity.

BY YAAKOV ZINBERG

Antibiotic resistance continues to be a major global health concern, and all data point towards the crisis worsening. The Centers for Disease Control and Prevention (CDC) reported last year that six antibiotic-resistant nosocomial infections, including methicillin-resistant *Staphylococcus aureus* and *Candida auris,* increased by a combined 20% in the United States during the COVID-19 pandemic and remained above prepandemic levels in 2022. Antibiotic-resistant infections are projected to claim the lives of more than 39 million people worldwide over the next 25 years, according to a recent study from the Global Research on Antimicrobial Resistance Project.

Although the use of broad-spectrum antibiotics has exacerbated antibiotic resistance at the population level, such medications are sometimes the only viable choice for individual patients. That's because it can take upwards of 48 hours to identify infectious agents in patient samples and assess how they fare in the presence of different antibiotics — a process known as phenotypic antibiotic susceptibility testing (AST). But patients in the most critical conditions, such as those with sepsis or bloodstream infections, can't wait that long to begin treatment.

Using traditional methods, bacterial identification was only possible after a positive blood culture is stained, subcultured, and incubated. Additionally, AST cannot be initiated until isolated colonies are inoculated with antibiotic.

"[AST] gets you to the answer of, 'What do I need to prescribe to get this patient better?'" said Robin Patel, MD, director of the Mayo Clinic's Infectious Diseases Research Laboratory in Rochester, Minnesota. "But the challenge has been that this is generally a slow process because it's sequential."

It's no surprise, then, that there's been a great deal of interest in rapid AST, an umbrella term for tests that deliver faster susceptibility results than standard AST. It's an approach that could combine diagnostic speed with specificity, allowing clinicians to provide the most effective treatment for patients while minimizing the potential for widespread antibiotic resistance.

A VARIETY OF APPROACHES

"We now have technologies that enable us to, in some cases, not have to grow bacterial cultures in the first place," Patel said. "In other cases, as soon as organisms are grown, we can identify them and do susceptibility testing all at once, rather than sequentially."

Rapid AST is not a single test or set of tests. In fact, "there are a tremendous number of very creative solutions that investigators have deployed," said Cédric Yansouni, MD, a medical microbiologist and associate professor at at McGill University Health Centre in Montreal, Quebec, Canada, who calls the diversity of technologies being proposed for speeding up AST "remarkable."

For example, several AST strategies simultaneously identify a pathogen and ascertain the minimum inhibitory concentration (MIC) for a range of antibiotics, sometimes directly from positive blood cultures.

One test involves an array of nanometer-sized sensors positioned above an antibiotic well to detect the emission of volatile organic compounds (VOCs), metabolic byproducts that can indicate growth and, in some cases, identify microorganisms based on species-specificity. The sensors change color based on the VOC emissions.

VOC detection is the basis for bioMérieux's Vitek Reveal system, which was shown in a 2022 study to provide highly accurate results in about 5 hours.

Single-cell imaging offers another promising approach. In this technique, bacteria are grown in single-cell channels, thereby reducing incubation times. The channels have different antibiotic conditions, and bacteria can be imaged via light absorbance, fluorescence, or other microscopy techniques.

PROGRESS IN PRACTICE

To get a sense for the variety of proven rapid AST technologies, look no further than the Food and Drug Administration (FDA) approvals in 2024 — a "banner year," according to Patel. Four tests received 510(k) clearance last year, including:

- Selux Diagnostics' Positive Blood Culture Separator, which isolates the bacterial sample from a positive blood culture bottle in advance of AST;
- Affinity Biosensors' LifeScale AST system, which leverages microfluidics and artificial

THESE TESTING SYSTEMS REDUCE THE AMOUNT OF TIME NEEDED TO SWITCH FROM EMPIRIC THERAPY TO A PATHOGEN-DIRECTED ANTIBIOTIC TREATMENT STRATEGY ... WHILE NOT SACRIFICING MUCH IN TERMS OF ACCURACY.

intelligence to measure bacterial replication and MICs;
- Q-linea's ASTar instrument, which uses high-speed time-lapse microscopy imaging of bacteria for MIC determination; and
- bioMérieux's Vitek Reveal, which earned the FDA's Breakthrough Device Designation in 2022.

Numerous pilot studies and larger trials have demonstrated that these testing systems reduce the amount of time needed to switch from empiric therapy to a pathogen-directed antibiotic treatment strategy compared with standard testing, while not sacrificing much in terms of accuracy accuracy. They also can enable more rapid de-escalation of unneeded therapy.

Accordingly, clinical microbiology laboratories are beginning to adopt rapid AST methods, albeit in a limited fashion. A 2022 study from the Antibacterial Resistance Leadership Group found that, of 96 laboratories surveyed from across the United States, nearly all used some form of rapid testing directly from positive blood culture, though nearly 80% that do used only one or two panels or platforms; additionally, the most commonly used tests focus on bacterial identification.

OBSTACLES TO IMPLEMENTATION

The reason rapid AST hasn't been adopted more broadly is not technological as much as it is a function of laboratories' capacity.

"There are currently, or will be soon on the market, several platforms that are able to give antimicrobial susceptibility results within a couple of hours directly from a positive blood culture," said Yansouni. "These have the potential

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UNLESS IT CAN BE COMPLETED IN A SINGLE SHIFT, RAPID AST REQUIRES A 24/7 WORKFLOW TO BE USEFUL — WHICH MOST LABS DO NOT HAVE THE STAFF OR RESOURCES TO MAINTAIN.

to provide meaningful information very quickly to clinicians. However, in order to be useful, a lab needs to also have the means of providing a species identification within the same time frame."

The interpretation of susceptibility results depends directly on the species of bacteria identified. A given MIC, for instance, might be interpreted as susceptible in a gram-positive bacterium but resistant in a gram-negative one. In other words, rapid AST is only as fast as the bacterial identification test it's paired with. That means that, unless it can be completed in a single shift, rapid AST requires a 24/7 workflow to be useful — which most labs do not have the staff or resources to maintain.

"If a patient's blood culture becomes positive at 2 a.m., you need to have staff that are able to run and report that rapid diagnostic test immediately," Patel explained. "Not only that, but you have to have someone on the other end receiving that result at that time."

Figuring out how rapid AST fits into laboratory antimicrobial stewardship is essential, said Linoj Samuel, PhD, division head of clinical microbiology for Henry Ford Health in Detroit. "You can do rapid AST, but if, at the end of the day, no one utilizes that result in a timely manner, that's just a wasted effort." The goal, he said, is to "build a system that ties the lab result to the provider and patient, and then go back to demonstrate that all that effort actually resulted in meaningful change." Such change could mean not only faster times to appropriate therapy but also improved mortality, resource utilization, and length of stay in the ICU.

Of course, cost is also a consideration. Most rapid susceptibility tests are used for sepsis and other inpatient scenarios, so there is no direct reimbursement, said Samuel. The instruments can be prohibitively expensive as well.

Individual labs will need to weigh the clinical benefits, costs, and diagnostic stewardship considerations for each rapid AST platform against their own testing workflows. In certain cases, a test may be desirable due to its price. For example, matrix-assisted laser desorption/ionization mass spectrometry has seen widespread adoption for routine bacterial identification mostly because it lowers reagent costs and is less labor-intensive.

As labs work this out, there's no shortage of new testing methodologies in the pipeline to look forward to. For example, one group in South Korea has proposed a method capable of performing bacterial identification and AST directly from blood without preincubation. They used magnetic nanoparticles that capture bacteria in blood samples from patients with suspected sepsis, eliminating the need for any culture-amplification. This investigational technique showed very high accuracy while providing results within an hour instead of over 1 day.

Additionally, genotypic AST — which detects the presence of specific antibiotic-resistance genes — is an active area of research. In fact, several genotypic assays that detect resistance genes or associated mutations have recently become commercially available. It's not hard to imagine a future in which patients can receive both phenotypic and genotypic susceptibility testing to guide their antibiotic treatment.

FUTURE DIRECTIONS

It's too early to tell if rapid AST will make a dent in the global antibiotic-resistance crisis. But there's no doubt that a continued emphasis on evaluating these tests with real patients is crucial for maximizing their potential benefit.

"If we're going to encourage adoption of these new technologies, it would be really helpful to see more labs incentivized to use them and more funding available to do the kind of studies needed," such as multi-center studies on outcomes, Samuel said.

"By generating data on clinical utility," Patel added, "laboratories and institutions can understand the potential value of offering a test to the care of their patients."

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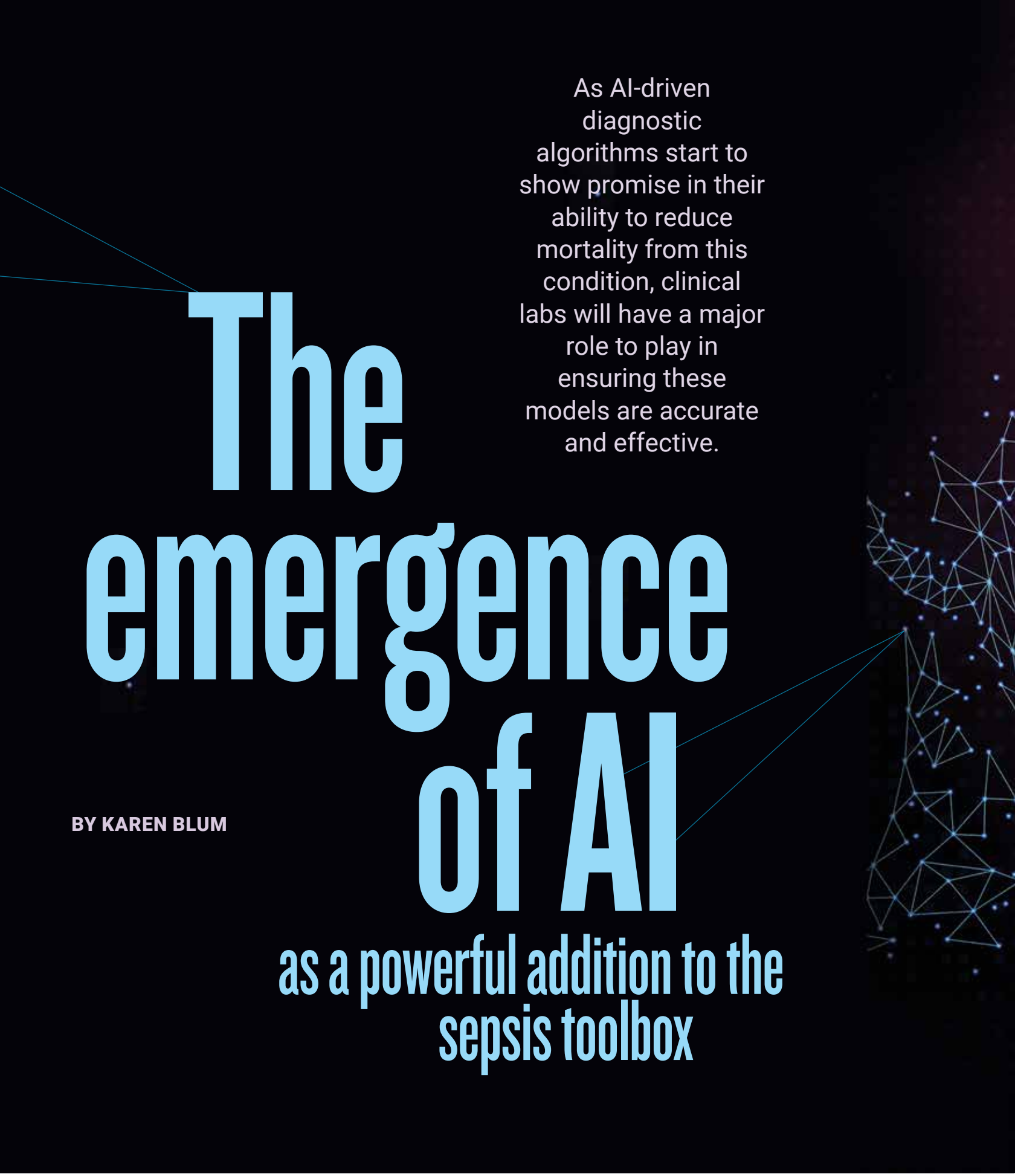
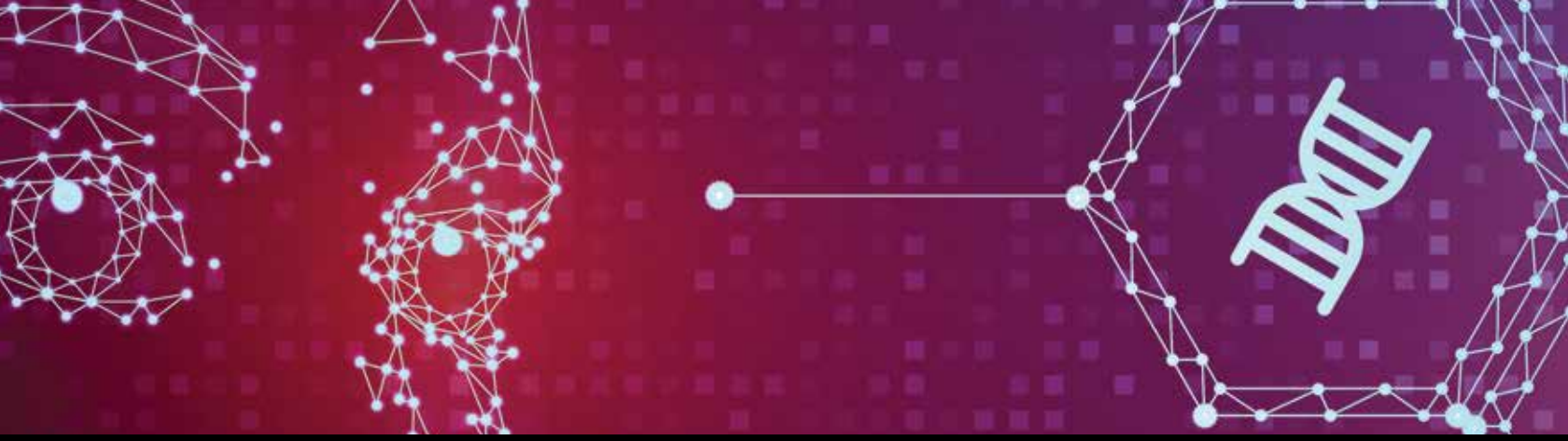
As AI-driven diagnostic algorithms start to show promise in their ability to reduce mortality from this condition, clinical labs will have a major role to play in ensuring these models are accurate and effective.

The emergence of AI

as a powerful addition to the sepsis toolbox

BY KAREN BLUM





In sepsis management, time is of the essence. Every hour that passes before a patient is identified and started on treatment puts them at risk for organ failure or death. Knowing this, some clinicians have been trying new methods to increase earlier sepsis detection and management by developing algorithms that employ artificial intelligence (AI) to evaluate laboratory values and other data to alert providers to the presence of sepsis, which affects some 50 million people globally. Although the performance of these algorithms varies so far, this overall trend presents a perfect opportunity for laboratory medicine professionals to showcase their knowledge.

USING AI TO AUGMENT HUMAN EXPERTISE

AI is just one of several solutions emerging for sepsis detection, thanks in part to biomarkers for the condition that can be measured in the blood, such as circular RNAs, protein C, and prokineticin 2 (Int J Mol Sci 2024; doi.org/10.3390/ijms25169010), said Damien Gruson, PhD, head of the department of clinical biochemistry at Cliniques Universitaires Saint-Luc in Brussels, Belgium, and chair of the Division on Emerging Technologies of the International Federation of Clinical Chemistry and Laboratory Medicine. Other emerging solutions include point-of-care testing and omics options such as genomics and high-throughput sequencing.

"All together, these tools should help clinical teams to better diagnose and manage the patient," Gruson said. "It's not a substitution of the healthcare workforce by the technology. It's the amplification of human intelligence by artificial intelligence."

For example, a multidisciplinary team at the University of California San Diego (UCSD) School of Medicine developed COMPOSER (COnformal Multidimensional Prediction Of SEpsis Risk), a deep learning model for early sepsis prediction. Once a patient checks into the emergency department, the algorithm starts monitoring 150 types of datapoints, including lab results, vital signs, home medications, comorbidities, and demographics to look for possible signs of sepsis. If the program suspects a person is septic, or heading that way, it sends an alert through the electronic health record (EHR) to the nursing staff, who can then review these values with the physician to confirm and determine treatment.

In a recent study (NPJ Digit Med 2024; doi: 10.1038/s41746-024-01234-1), UCSD clinicians reviewed records from 6,217 adult septic patients presenting to two of its hospital emergency departments, before and after the COMPOSER tool was deployed. The use of the deep learning tool was associated with a 17% relative decrease in in-hospital sepsis mortality and a 10% relative increase in adhering to an evidence-based management guideline known as the sepsis bundle.

They also found less organ injury 72 hours from the time of sepsis detection. Once the tool was activated, it generated an average of 235 alerts per month, corresponding to 1.65 alerts per nurse per month. In more than half of cases, a nurse responded that they would notify the physician immediately.

The idea behind the program was to help identify sepsis in cases where it might not be obvious, said Gabriel Wardi, MD, MPH, an associate professor of emergency medicine and chief of the division of critical care at UCSD, who helped develop the program.

"If someone comes in with a very low blood pressure, high fever, high heart rate — that will be picked up immediately," said Wardi. "Where the tool adds value is where there's diagnostic uncertainty with these patients." People with vague symptoms often have significant delays with their treatment, he said.

THE NEED FOR LABS TO TAKE AN ACTIVE ROLE

Researchers at other academic medical centers including Duke, the University of Pennsylvania, and Johns Hopkins also have

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designed AI-enabled algorithms to detect sepsis, with promising results. But not all tools have fared as well. The EHR firm Epic offers its own sepsis detection model, but when investigators at the University of Michigan went to validate it in some of their hospital units, they found the tool correctly sorted patients on their risk of sepsis only 63% of the time, not 76%–83% of the time as reported by the company. The tool also sent out too many alerts regarding patients who turned out not to have sepsis (JAMA Intern Med 2021; doi:10.1001/jamainternmed.2021.2626). The researchers determined that the model was trained on data defining the onset of sepsis as the time a clinician intervened, not necessarily when it started, which skewed results.

Clinicians in St. Louis determined the Epic model wasn't a fit for them for similar reasons, said Ronald Jackups Jr., MD, PhD, chief medical information officer for laboratories at BJC Healthcare in St. Louis and professor of pathology and immunology at Washington University School of Medicine. As such, he and his colleagues are not using any AI tools for sepsis detection.

It is a good reminder that all such tools need to be validated by multidisciplinary groups including frontline clinicians, data scientists, information technology specialists, and others before adopting them, especially if they're being adopted across settings. Laboratorians should be key members of such teams, said Jackups, president of the Association of Pathology Informatics (API). Laboratory leaders also should take an active role in the development of such programs and get involved with hospital committees and initiatives surrounding identification and treatment of sepsis.

"Those groups frequently use lab test results to drive these decisions but may not directly reach out to laboratory leaders to include them as subject matter experts," he said. "It is our job to reach out and make sure we're included in those discussions. That gives us the opportunity to provide our expertise on the utility of these tests: when they should be ordered, how they should be interpreted, and whether alerts are valuable in this process."

API partnered with Project Santa Fe Foundation on a new Diagnostic Medicine Consortium aimed at maximizing the predictive value of information generated by diagnostics.

"One of the major goals for the future of laboratory medicine is to get out of the laboratory and start assisting the front-facing clinical services with not just understanding lab tests, but applying them to improve patient care," he said. "This is exactly one of those kinds of initiatives where we can show that."

"It is our job to reach out and make sure we're included in those discussions. That gives us the opportunity to provide our expertise on the utility of these tests." — Ronald Jackups Jr., MD, PhD

To help, clinical laboratories can work to standardize their data as needed to allow comparisons among hospitals or within different areas of the hospital, Gruson said. They also could incorporate diagnostic testing for biomarkers and host response to infection, said Wardi. In the case of expensive tests, AI programs potentially could help clinicians and laboratories prioritize which patients to run tests on, "which allows us to both manage costs and improve care," said Suchi Saria, MSc, PhD, the John C. Malone Associate Professor of computer science at the Johns Hopkins Whiting School of Engineering in Baltimore, and associate professor of statistics and health policy at Hopkins' Bloomberg School of Public Health. Saria also is the founder of Bayesian Health, a clinical AI platform company spun out of her university research on the TREWS (Targeted

Real-Time Early Warning System) sepsis detection tool, which has demonstrated an 18.7% reduction in sepsis mortality (Nature Medicine 2022; doi.org/10.1038/s41591-022-01894-0).

HURDLES ON THE ROAD TO WIDESPREAD ADOPTION

AI models for sepsis and other conditions could become commonplace within the next 5 to 10 years, Jackups said. But there are several hurdles to more widespread use. One is trust in output from alerts where users don't understand the complex algorithm driving the program, known as the "black box." The Food and Drug Administration is one of several groups that have attempted to establish guidelines.

"The most important guideline is that the alert shouldn't be making the decision — the alert should be providing enough information and knowledge so that the ordering provider can make an appropriate decision," Jackups said. That includes presenting as much useful information on why an alert occurred and what the next steps could be, without dictating those steps. "Those kinds of alerts are much more likely to be understood and followed by clinicians, as opposed to 'black box' alerts that simply give a directive without fully explaining why the alert is even occurring."

Another hurdle is how to build models to be early and accurate in their data while also driving adoption, Saria said. Ideally, programs need to be integrated into the EHR and workflows and work across settings from critical care to the emergency department and beyond. Saria's approach has resulted in a nearly 90% adoption rate among providers (Nature Medicine 2022; doi.org/10.1038/s41591-022-01895-z).

"You can have a perfectly validated tool that has really high sensitivity and positive predictive value and then completely fail to change practice when implemented," Jackups added. "It is critical for someone with an understanding of change management to be able to observe how providers use these kinds of alerts and react to them. That culture is institution-dependent."

Wardi found a generational divide: Younger colleagues were excited about using the COMPOSER tool, while some of the senior physicians essentially said, "thanks but no thanks." He sat down with some of them individually to encourage them to think of the tool as a second set of eyes in a busy emergency department, and if an alert went off to at least take another look at their patient. "That actually worked quite well," he said.

Overall, said Wardi, "Where I see this going is to have an emphasis on multimodal data, which isn't just getting data from the EHR but rather bringing in the clinical notes, and novel tests to assess host response to infection and develop a whole new kind of domain of data that will hopefully — at least from what I've seen based on our preliminary work — really improve how these models perform to become much more useful for clinicians to and give them a very high predictive value."

The technology also could be used cross-purpose for multiple other conditions, from earlier identification of pressure ulcers to helping determine which patients would benefit from palliative care, Saria said.

"I see this huge opportunity for what I call intelligent care augmentation," she said. "We're taking AI and a smart, real-time platform that augment the capabilities of the care team, which in turn helps them parse data to identify high-quality, validated, robust clinical signals that are more proactive than reactive, and enables smart workflows. It enables them to give the right targeted treatments and provide better, faster, and smarter care — while also saving them a huge amount of time."

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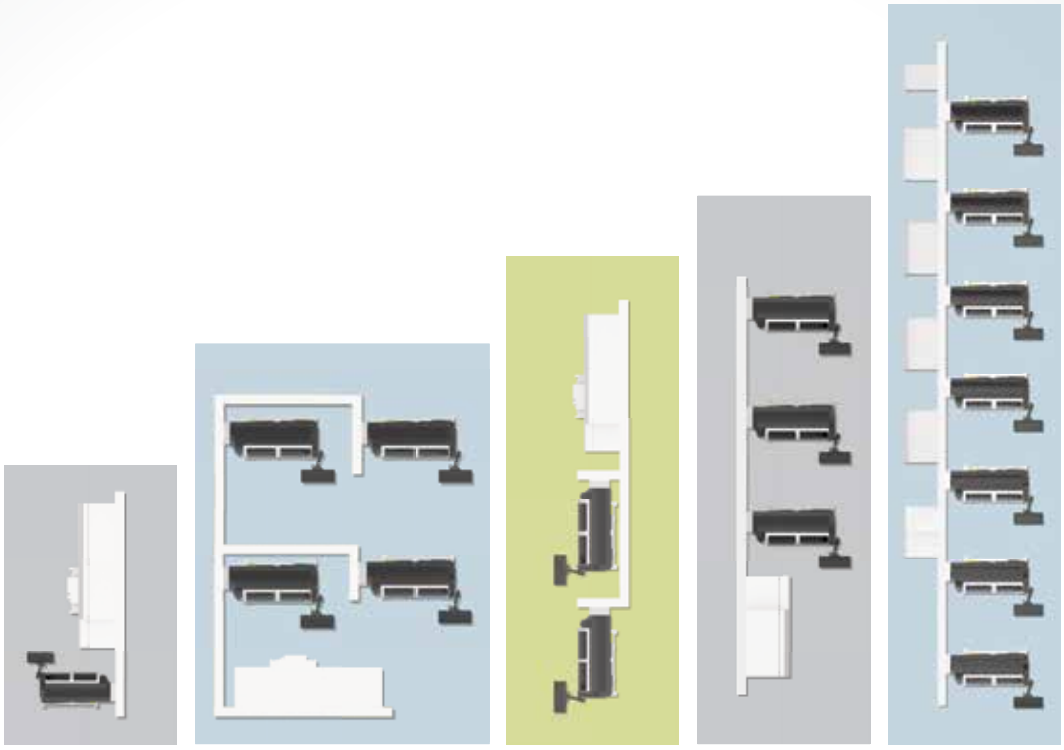

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Regulatory Roundup

FDA clears acute infection and sepsis test

Inflammatix recently announced Food and Drug Administration marketing authorization for its TriVerity Test System for patients with suspected acute infection or sepsis.

Using precise measurements of a patient's immune response, TriVerity combines highly accurate bacterial-viral infection scoring with an all-cause illness severity risk evaluation, giving clinicians a rapid, holistic snapshot of a patient's status.

TriVerity measures the expression levels of 29 genes associated with the host immune response to infection. Using validated algorithms with artificial intelligence and machine learning, the test interprets host response information to give three scores for likelihood of bacterial infection, viral infection, and severe illness.

Because TriVerity provides a precise measure of infection likelihood and risk stratification, the test can help ease emergency department overcrowding and reduce length of stay for admitted patients, the company said.

In 2019, Inflammatix won the Association for Diagnostics & Laboratory Medicine's (formerly AACC's) Disruptive Technology Award for its rapid HostDx tests, which read the immune system to improve diagnosis of acute infections and sepsis.

FDA CLEARS MOLECULAR POINT-OF-CARE STI TESTS

Roche has announced Food and Drug Administration 510(k) clearance and a CLIA waiver for its cobas liat sexually transmitted infection (STI) multiplex assay panels.

The panels include PCR tests for chlamydia, gonorrhea, and *Mycoplasma genitalium* and provide results in 20 minutes. The tests have the potential to broaden access to accurate, easy-to-use diagnostics for patients in urgent care centers, retail clinics, and community health venues, Roche said.

Rapid molecular point-of-care testing could revolutionize clinical management of STIs — which are frequently asymptomatic — in decentralized and community-based healthcare settings, Roche officials added. The tests could enable more informed treatment strategies, better health outcomes for patients, and contain further spread by providing timely diagnosis.

QIAGEN MINI GASTROINTESTINAL PANEL GETS FDA CLEARANCE

Qiagen recently announced Food and Drug Administration clearance of its QIAstat-Dx Gastrointestinal Panel 2 Mini B.

The panel focuses on bacterial infections covering *Campylobacter*, *Salmonella*, Shiga-like toxin-producing *Escherichia coli* (STEC), *Shigella*, and *Yersinia enterocolitica*, all leading causes of gastrointestinal illness. The panel is designed to complement the QIAstat-Dx Gastrointestinal Panel 2 Mini B&V (Bacterial & Viral), which covers *Campylobacter*, *Salmonella*, STEC, *Shigella*, and *Norovirus*.

QIAstat-Dx Gastrointestinal Panel 2 Mini B runs on Qiagen's QIAstat-Dx system and leverages its ability to quickly multiply many genetic targets using real-time PCR technology in the same reaction, delivering results in about 1 hour and with less than 1 minute of hands-on time. Cycle threshold values and amplification curves provide laboratories with additional information in the context of

co-infections and are instantly viewable on the instrument touchscreen, with no additional software required.

SARS-COV-2 ASSAY GETS FDA CLEARANCE

The Food and Drug Administration granted 510(k) clearance to Hologic's Aptima SARS-CoV-2 assay.

The in vitro diagnostic test detects SARS-CoV-2 RNA from nasopharyngeal or nasal swab samples of people exhibiting signs and symptoms of a respiratory tract infection. Healthcare practitioners must perform the swabs.

The test uses Hologic's transcription-mediated amplification chemistry, which can detect and quantify genetic sequences to determine the presence of respiratory viral pathogens.

Samples are processed in Hologic's Panther system, which is used in labs across the United States and around the world, according to the company. Each Panther can provide initial results in less than 3 hours and process more than 1,000 tests in a 24-hour period. An additional Panther Fusion module can expand respiratory testing offerings.

FDA CLEARS BIOMÉRIEUX TESTS FOR GI PATHOGENS AND MICROORGANISM IDENTIFICATION AND ANTIBIOTIC SUSCEPTIBILITY

bioMérieux recently announced Food and Drug Administration 510(k) clearance for gastrointestinal and antibiotic susceptibility tests.

The Biofire Filmarray Gastrointestinal (GI) Panel Mid, a molecular panel, tests for 11 common bacteria, viruses, and parasites associated with gastroenteritis from one sample, with results available in approximately 1 hour. Designed for use on bioMérieux's Biofire Filmarray 2.0 and Torch PCR platforms, this panel requires about 2 minutes of hands-on time for setup, with an approximate run time of 1 hour.

Vitek Compact Pro is a system for microorganism identification and antibiotic susceptibility testing that will help clinical laboratories diagnose infectious diseases and combat antimicrobial resistance. The system will help industrial laboratories identify contaminants.

With an ergonomic design and a simplified workflow, Vitek is designed to improve overall efficiency by enabling laboratory technicians to spend less time on sample loading and processing. Ideally suited for small and medium-sized laboratories, it helps laboratories transition from manual workflows to automated ones, bioMérieux said.

POINT-OF-CARE RESPIRATORY TEST CLEARED WITH CLIA WAIVER

Visby Medical recently announced Food and Drug Administration (FDA) 510(k) clearance and a CLIA waiver for its Visby Medical Respiratory Health Test, a point-of-care assay that detects and differentiates between upper respiratory infections caused by influenza A and B and SARS-CoV-2.

The assay is the first rapid PCR, multiplexed, handheld test to receive these FDA designations after being granted Emergency Use Authorization in December 2022. The test fits in the palm of the hand and provides accurate results in under 30 minutes, according to Visby.

The test also enables clinicians to accurately diagnose and treat patients in remote care facilities and other resource-limited healthcare settings where centralized laboratory services are less accessible. Quicker diagnosis of patients with respiratory symptoms will help selection of the most appropriate treatments, the company said.

PANCREATIC CANCER TEST GETS NEW YORK APPROVAL

Clinicians in New York can now order a highly sensitive blood test designed to detect pancreatic cancer far earlier than conventional approaches.

ClearNote Health recently announced that the New York State Department of Health Clinical Laboratory Evaluation Program approved its Avantect Pancreatic Cancer Test.

The Avantect Pancreatic Cancer Test is for patients at high risk of pancreatic cancer, including those newly diagnosed with type 2 diabetes who are at least 50 years old, as well as those with a family history or a genetic predisposition.

The test was designed to detect pancreatic cancer in its earliest stages by profiling the epigenomic biomarker 5-hydroxymethylcytosine in cell-free DNA and combining that data with other genomic information. Unlike conventional methods, ClearNote's approach leverages the latest advances in machine learning and bioinformatics to provide a deeper understanding of the underpinnings of cancer development with unprecedented clarity, and to inform the next steps in a patient care pathway, ClearNote said.

Industry Playbook

Hims & Hers acquires at-home lab testing facility

The health and wellness company Hims & Hers Health recently announced plans to introduce at-home lab testing through its platform.

The company acquired an at-home lab testing facility, Sigmund NJ LLC, marketed as Trybe Labs. The acquisition will allow Hims & Hers to support at-home blood draws and more comprehensive testing, the company said.

The acquisition also allows Hims & Hers to offer a wide range of personalized treatments, supplements, and medications, while accelerating expansion into new clinical categories, including low testosterone, perimenopausal, and menopausal support, Hims & Hers added.

Using a blood lancet, customers will be able to learn more about their hormone levels, cardiac risk, stress markers, cholesterol, liver function, thyroid function, and prostate health.

Providers on the platform will then be able to use that information to help inform personalized treatment plans most appropriate for their individual patients, the company noted. Additionally, de-identified lab data will accelerate the company's artificial intelligence developments, including MedMatch by Hims & Hers. MedMatch models can identify real-time treatments that may be best suited for a patients' unique needs, the company added.

The new capability will help customers to take control of their health with deeper insights and enable providers to access a breadth of data and biomarkers that could help identify risk of disease before it develops, the company added. This in turn could facilitate more precise clinical decision-making.

DEAL FOCUSES ON MRNA BIOMARKERS FOR PANCREATIC CANCER BLOOD TEST

Mainz Biomed has entered into a license and option agreement with Liquid Biosciences to access a portfolio of novel mRNA biomarkers for detecting pancreatic cancer with a blood test, Mainz announced recently.

The companies plan to develop this blood-based test for potential future Food and Drug Administration (FDA) applications.

Under the agreement, Mainz has the rights to develop the test using Liquid's biomarkers through an exclusive license, with the unilateral option to acquire the exclusive global rights to the gene expression biomarkers.

These biomarkers have demonstrated a high degree of effectiveness in detecting pancreatic cancer. Coupled with Liquid's proprietary algorithm, they have an overall sensitivity of 95% and specificity of 98% for the detection of pancreatic cancer, Mainz said. The biomarker discovery process included multiple independent pancreatic cancer study cohorts. Using its proprietary Emerge platform, Liquid identified a panel of clinically relevant mRNA biomarkers from a blood-based cohort of 285 subjects, including 35 pancreatic cancer patients. Liquid further confirmed the biomarkers with two additional independent cohorts, confirming the strong clinical contribution of

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each biomarker shown in the initial discovery phase. Results will be replicated after integrating the biomarkers into a new product. It could potentially be a robust and accurate screening test for pancreatic cancer, Mainz said.

Mainz officials said the product could drive "a paradigm shift in how we can detect pancreatic cancer." They added that the two companies plan to develop this pancreatic cancer screening test jointly. That process will include enhancement of commercial assays, refinement of algorithms, and preparation for potential FDA application and approval.

The test can help providers diagnose aPAP earlier and avoid misdiagnoses.

FINGERPRICK TEST FOR RARE AUTOIMMUNE LUNG DISORDER LAUNCHED

Savara recently announced the U.S. launch of its aPAP ClearPath Dried Blood Spot (DBS) Test in the United States.

Using a fingerprick blood sample, the DBS test helps diagnose pulmonary alveolar proteinosis (aPAP), a rare autoimmune lung disease caused by antibodies that target granulocyte-macrophage colony stimulating factor (GM-CSF) protein. The disease involves abnormal build-up of proteins and lipids in the lungs' air sacs, causing impaired gas exchange. Clinical symptoms include shortness of breath, cough, fatigue, fever, chest pain, and coughing up blood. In the long-term, the disease can lead to serious complications, including lung fibrosis and the need for a lung transplant.

The DBS test has demonstrated a high correlation between levels of GM-CSF in dried and traditional serum samples and has achieved 100% analytical sensitivity in a cohort of individuals with confirmed GM-CSF autoantibody status, Savara said. Savara partnered with TrilliumBiO, which has a CLIA-certified lab, to develop and validate the test.

Savara officials said the test provides a convenient alternative to traditional venous blood draws. The test can help providers diagnose aPAP earlier and avoid misdiagnoses.

DEAL AIMS TO PROVIDE DIRECT-TO-CONSUMER EARLY DEMENTIA AND ALZHEIMER'S TEST

Neurogen Biomarking and Quanterix Corporation have announced an exclusive agreement to use antibody technology to measure a blood biomarker that serves as an early indicator of dementia and mild cognitive impairment (MCI) due to Alzheimer's disease (AD).

The agreement gives Neurogen Biomarking exclusive rights to commercialize Quanterix's ultrasensitive technology in direct-to-consumer testing in the United States, Europe, and Asia.

The partnership will leverage Quanterix's antibody technology to detect phosphorylated tau217 (P-tau217). Specifically, Neurogen Biomarking will use this technology to develop a care platform that includes an at-home blood test that measures P-tau217. A robust body of literature shows that P-tau217 levels in blood correlate strongly with AD pathology and disease progression, supporting its use as a reliable biomarker, according to Neurogen Biomarking.

The company's patient-initiated platform will also provide streamlined telehealth appointments with board-certified neurologists, offering health education and a complete Brain Health Plan with actionable next steps for personalized care.

Neurogen Biomarking expects to make its care platform commercially available in the second quarter of 2025 to people with memory and other cognitive challenges and people concerned about symptoms that may be associated with AD.

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Ask The Expert

What labs need to know about autoantibody testing for Graves' disease

By Damien Gruson, PhD, EuSpIm, FESC, FHFA, FADLM

What is testing for TSH receptor autoantibodies used for?

a: Thyrotropin and thyroid stimulating hormone (TSH) receptor antibodies (TRAbs) are central to the pathophysiology of Graves' disease (GD). They are directed against the TSH receptor (TSHR) on thyroid follicular cells and are categorized based on their effects. Thyroid-stimulating antibodies (TSAbs) activate the TSHR, mimic TSH, and drive excessive thyroid hormone production, while thyroid-blocking antibodies (TBAbs) inhibit TSH from binding.

TRAbs are invaluable in differentiating GD from other causes of hyperthyroidism. Beyond diagnosis, TRAbs also serve as a tool to predict disease prognosis and monitor therapy response. Elevated TRAb levels can signal active disease, while declining or absent TRAbs often indicate remission. This makes TRAb testing essential for tailoring long-term management strategies.

What TRAb assays are currently available?

Laboratories currently rely on three primary types of assays to measure TRAbs.

Competitive-binding immunoassays are the most commonly used because of their automation and accessibility. They measure TRAbs that compete with TSH or monoclonal antibodies for binding to the TSHR. Examples include TBII assays, which provide quantitative results for overall TRAb levels but do not differentiate between TSAbs and TBAbs.

There are also bridge-based immunoassays, which offer improved specificity and focus more on thyroid-stimulating immunoglobulins (TSI), which are directly associated with GD activity. They have better diagnostic accuracy in cases of ambiguous or borderline thyroid function tests but remain limited in availability compared with competitive-binding assays.

Cell-based bioassays evaluate the functional activity of TRAbs by measuring their biological effects, such as cyclic AMP production in response to receptor activation. While more informative, they are less widely adopted due to higher complexity and operational demands.

What are these assays' limitations?

Despite advancements in assay technologies, significant limitations persist. For example, traditional immunoassays, such as TBII, often face specificity challenges, failing to distinguish between stimulating and blocking antibodies. This is critical in cases where both types coexist, as seen during GD disease progression or therapy. Competitive-binding assays lack functional data, which is crucial for understanding the biological activity of TRAbs. Functional bioassays address this but are labor-intensive and less scalable.

The limited availability of novel methods presents another challenge for laboratories. While emerging bioassays show promise, their adoption is hindered by cost and logistical constraints.

What lies ahead for TRAb testing?

One growing trend is to consolidate TRAb testing with thyroid function panels on a single platform in order to enhance automation and integration. This streamlines the workflow and reduces turnaround times.

Efforts are underway to develop refined assays that selectively detect TSAbs. These tests would provide clearer insights into GD activity and progression, especially in complex clinical scenarios. Additionally, international scientific societies are working to standardize TRAb assay methodologies and reference ranges. This effort will improve comparability across laboratories and enable better clinical decision-making.

Lastly, artificial intelligence holds great promise for assay design and in silico modeling of antibody-receptor interactions, paving the way for next-generation assays that are highly sensitive and specific.

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Product Spotlight

Revolutionizing laboratory diagnostics: The DZ-Lite™ c270 analyzer

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The DZ-Lite™ c270 supports more than 80 CLIA-categorized tests, making it a valuable tool for labs striving to maintain high standards of accuracy and compliance. The combination of its versatility in testing and high throughput makes it an essential asset for laboratories seeking to streamline their workflow and reduce operational costs.

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