September 2021

CLN Clinical Laboratory News

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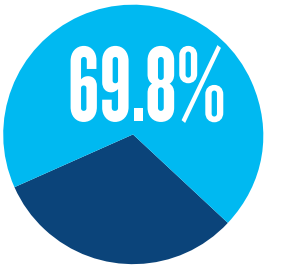
INAPPROPRIATE SARS-COV-2 TEST ORDERS



Orders that did not meet a laboratory's indications for rapid testing

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An IVD Investment Renaissance

New Guidance on Acute Kidney Injury

NGS Hype vs. Reality

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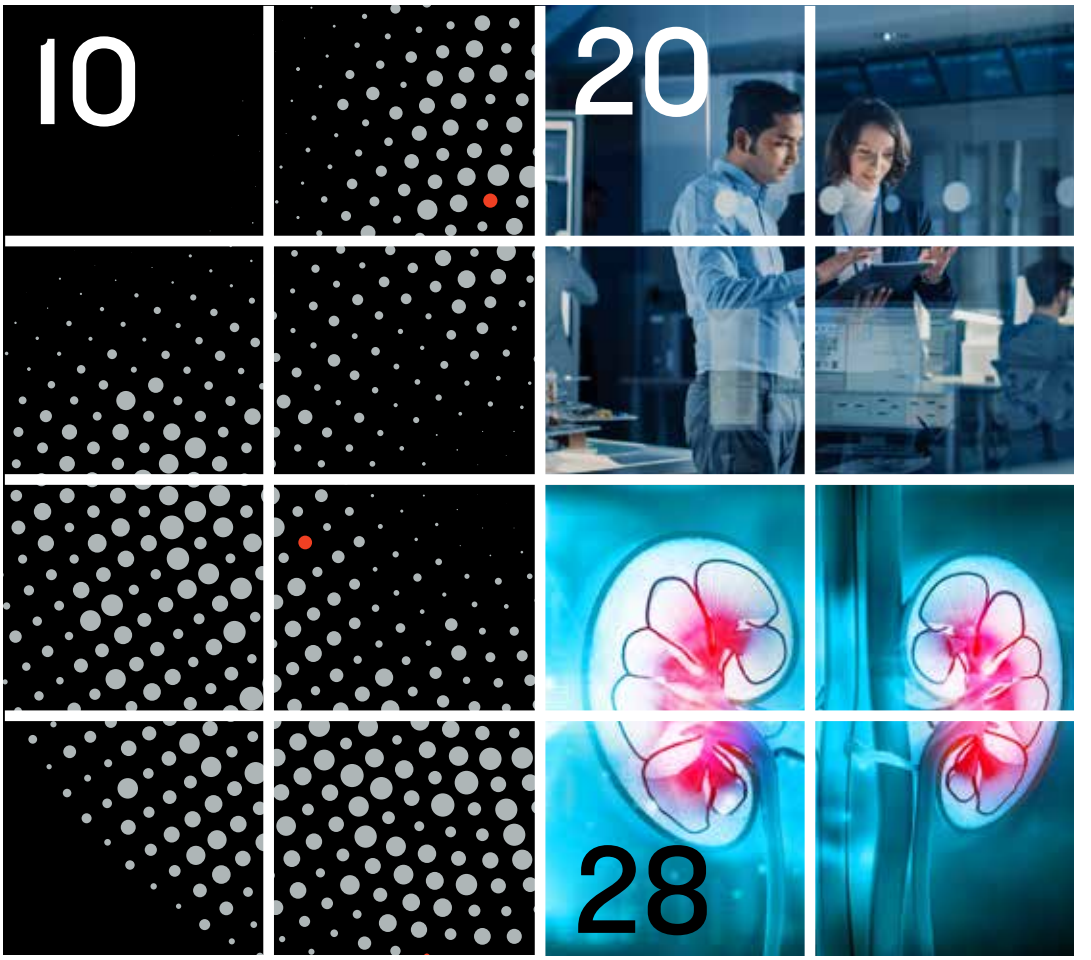
Features



Departments

"Analytically, the total AED level is less cumbersome, less costly, and less time-consuming to measure. Nevertheless, the free fraction most accurately reflects the active component of AEDs, and can be of clinical utility in certain scenarios."
p52

Federal Insider

Report: CDC Must Change Its Approach to Public Health Emergencies

A report from the Government Accountability Office (GAO) catalogues the Centers for Disease Control and Prevention's (CDC) failures that contributed to numerous problems with SARS-CoV-2 testing during the COVID-19 pandemic and makes recommendations for how the agency should overhaul its strategies.

A top recommendation is that CDC develop a plan with stakeholders to improve surge capacity for testing. This plan should cover timelines, agency and stakeholder roles and responsibilities, gaps from preparedness exercises, and more.

Key to the surge capacity plan will be a way to improve preparedness for test kit manufacturing. "Establishing contracts with test kit manufacturers in advance of a public health emergency could allow CDC to supplement the supply produced by CDC and aid in the rapid manufacturing and deployment of test kits during a future public health emergency," the report says. It underscored that "the agency did not have manufacturing contracts in place prior to the COVID-19 pandemic that could have supported the testing response."

While CDC did meet with public health and private laboratory organizations beginning in 2018, the report notes that CDC "has not yet developed a plan for enhancing laboratory surge testing capacity that identifies objectives and outlines agency and stakeholder roles and responsibilities for achieving these objectives within defined time frames."

The report lists numerous ways that CDC's response contributed to slower testing early in the pandemic. These include guidelines for who should be tested that were too narrow; poor communication with public health laboratories; selecting a testing platform for the CDC SARS-CoV-2 test that only 12 public health laboratories had available; and the critical quality control failures that led to CDC releasing a flawed test.

CDC has begun to deal with problems, however, and the report details several initiatives. Among them, CDC will require all tests it develops to have clearly defined approval criteria to avoid another flawed test, and will require CDC labs to be accredited. The agency is also promising to boost collaboration with laboratory stakeholders, survey laboratories to improve understanding of surge capacity, and work with contractors on test kits rather than doing the work in-house.

SEN. BALDWIN INTRODUCES DISEASE X ACT

Democratic Senator Tammy Baldwin of Wisconsin introduced legislation, the Disease X Act, that would fund countermeasures to combat future pandemics. The bill would provide $500 million per year for 4 years, starting in Fiscal Year 2022, for the Biomedical Advanced Research and Development Authority (BARDA) at the Department of Health and Human Services (HHS)

The bill envisions a Disease X Medical Countermeasures Program aimed at developing responses to unknown viral threats. BARDA would work with public health agencies to leverage expertise across the government to inform a strategic approach to medical countermeasures development.

The bill calls for HHS and the Department of Defense (DOD) investment strategies to work together, with HHS leading on products needed to protect the public and DOD taking the lead on products for military personnel.

"Infectious disease outbreaks now occur three times more often than they did 40 years ago. The next pandemic, driven by an unknown Disease X, will come," said Senator Baldwin. "We should not be waiting for the next viral threat to emerge. We must invest in the development of novel antivirals, vaccines, and diagnostics for unknown threats now so that we are better prepared to control the spread than we were at the start of the COVID-19 pandemic."

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Bench Matters

Urine Reflex Testing: Why and How?

By Yi Xiao, PhD

Allison B. Chambliss, PhD, DABCC, FAACC

Urinalysis (UA) commonly consists of physical, chemical, and microscopic evaluations with increasing complexity, cost, and turnaround time. UA is also multidisciplinary in that it may be performed in the core lab or by point-of-care and may be a manual or automated assay. Bacteria causing urinary tract infections (UTIs) may further be identified and characterized by urine cultures in the microbiology lab.

To boost efficiency, many laboratories have implemented reflex testing approaches. If paired with carefully designed electronic order options and clinical decision-support systems, this strategy has the potential to optimize test utilization, improve result turnaround times, and reduce laboratory costs for reagents and labor.

Reflex testing generally takes two forms. In reflex-to-microscopic approaches, the laboratory first performs a chemical UA to detect abnormalities such as blood, protein, glucose, and indirect indicators of bacterial infection (e.g., leukocyte esterase and nitrite). Abnormal chemical UA results then trigger subsequent microscopic UA to look for cells, bacteria, yeast, casts, and crystals. Some laboratories also use a reflex-to-culture approach and only perform urine cultures if infection-relevant chemical or microscopic UA findings, or both, are detected.

Our hospital system's leadership was interested in implementing a reflex-to-culture approach to reduce the reporting of clinically insignificant catheter-associated urinary tract infections (CAUTI), alleviate misinterpretation or over-interpretation of clinically insignificant positive culture results, and support antibiotic stewardship. However, there are currently no evidence-based guidelines on how to define UA reflex criteria or implement reflex approaches.

Validating Urine Reflex Criteria

Although UA reflex approaches are now widely used and discussed in the literature, data involving modern automated UA methods is limited. While most studies that investigated reflex-to-culture criteria compared manual microscopy results to urine culture results, we were interested in implementing a compounded reflex approach—chemical UA with reflex-to-microscopic UA for general UA orders, and chemical UA with reflex-to-microscopic UA followed by reflex-to-culture for reflex culture UA orders. We also wanted to use an automated UA system as the primary UA method.

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We performed our own retrospective study to determine how well chemical UA and microscopic UA results compared with each other and with urine culture results. Our goal was to estimate the significance of the diagnoses that would be missed and the numbers of microscopic UA and cultures that could be avoided by our proposed reflex UA approaches.

Using our proposed reflex-to-microscopic reflex criteria (hazy or cloudy appearance, positive hemoglobin, glucose ≥1,000 mg/dL, positive protein, positive leukocyte esterase, or positive nitrate), the chemical UA showed a sensitivity of 93%, specificity of 57%, and negative predictive value of 91% for positive microscopic UA results, defined as red blood cell or white blood cell (WBC) count ≥ 4/hpf or any detectable presence of bacteria (J Appl Lab Med 2020; doi:10.1093/jalm/jfaa011). A reflex-to-microscopic approach would have led to a 34% reduction in the number of microscopic UA performed, and the frequency of missed positive microscopic UA was 3%. Of the samples with urine culture results available (n=3,127), 6% were negative for all chemical UA criteria but had clinically significant positive urine cultures, indicating fairly good performance of negative chemical UA alone in ruling out culture-positive UTIs. Based on our data, along with support from the literature, we ultimately decided to implement a standardized reflex-to-microscopic approach using the aforementioned criteria and to use WBC count ≥ 10/hpf for implementing a new reflex-to-culture approach.

Workflow Challenges and Clinical Considerations

Standardizing the urine reflex testing workflow across our health system yielded many lively discussions about sample collection and transportation between laboratory areas. One major issue we had to tackle first was the urine specimen container. Some of our hospitals already used a urine collection kit with a boric acid preservative tube for culture, while others used standard urine collection cups. Because the UA would have to be performed and resulted prior to determining whether the urine culture should be started, all of our laboratories had to switch to the standard collection kit.

We also debated whether the preemptive urine culture tube should be held in the core lab or the microbiology lab, and how to alert the microbiology lab of the need to perform the culture. We decided that having a new specimen label for urine culture automatically printed in the microbiology lab upon a positive UA result would be a good trigger.

Laboratories setting up their own urine reflex workflows should keep their specific patient populations in mind. Importantly, complete UA and urine culture should typically be concurrently tested for pregnant women, neonates, and immunocompromised individuals regardless of chemical or microscopic UA results. Our laboratories designed a clinical decision support message (pop-up alert) on the reflex-to-culture order in the electronic order system to inform clinicians of which patient populations should have urine culture ordered directly instead. Similarly, the standalone urine culture order, if visible to providers, may include an alert indicating its appropriate criteria. Other laboratories have described having multiple order options for different patient populations, such as microscopic UA and urine culture reflexed simultaneously for neutropenic patients.

Overall, it is important to keep key clinical stakeholders involved: Our planning involved frequent communication with leadership in infectious diseases, infection prevention, hospital quality, and patient safety. Successful urine reflex testing workflows require a balance of stewardship enforcement with room for clinical judgement. Finally, although our labs can appreciate the reduction in labor, improvements in patient outcomes or CAUTI rates remain to be determined.

Acknowledgements

The authors would like to thank the laboratory directors and staff of the Los Angeles County Department of Health Services for the many fruitful discussions surrounding reflex urinalysis approaches. In particular, we thank Tam Van, PhD, for providing data and data analysis. We also thank Melanie Yarbrough, PhD, for her critical review of this article.

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The Sample

Rapid SARS-CoV-2 Test Orders Found Inappropriate

An audit of rapid SARS-CoV-2 real-time reverse transcription-polymerase chain reaction (RT-PCR) test orders at a tertiary medical center reveals widespread inappropriate ordering and the need for better guidance for clinicians, a recent paper said.

A retrospective review of the first 500 orders for the rapid Xpert Express SARS-CoV-2 RT-PCR over two weeks found that 69.8% of the orders did not meet the institution lab's indications for rapid testing. The indications included emergency surgery, emergent obstetric procedures, behavioral health admission, pediatric admissions, and discharge to skilled care facilities (J Appl Lab Med 2021; doi: 10.1093/jalm/jfab081).

The majority of inappropriate orders were indicated for acute emergency surgery. But 49% of patients with these orders never had surgery. Also, 79% of these orders came from the trauma or emergency departments and had no other indication for testing.

Orders were also inappropriate in about 77% of indicated obstetrics cases, 68% of indicated behavioral care cases, and 35% of cases of patients indicated for testing for discharge to skilled care facilities. In contrast, the researchers deemed tests for all pediatric indications appropriate.

Although the study did not examine specific reasons for inappropriate test orders, previous studies note that they often arise from providers' lack of knowledge.

In the current study, inappropriate orders may have resulted from clinicians seeing a potential need for emergent surgery for traffic accidents and gunshot injuries, the researchers postulate. However, hospital guidelines direct clinicians to order SARS-CoV-2 tests only after patients are definitively scheduled for surgery.

The findings show an opportunity for laboratory stewardship, the researchers added. They suggested that the electronic health record could be used to give evidence for the indications and to educate clinicians to direct tests appropriately and flag or stop inappropriate orders.

BLOOD TEST PROPOSED FOR EARLY DETECTION OF ALZHEIMER'S DISEASE

Comprehensive profiling of the Alzheimer's disease (AD) plasma proteome could serve as a foundation for a blood-based AD test, according to a recent paper.

The authors developed a scoring system that distinguishes AD patients from healthy people based on a biomarker panel with 19 plasma proteins. The panel and scoring system identified AD patients with more than 96% accuracy (Alzheimers Dement 2021; doi: 10.1002/alz.12369).

The researchers quantified 1,160 plasma proteins in a Chinese cohort of 106 patients with AD and 74 healthy controls via high-throughput proximity extension assay (PEA). They validated the results in an independent cohort. In the subgroup analysis, the researchers used plasma biomarkers for amyloid, tau, phosphorylated tau, and neurodegeneration as endophenotypes of AD.

The researchers found 429 dysregulated proteins in AD patients' plasma. They selected 19 "hub" proteins as representative of the AD plasma protein profile: KLK4, CD8A, LIF-R, hK14, AOC3, GSAP, NELL1, GAMT, CD164, LGMN, VPS37A, VAMP5, NFKBIE, TMSB10, PRKCQ, PRDX1, CASP-3, CETN2, and LYN. These hub proteins formed the basis of the scoring system, which accurately classified clinical AD with area under the curve equal to 0.9690–0.9816.

Specific hub proteins showed disease-stage-dependent dysregulation, which can delineate AD stages, the researchers wrote. However, it remains unclear whether the biomarkers sufficiently capture the whole signature of the AD blood proteome.

Comprehensive profiling of the AD plasma proteome might help clarify the signatures of AD blood and disease staging, the researchers wrote. They called for prospective longitudinal studies of mild cognitive impairment, AD, and other neurodegenerative diseases to determine the panel's specificity.

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1. Giannella, Maddalena, et al. "Antimicrobial and Resource Utilization with T2 Magnetic Resonance for Rapid Diagnosis of Bloodstream Infections: Systematic Review with Meta-analysis of Controlled Studies." Expert Review of Medical Devices (2021).

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POSSIBLE PANCREATIC CANCER BIOMARKER PROPOSED

A recent study suggested that the protein pentraxin 3 (PTX3) may be a specific diagnostic biomarker for pancreatic ductal adenocarcinoma (PDAC) (npj Precis Onc 2021; doi: 10.1038/s41698-021-00192-1).

Computed tomography (CT) scanning is usually used for diagnosis of pancreatic cancer in general. Although CT can detect the presence of a pancreatic mass, it cannot distinguish pancreatic cancer from other non-cancerous pancreatic diseases. This situation poses frequent diagnostic dilemmas in clinical practice and drives the need for biomarkers for early detection of PDAC.

The researchers measured serum PTX3 via an enzyme-linked immunosorbent assay in serum from 140 patients who donated blood when they were diagnosed with PTX3 and 127 controls who were either healthy volunteers or diagnosed with other conditions, including pancreatitis, intra-ductal papillary neoplasms, and gallstones.

The researchers determined that PTX3 concentration above 4.34 ng/mL had a sensitivity of 86%, specificity of 86%, positive predictive value of 97%, and likelihood ratio of 6.05 for PDAC. They add that this profile is superior to CA 19-9 and carcinoembryonic antigen (CEA) for detecting PDAC.

In in vitro and ex vivo analysis of PTX3 in human PDAC, cell lines and a transgenic mouse model for PDAC suggest that PTX3 is released from stroma cells, mainly in primary sclerosing cholangitis (PSC), the researchers added. In activated PSC, PTX3 secretion might possibly be downregulated by making PSC inactive using all-trans-retinoic acid (ATRA).

PTX3 organizes hyaluronan in conjunction with the gene TSG-6 and facilitates stellate and cancer cell invasion. A previous trial has shown PTX3 had no prognostic or predictive role in testing chemo-radiotherapy without stromal targeting. In another trial, stromal modulation by ATRA even at first dose is accompanied with serum PTX3 response in patients who later go on to demonstrate disease control, but not those in whom the disease progresses.

The researchers call for further testing of PTX3 in prospective, larger, multicenter cohorts and within clinical trials that target stroma.

Further analysis conducted by the team in human PDAC samples, pancreatic cancer cell lines, and a mouse model of pancreatic cancer confirmed that PTX3 is, indeed, released predominantly from pancreatic stellate cells when they have been activated in response to signals from cancer cells.

In a multicenter European cohort, the researchers measured PTX3 in serum from patients who donated blood when they were diagnosed and untreated for PDAC, as well as controls diagnosed with other conditions including pancreatitis, intraductal papillary neoplasms, and gallstones.

The researchers found that serum PTX3 levels about 4.34 ng/mL have a sensitivity of 86%, specificity of 86%, positive predictive value of 97%, and likelihood ratio of 6.05 for detection of PDAC. These characteristics are superior to those of serum 19-9 and CEA for detection of PDAC, the researchers wrote.

Next-Generation Sequencing for Infectious Diseases Diagnostics

BY HUANYU WANG, PHD, D(ABMM)
AND SOPHONIE JEAN, PHD, D(ABMM)

—Is It Worth the Hype?

The technology has changed how we respond to outbreaks like the COVID-19 pandemic, and evidence is building for clinical use.

Molecular diagnostic methods have undergone explosive growth in the last decade and play an increasingly important role in clinical microbiology laboratories. These methods can rapidly detect the presence or absence of nucleic acids from organisms in a specimen without waiting for growth from culture. Real-time polymerase chain reaction (PCR), the most commonly used molecular diagnostic in clinical microbiology laboratories, amplifies pathogen-specific nucleic acids, allowing for detection and quantification of a pathogen's genetic material in a specimen with high sensitivity and specificity. PCR-based tests have been developed further into multiplex assays that allow for simultaneous detection of several agents. However, even multiplex PCRs can only identify predefined targets, so one must have suspect organisms or targets in mind in order to detect them.

Next-generation sequencing (NGS)-based tests present the possibility of an agnostic diagnostic method capable of comprehensive detection of multiple pathogens simultaneously and directly from a patient sample. Despite the incredible promise of NGS-based tests for infectious diseases, the question remains whether we are able to overcome significant hurdles to make this testing relevant on a wider scale.

WHAT IS NGS?

In the past three decades, many NGS platforms have emerged that enable high-throughput massively parallel sequencing of thousands to billions of DNA fragments. This is in contrast to the single DNA sequences generated with first-generation Sanger sequencing methods that are used to identify unknown microbes present in a clinical sample or resolve mutations in known genes. Sanger sequencing can be difficult to interpret when performed on complex or polymicrobial samples, so it is usually only performed on pure microbial isolates or clinical samples that are normally sterile.

A major advantage of NGS compared with PCR is that prior knowledge of the target organism(s), and thus target-specific primers, is not required. NGS can also generate sequences of numerous pathogens in one sequencing

run, and reliably identify multiple organisms that may be present in one specimen. In recent years, both the instrumentation and the running costs of NGS have decreased significantly, making it more suitable for clinical usage. The differences in molecular approaches for diagnosis of infectious diseases are summarized in Table 1.

In NGS, genomic material in a clinical specimen or isolate is fragmented, randomly amplified, and used to prepare a library of genomic fragments that are then sequenced. The sequencing method varies by different NGS platforms. Two commonly used sequencing platforms are Illumina and Ion Torrent. Illumina uses sequencing by synthesis during which a fluorescence signal is created when a nucleotide is incorporated, while Ion Torrent sequencers measure the changes in pH generated during incorporation of nucleotides. The signals generated from fluorescence or pH changes for each genomic fragment are independently and simultaneously recorded and translated into nucleotides (A, C, G, or T). Using bioinformatics software, the sequenced fragments are then assembled with or without (de novo assembly) the use of a reference sequence.

Nanopore also has emerged as an attractive sequencing platform. Unlike Illumina and Ion Torrent platforms, Nanopore allows sequencing of a single strand of DNA with a maximum length of up to a few hundred thousand base pairs without active DNA synthesis. The signal of ionic current changes is recorded when the single-stranded DNA passes through a protein nanopore and is translated into nucleotides. This enables direct, real-time analysis of DNA or RNA fragments and a reduction of sequencing time from days to hours. Nanopore's MinIONs sequencer is particularly attractive because despite its small device size and low equipment cost, it maintains good performance in pathogen detection and surveillance.

NGS-based WGS is a powerful tool for rapid discovery of novel pathogens, which has changed how we can respond to outbreaks like the COVID-19 pandemic.

PRACTICAL APPLICATIONS OF NGS

Major applications of NGS in clinical microbiology laboratories include: whole genome sequencing, metagenomic NGS (mNGS), and targeted NGS (tNGS). WGS is the sequencing and assembly of an entire microbial genome directly from a specimen or clinical isolate. A common application of WGS is the simultaneous identification and typing of microbial pathogens for hospital and public health epidemiological studies. It provides better resolution and more information when compared to sequencing by the Sanger method or traditional pulse field gel electrophoresis (*1*). In addition, WGS from clinical isolates, particularly for gram-negative bacteria and members of the *Mycobacterium tuberculosis* complex, is a powerful tool to detect and characterize resistance markers.

Finally, WGS is an important tool for emerging pathogen detection and characterization. In December 2019, lower respiratory specimens from a cluster of patients with pneumonia of unknown cause all linked to a seafood market in Wuhan, China, were collected and underwent WGS. Bioinformatic analysis revealed that sequences from these samples were of an unknown pathogen that matched the genome of lineage B betacoronaviruses, including SARS-CoV. This virus was later named SARS-CoV-2. Without NGS-based WGS technology, it would have taken weeks to months to culture the virus for identification. Thus, NGS-based WGS is a powerful tool for rapid discovery of novel pathogens, which has changed how we can respond to outbreaks like the COVID-19 pandemic.

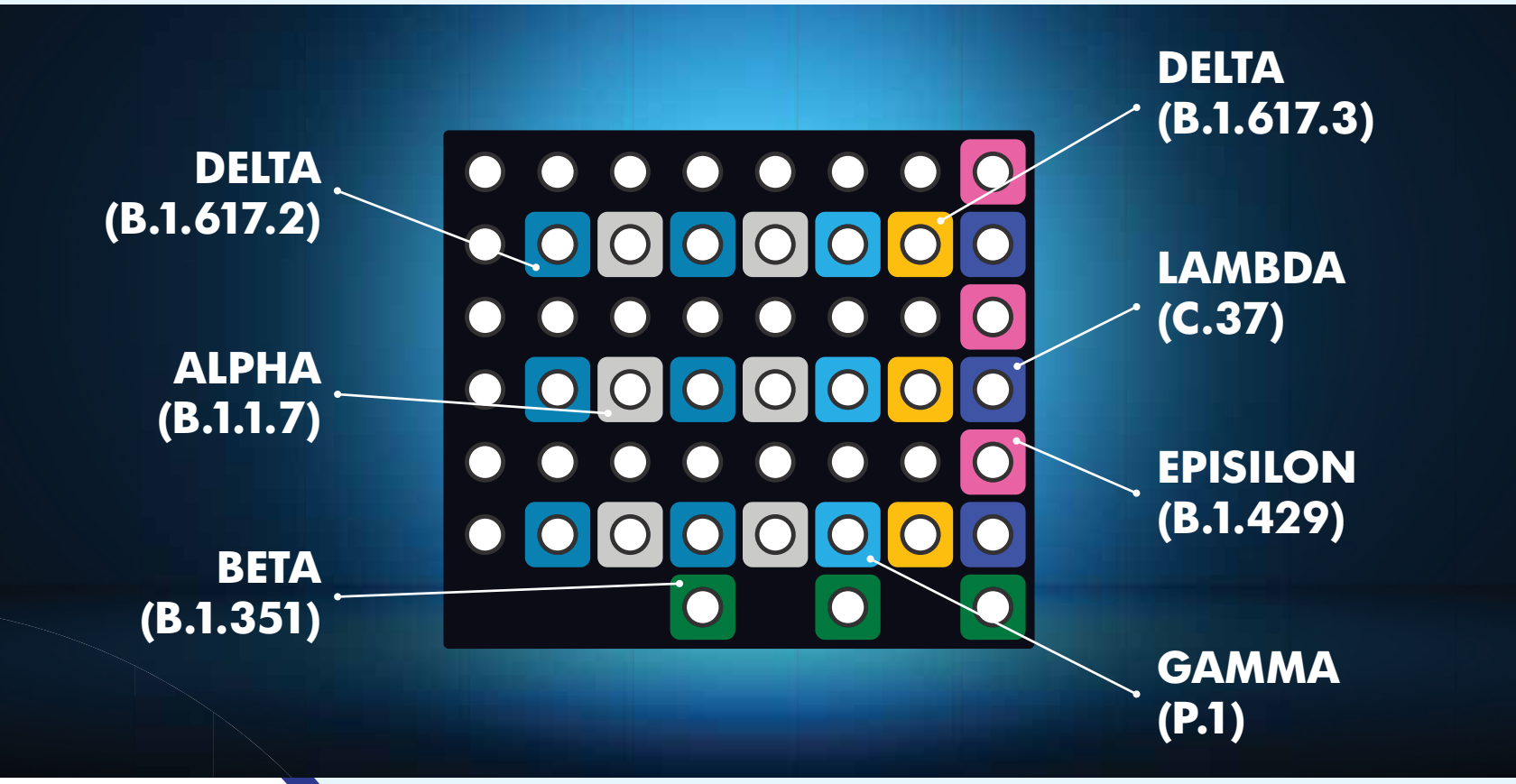
Metagenomic NGS (mNGS) allows for sequencing all the nucleic acids directly from patient specimens including pathogen and human DNA and RNA without culture. This method provides an unbiased detection of all microbial groups, resistance markers, and virulence factors, as well as host biomarkers associated

T1 Comparison of Molecular Methods for Diagnosis of Infectious Diseases

	Real-time PCR	Sanger Sequencing	Targeted Next-Generation Sequencing (tNGS	Metagenomic Next-Generation Sequencing (mNGS)
Prior knowledge of the target[1]	Yes	No[2]	No[2]	No
Enrichment of the target	N/A	Yes	Yes	No
Direct detection from clinical sample or microbial isolate required	Direct from sample or microbial isolate	Normally sterile sample2 or microbial isolate	Direct from sample or microbial isolate	Direct from sample or microbial isolate
Turnaround time	< 8h	< 8h	1-7 days	1-7 days
Relative ease of in-house implementation	Low	Low to Moderate	Moderate to High	High
Example of clinical application	Target-specific PCRs (i.e., *Mycoplasma pneumoniae*, methicillin-resistance in *Staphylococcus aureus*)	Microbial identification and strain typing (i.e., 16S rDNA sequencing)	Broad range PCR (i.e., universal fungal PCR)	Unbiased pathogen detection (i.e., Karius)

Abbreviations: not applicable—n/a.
[1] Target may be a microorganism or a gene of interest.
[2] Requires knowledge of potential pathogens group (i.e., bacteria, fungi, viruses, or parasites).

IT'S TIME FOR A SPIKE IN THE WORLD'S ABILITY TO IDENTIFY THE LATEST COVID-19 VARIANTS.



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with different disease states. Prior knowledge of a potential pathogen is not required for this type of diagnosis. Clinical tests have been developed to detect the nucleic acids of microbes from various specimen types such as blood, joint fluid, and cerebrospinal fluid (CSF) to aid the diagnosis of various infections (*2*,*3*). A significant limitation of mNGS is that most of the nucleic acids in clinical samples are from the host, so the host genome dominates sequence reads. This can result in decreased analytical sensitivity for detection of pathogens present at relatively low burden.

mNGS was used to diagnose a case of neuroleptospirosis in a 14-year old, immunocompromised boy with meningoencephalitis after 4 months of illness and negative conventional test results.

TNGS uses a process to enrich for microbial sequences of interest before library preparation to improve analytical sensitivity. The most common enrichment method for clinical applications is amplification of a highly conserved region of bacteria or fungi before sequencing. For example, in tNGS for bacteria, the primers are designed to detect and amplify the 16S ribosomal RNA gene, present in all bacteria. Another example of this enrichment method is the use of PCR to first enrich for SARS-CoV-2 RNA in clinical samples before performing NGS to detect mutations of the viral genome. This technique also can be used to detect mutations associated with resistance in viruses such as HIV, hepatitis B, and cytomegalovirus directly from clinical samples with high sensitivity. The enrichment step amplifies the nucleic acids of the target to millions of copies, significantly increasing the number of target-specific sequencing reads when compared with mNGS, where the majority of the sequence reads are from the host genome.

WHAT NGS-BASED TESTS ARE CURRENTLY AVAILABLE?

To date, no NGS-based tests for diagnosis of infectious diseases have received premarket approval or 510(k) clearance from the U.S. Food and Drug Administration (FDA). However, several laboratory-developed, NGS-based tests for pathogen detection directly from patient samples are available under CLIA certificates at select commercial and reference laboratories. A selection of these tests is listed in Table 2. While not an exhaustive accounting of all NGS tests currently available or in development, the most popular NGS-based tests for infectious disease diagnoses are discussed below.

TNGS tests for pathogen detection directly from clinical samples are available from several reference labs. These tests, usually called "universal" or "broad range" PCR, begin with amplification of genes such as the 16S rRNA region for bacteria or the internal transcribed spacer (ITS) region for fungi using universal primers. The amplified gene is sequenced, and results are compared to known sequences in curated databases for organism identification. This testing is available for samples from normally sterile sites (CSF, sterile body fluids, tissues, etc.), and has been useful in patients with high suspicion or evidence of an infectious process on histopathology, but with negative cultures or conventional tests. Universal PCR testing can be particularly useful for detection of fastidious or uncultivable organisms, such as *Bartonella* or *Mycoplasma*, in deep-seated infections such as endocarditis, osteomyelitis, and native/prosthetic joint infections (*4*).

The mNGS Pathogen Dx test from the Department of Clinical Microbiology at University of California, San Francisco was the first described clinical mNGS test for unbiased pathogen detection directly from patient samples. This test detects bacterial, fungal, parasitic, and RNA and DNA viruses from CSF samples, and is available to external clients. In a landmark case, first reported in 2014, mNGS was used to diagnose a case of neuroleptospirosis in a 14-year-old immunocompromised boy with meningoencephalitis after four months of illness and negative conventional test results (*5*). In clinical validation studies, this test was reported to have clinical sensitivity and specificity of 73% and 99%, respectively, for pathogen diagnosis compared to conventional clinical testing (*6*).

The Karius Test, which detects microbial cell-free DNA from blood

T2 Selected NGS-based Tests for Pathogen Detection Directly From Clinical Specimens

Test name	Testing laboratories	Sample type	Methodology	Analytes detected	Reporting	Reference
Broad Range Bacterial PCR and Sequencing	Mayo Clinic Labs University of Washington	Sterile sites, tissue (fresh and formalin fixed paraffin embedded)	tNGS[1]	Bacteria, Mycobacteria	Qualitative[2]	4
The Karius Test	Karius (Redwood City, CA)	Plasma	mNGS	> 1,000 Bacteria, fungi, parasites, DNA viruses	Quantitative, DNA molecules/µL (MPM)	7
mNGS Pathogen Dx	University of California San Francisco Clinical Microbiology Laboratory	CSF	mNGS	Bacteria, fungi, parasites, DNA/RNA viruses	Qualitative	6

[1] NGS testing may be reflexive from Sanger sequencing if results are inconclusive or indicate multiple organisms.
[2] Varies by performing laboratory. Some reports may be semi-quantitative if multiple organisms are detected.

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plasma samples, is among the most popular commercially available NGS tests. This test has two major advantages: sample type and turnaround time. First, the Karius Test is performed on plasma, an abundant, easy-to-collect, and noninvasive sample, unlike CSF or surgically collected samples. The use of plasma is based on the premise that during sepsis or serious infections, fragments of nucleic acids from the offending pathogen are shed into the bloodstream. Thus, microbial cell-free DNA in plasma can be a marker, not only for bloodstream infection or sepsis, but also other serious infections such as pneumonia, deep-seated abscesses, endocarditis, etc.

Secondly, the Karius Test has a stated turnaround time of 2 working days from sample receipt. While there may be delays due to shipping, this is generally shorter than most culture-based or reference/send-out laboratory tests. The Karius Test can detect more than 1,000 bacteria, fungi, parasites, and select DNA viruses. Detected microorganisms are reported quantitatively as DNA molecules per microliter of plasma (MPM), and are compared to reference MPM ranges established in healthy, asymptomatic individuals. In an initial clinical validation study of 350 emergency department patients meeting sepsis alert criteria, this test had a sensitivity of 92.9% when compared with a composite reference standard including microbiological testing and clinical adjudication (*7*).

CLINICAL UTILITY OF METAGENOMIC NGS TESTS FROM PATIENT SAMPLES

There is no prospective controlled clinical trial data evaluating the utility of NGS-based tests for agnostic pathogen detection directly from clinical specimens. Most available publications are case reports or retrospective studies comparing the results of diagnostic NGS tests to standard of care testing. Patient outcome data are often not included, making it difficult to ascertain the clinical impact of this testing. Theoretically, agnostic mNGS may offer a significant advantage over conventional testing in specific patient populations, such as the immunocompromised, in whom obscure or rare pathogens may be disease causing or in specimens from patients previously treated with antimicrobials, where culture-based testing may be falsely negative.

While numerous case reports have described diagnoses made from mNGS that otherwise would have been missed using conventional testing, when evaluated systemically, the clinical utility of mNGS tests remains questionable. Several independent retrospective studies have now reported limited utility of both CSF and plasma mNGS assays for unbiased pathogen detection.

Recently, a large, single-center retrospective study of CSF samples submitted for mNGS reported an overall positivity rate of 15% (12/80). Of the 12 positives, only five were deemed potential pathogen detections. Patient outcomes were only available for three out of five patients with potential pathogens, two of which had changes in management due to mNGS results (*8*). The results of this study are in contrast to a multicenter prospective clinical study evaluating the clinical impact of CSF mNGS in 204 pediatric and adult patients, where mNGS detected 55% of infections, with 22% being solely detected with mNGS (*9*). In this multicenter study, 54% of solely mNGS diagnosed infections directly impacted management and treatment decisions of the treating physicians (*9*). These contrasting results suggest that the clinical impact of mNGS from CSF can be quite variable across institutions and patient populations. In patients with CNS disease and high suspicion of infection despite negative microbiologic tests, mNGS from CSF may be beneficial, but additional studies are needed to identify optimal utilization criteria.

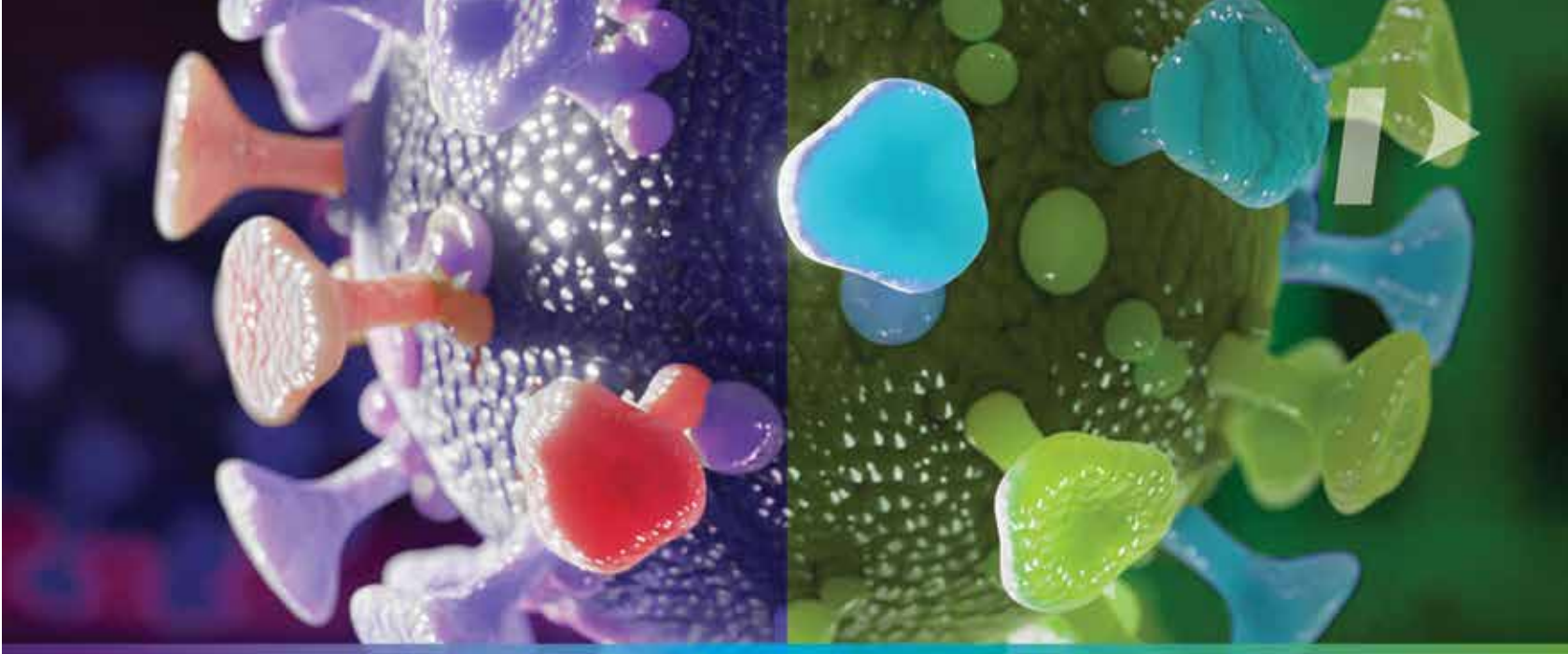
More data evaluating the real-world clinical impact of plasma mNGS is now available. In a multicenter retrospective study of a cohort of 82 patients, including children and immunocompromised patients, the Karius Test was only positive in 61% of cases, and only affected patient management in 11% of cases (*10*). This was due to a majority of cases positive for microorganisms being deemed non-contributory to the infectious process or confirmation of diagnoses from conventional test results. Similar studies from single-center pediatric institutions also found low overall performance that rarely resulted in changes to antimicrobial management with plasma mNGS when compared to conventional testing (*11,12*).

While the studies mentioned above included both immune competent and immunocompromised patients, there does appear to be a trend toward greater clinical utility of plasma mNGS in highly immunocompromised patients, particularly those at high risk for invasive fungal infection (IFI). This may be due, in part, to the lack of sensitive diagnostics capable of timely detection of the opportunistic pathogens, to which this patient population is uniquely susceptible (*13*).

While numerous case reports have described diagnoses made from mNGS that otherwise would have been missed using conventional testing, when evaluated systemically, the clinical utility of mNGS tests remains questionable.

Importantly, all major studies evaluating plasma mNGS report missed detections compared to conventional testing. While some missed detections are inherent to the test limitations (e.g., detection of RNA viruses by DNA sequencing-based tests), others have occurred with "claimed" organisms capable of being detected by the test, such as *Staphylococcus aureus, Candida* spp., *Mycobacterium tuberculosis*, nontuberculous mycobacteria, and DNA viruses (HSV, adenovirus) among others (*10,11*). This underscores that mNGS is not sufficient to replace traditional testing methods, and should always be performed in addition to conventional testing.

At more than $2,000 per test billed directly to the patient, the cost associated with mNGS should not be overlooked, especially since this testing is additive to current standard of care diagnostics. As such, indiscriminate use of mNGS coupled with low rates of clinically significant or actionable results can lead to a relatively low return on investment.



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Another limitation of mNGS-based diagnostics for infectious diseases is the decreased clinical specificity due to the detection of commensal microorganisms. Studies with both the CSF and plasma mNGS tests have reported clinical false-positives deemed to be unlikely causes of the disease presentation by the clinical care team or reviewing specialists (*8,10,11*). In rare instances, the results of mNGS tests can lead to unnecessary treatment or additional diagnostic investigations (*10*).

Finally, molecular detection alone does not yield antimicrobial susceptibility information. This may limit the ability to target antimicrobial therapy and inadvertently extend utilization of broad-spectrum antimicrobials. All of these concerns highlight the importance of performing these tests in consultation with specialists in infectious diseases, clinical microbiology, and pathology to appropriately adjudicate the clinical significance of findings and determine their effect on patient management.

CURRENT LIMITS TO IMPLEMENTATION

Overall, use of this technology as a clinical diagnostic is still in its infancy. While it remains potentially powerful, more studies are needed to determine best use and interpretation of results. To date, mNGS tests are limited to select reference laboratories, as the instrumentation and technical expertise are not yet available to most clinical labs. Furthermore, guidelines for method validation, interpretation, and evaluation/proficiency testing have been proposed but are not yet standardized across the discipline, limiting widespread implementation.

Improvements to NGS technology that further reduce costs and the availability of commercial bioinformatics tools also will timulate more widespread test development. Such development can lead to future applications, including mNGS tests for other sample types. Already mNGS research tests for diagnosis of pneumonia using lower respiratory samples and prosthetic joint infection from joint fluids are in development.

It is clear that NGS has great potential to revolutionize diagnostic testing for infectious diseases. However, in its current form, it cannot replace current standard of care testing. Additionally, evidence does not yet support indiscriminate or screening-based use to rule in/out infection based on NGS test results alone. To date, best practice for use of these types of tests appears to be in patient populations where infection is suspected but conventional testing is negative, and in consultation with treating physicians, ID specialists, and clinical microbiologists to determine appropriate use and interpretation.

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FROM BUST TO BOOM

IN Diagnostics Innovation

A flood of cash has poured into the industry after the pandemic's painful toll stretched laboratories and awoke the world to the value of testing.

BY JEN A. MILLER

The COVID-19 pandemic put unprecedented pressure on clinical laboratories and in vitro diagnostics (IVD) companies. A glaring lack of test kits, supplies, and staff drove record amounts of money into the IVD space, both from governments and venture capital. Diagnostic testing companies received $5.3 billion in capital alone in 2020, compared to $2.3 billion in 2019, according to Outcome Capital, a life sciences advisory and investment banking firm.

But what happens next? Will that level of investment remain? Has research and development in other categories suffered? And how will technologies developed during the pandemic affect laboratory testing going forward? We asked experts from the industry what they anticipate for the future.

SHIFTING TO THE NEW NORMAL, WITH COVID-19 LESSONS IN MIND

The abrupt turn toward meeting the demands of the pandemic both sidelined a range of routine medical procedures and testing and demanded investment in SARS-CoV-2 technologies, reagents, and other supplies no one anticipated. That affected companies in different ways, though representatives from Beckman Coulter, Roche, and Siemens Healthineers all said that they've had a strong 2021 so far and anticipate the same to be true for 2022.

Moreover, these and other companies expect their innovations from the pandemic to play a key role in the future, along with a renewed focus on better processes and moving testing closer to patients—whether that's at the hospital bedside or at home. The amount of money put into diagnostic testing during the pandemic from private capital, governments, and nonprofits will "bring forward

the next generation of testing to market," said Deepak Nath, PhD, president of laboratory diagnostics at Siemens Healthineers.

"We've always been keenly aware of the value that diagnostics bring to patient care and just how much of clinical decision-making rests on diagnostics and diagnostic products. The awareness and increased investment are a good thing for the industry," he added.

The crisis had uneven effects on research and development budgets as the world raced for COVID-19 solutions. Chris Hagen, vice president and general manager at Beckman Coulter Diagnostic's North American Operations, said that while this may have momentarily pulled work away from other projects, it has led to process improvements that will benefit all development moving forward.

"When you put a research and development organization through the wringer and ask them to be very innovative, they very quickly build new muscle in the process of developing, validating, and going through the studies to gather data," he said. He anticipates that they'll be able to leverage what they learned in the development of SARS-CoV-2 serology assays for future projects.

The pandemic also has underscored the value of laboratory data and insights, as well as the need for clinical laboratorians to contribute to population health initiatives. "There's been a push within the hospital environment for Lab 2.0 for a while now," he added. "The pandemic just reinforced the need for that evolution."

The pandemic also "provided opportunities to engage new customers as we worked together to expand access to SARS-CoV-2 testing," said Matt Sause, president and CEO of Roche Diagnostics North America, which is vital given the spike in the number of cases due to the more infectious delta variant. Roche invested more than $300 million to increase testing capabilities, which Sause said will double their global installed base of instruments and allow the production of millions of tests per week by the end of 2021.

> When you put a research and development organization through the wringer and ask them to be very innovative, they very quickly build new muscle.
>
> — CHRIS HAGEN

CREATIVITY AMID THE CHAOS IN EUAS

The ability to tap an emergency use authorization (EUA) from the Food and Drug Administration (FDA) as a rapid path to market also spurred innovation. Before COVID-19, the most EUAs granted for one public health emergency had been in response to the 2009 H1N1 swine flu. FDA has issued more than 400 EUAs related to COVID-19.

"FDA's changing the regulatory pathway and allowing for this emergency use authorization has probably been the single largest positive impact in the overall development process in bringing something to market," Hagen said.

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> Many of these companies will disappear, and a few of them will be gobbled up by the big guys
> — CRAIG STEGER

Global cooperation also has pushed the market forward. Roche's Sause noted that the company benefited from the knowledge gleaned and shared worldwide. The company's experience with COVID-19 "accelerated our innovation and ability to bring tests to market," he noted. "Developing, securing regulatory approval, manufacturing, and distributing tests to our customers within a matter of months is unheard of in the diagnostics industry."

The EUA greatly benefited "early stage, entrepreneurial diagnostic companies," said Craig Steger, senior vice president of life science and diagnostics practice lead at Outcome Capital, though not all of those products—whether from small companies or established giants of the industry—were successful. Some antibody tests didn't work or were so inaccurate that they were as good as guessing, he added.

Consolidation, however, is inevitable. "Many of these companies will disappear, and a few of them will be gobbled up by the big guys," Steger said, adding that larger firms will wait to see which of the products developed by startups hold up before inquiring about a merger or acquisition.

Sause noted that the pandemic has also created opportunities within a new category of testing in at-home and retail, "which have historically had large barriers to entry," he said. "It will be interesting to see how this gets leveraged and plays in concert with traditional testing infrastructure."

REVERSION TO THE MEAN OR A NEW ERA OF INVESTMENT?

COVID-19 has changed the way that companies and investors think about the future of laboratory medicine. Sause underscored the way it's driving testing closer to patients with a focus on at-home and point-of-care solutions, developing better sample collection techniques, and strengthening supply chains to ensure that companies are prepared to handle increases in volume associated with high numbers of case counts. Companies also see the need to integrate digital offerings with testing solutions, especially considering the popularity of telemedicine and remote diagnostics.

The pandemic also put a spotlight on what has long been a problem in laboratory medicine: staffing shortages. Hagen said that once SARS-CoV-2 tests were readily available, their customers faced the problem of having access to tests but not enough people to run them.

The problem now is "can I manage routine testing and SARS-CoV-2 testing on top of it?" As an example, he mentioned Beckman's DxA 5000

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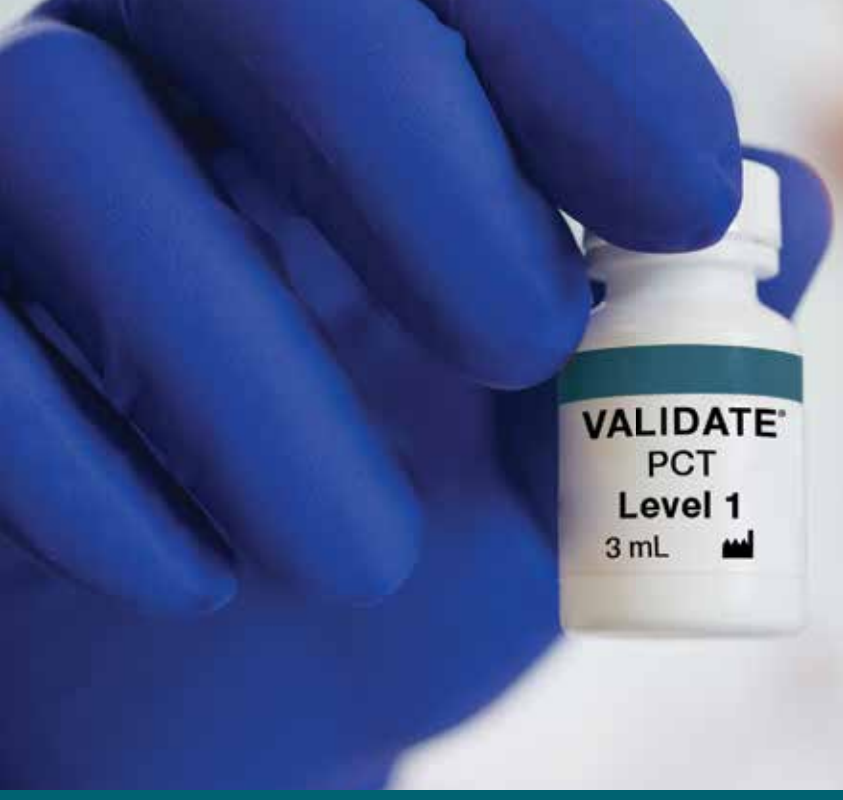

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Fit workflow automation system, designed to support small to mid-sized laboratories that can't afford to invest in the largest systems adopted by some reference laboratories. Information technology (IT) investments are also important, he said. Some of his customers had to manually report COVID-19 case counts to local governments and health departments, a drain on staff time that also opens the door to possible reporting errors.

"In addition to handling the current pandemic, the demand from COVID-19 has highlighted the need for automated solutions that can scale to support a wide variety of test volumes both within and outside a pandemic," he said.

Hagen also believes that the pandemic will discourage the recent trend of outsourcing more testing to independent laboratories. After some hospitals faced 7- to 10-day turnaround times for SARS-CoV-2 tests they sent out, health system leaders see the value of supporting their own hospital's laboratories.

"Hospitals have learned that they need a lab onsite, in their local community, so that when something like a pandemic happens, they can address the needs of their community immediately," he said. For these reasons, he anticipates that diagnostic companies will continue to see investments in workflow automation and clinical IT that make doing this kind of testing on site easier and faster.

Whether or not the current level of investment in the diagnostics space continues is an open question, said Obed Ben-Johnson, PhD, managing director of Outcome Capital. The IVD space hasn't had this much attention since the mid-1980s, in response to the emergency of HIV and its potential effects on the worldwide blood supply. "The COVID-19 crisis created a renewed interest in this segment, particularly by venture capital which has historically shied away from in vitro diagnostics," he said. "So maybe there's some renewed interest longer-term, but that's yet to be seen."

Jen A. Miller is a freelance journalist who lives in Audubon, New Jersey. @byJenAMiller

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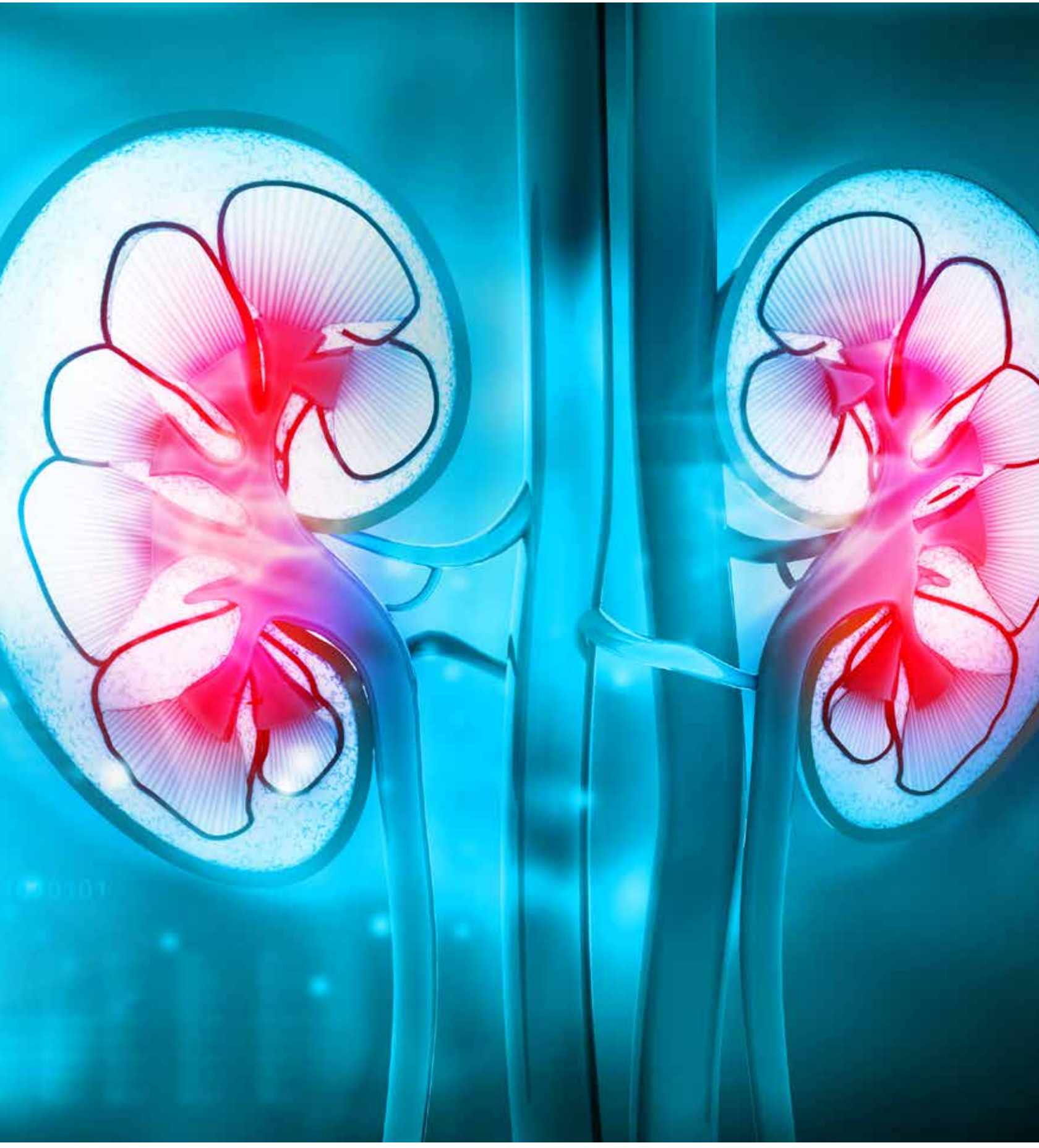
The Latest Guidance on Acute Kidney Injury

New evidence-based diagnostic thresholds promise greater precision and fewer false positives.

BY KAREN BLUM

A new guidance document on laboratory investigation of acute kidney injury (AKI) released by the AACC Academy aims to better guide clinicians and laboratorians in their evaluations of AKI, with the goal of promoting best practices to improve patient outcomes.

The evidence-based guidance, compiled by a multidisciplinary group of laboratory scientists and nephrologists and published in May (J Appl Lab Med 2021;jfab020. doi:10.1093/jalm/jfab020), features 13 findings and recommendations regarding monitoring for AKI, traditional and new biomarkers affiliated with the condition, and the potential value of instituting automated alerts and eliminating unnecessary testing. Notably, these recommendations include a proposal to use new diagnostic thresholds, called the 20/20 AACC AKI criteria, when determining whether a patient has AKI with creatinine testing.



NEW BIOMARKERS LEAD TO NEW CHALLENGES

AKI is defined as a sudden episode of kidney damage or failure. It affects up to 15% of hospitalized patients and can lead to serious complications or death. It is essential that clinicians are aware of the clinical presentation of AKI and that laboratorians provide them with the right tools to aid in early diagnosing and staging, the guidance authors said.

"Recent literature provides strong evidence that AKI is independently associated with higher risk of cardiovascular events after hospital discharge, affects short- and long-term outcomes in liver failure patients, and is associated with higher 60-day mortality in patients with septic shock," the authors wrote. Moreover, the 72-hour period immediately after AKI can impact kidney-specific outcomes such as progressive chronic kidney disease or need for long-term dialysis, they said.

AKI traditionally has been identified in hospitalized patients through a rise in blood creatinine and/or a fall in urine output, as recommended by the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines, said Joe El-Khoury, PhD, DABCC, FAACC, chair of the guidance writing committee and director of the Clinical Chemistry Laboratory at Yale-New Haven Health in Connecticut. However, there have been significant developments over the last decade in this space, he said.

New biomarkers and electronic tools have emerged that potentially can help predict which patients are at greater risk for developing AKI or identify early changes. This includes a Food and Drug Administration-approved test (NephroCheck) that detects the presence of the urinary biomarkers tissue inhibitor metalloproteinases 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7). But literature studies and access to these technologies have been variable, leading to some disparities in the identification and management of AKI among medical centers, El-Khoury said.

"I hope this document will stimulate a conversation between laboratorians and clinical care providers to redefine AKI based on biological and analytical variability, and based on the studies we've looked at and recommend," he said. "We also hope they have a conversation about the role of emerging markers and try to talk them out of using those without the strong evidence needed to show an effect on clinical outcomes," as inappropriate use of these markers can add costs and yield false-positive results.

DETECTING AKI WITH GREATER PRECISION

One of the guidance's major recommendations is to implement new thresholds for diagnosing AKI, called the 20/20 AACC AKI criteria. The authors noted that studies have shown using the KDIGO guidelines of a +0.3 mg/dL change in baseline creatinine as a sign of AKI can lead to high false-positive rates (CJASN 2015;10:1723-31) in as many as 30.5% of those with chronic kidney disease. The new AACC guidance instead recommends using a +0.20 mg/dL (~20 µmol/L) change in creatinine when baseline is less than 1.00 mg/dL (~90 µmol/L), or a +20% change when baseline blood creatinine is greater than 1.00 mg/dL. This could improve sensitivity for AKI detection, the authors said, and is supported by results of a recent study of nearly 15,000 patients demonstrating same-day changes of 0.20 mg/dL or 20% are associated with all-cause mortality (Sci Rep 2020;10:6552).

The new criteria aim to make AKI diagnosis more precise, explained coauthor Chirag Parikh, MD, PhD, director of nephrology for the Johns Hopkins University

"I hope this document will stimulate a conversation between laboratorians and clinical care providers to redefine AKI based on biological and analytical variability."
–Joe El-Khoury

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School of Medicine, in Baltimore. If baseline creatinine is low, around 0.5 mg/dL (seen in older adults and young children), it can take longer to achieve a 0.3 absolute increase, he said, whereas if baseline creatinine is high, around 4 mg/dL, a 0.3 absolute change is "meaningless," so the percentage change makes more sense.

"We suspect moving to these new criteria will help us detect AKI earlier, and act more appropriately, because right now nephrologists who know about the KDIGO guidelines know its limitations and use clinical experience to make decisions for these patients," El-Khoury said. "This addresses that in a big way, and helps them have a solid, evidence-based reference to make a decision."

OTHER RECOMMENDATIONS ON TESTING FOR AKI

The guidance also recommends clinicians and laboratories only employ creatinine assays with intralaboratory analytical variability of 3.4% or less; eliminate testing for urine eosinophils to confirm or exclude acute interstitial nephritis; and be cautious when using measures of the protein cystatin C in predicting renal recovery. And it states that more evidence is needed to fully endorse TIMP-2/IGFBP7 measures as part of routine risk assessment of AKI, and to assess the value of automated electronic record alerts to notify providers of patients with creatinine changes.

"I see this as a reflection of all the guidelines, and bringing nephrologists and laboratorians together—which has not been done enough—to highlight where the low-hanging fruits are in terms of eliminating some wasteful testing and thinking appropriately about AKI diagnoses and what the future holds," Parikh said.

The document is timely, and is a good reminder when trying to determine a patient's baseline creatinine that if you are treating someone who came from another hospital, to be aware of potential differences or biases among methods to measure creatinine, commented KT Jerry Yeo, PhD, DABCC, FAACC, medical director of the Clinical Chemistry, Clinical Pharmacogenomics, and Translational Mass Spectrometry Laboratories, and professor of pathology, at the University of Chicago.

"The summary table is good in that it goes through some classic, traditional biomarkers including the use of fractional excretion of sodium (FENa)," Yeo added. "Mainly what I like is it tells someone like myself that I need to work with a clinician, because some of this information like analytical and intra-individual variability for creatinine can ultimately affect the interpretation of what constitutes a real change in creatinine over baseline, and not just by chance. It's very helpful, and it tells us what is ready for prime time and what maybe still needs to be sorted out."

Diagnosing AKI is particularly tricky. Creatinine is not produced by the kidney but by the muscle, Parikh said. The accumulation of creatinine is used as an indirect measure that kidney filtration has decreased. It's not as direct as measures of cardiac troponin, for example, where a rising level strongly indicates heart damage, added El-Khoury. The way kidney injury is conceptualized is if filtration decreases abruptly.

"At some point, if there is a lot of injury, the filtration function will fail, but there is frequently a disconnect when the two are not going together, so you can have decreased filtration but no injury, or a little injury but no decrease in filtration," Parikh said. "This compounds to make a difficult definition."

There are often fluctuations in kidney function when patients are acutely ill, said John Lieske, MD, a nephrologist with the Mayo Clinic in Rochester, Minnesota. Sometimes that's reversible and mostly hemodynamic,

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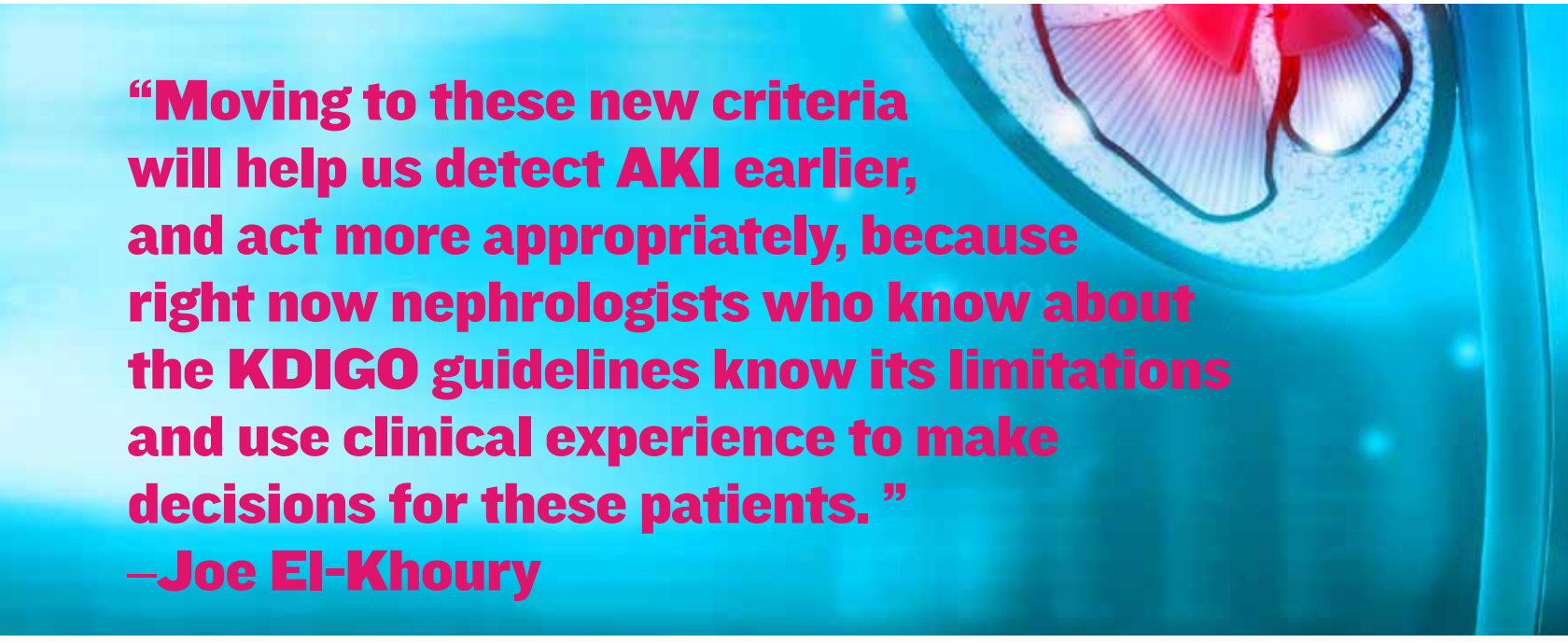

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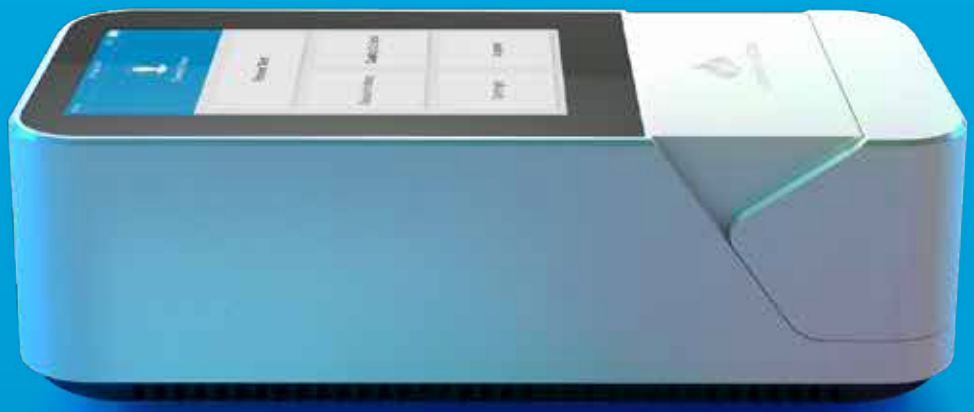

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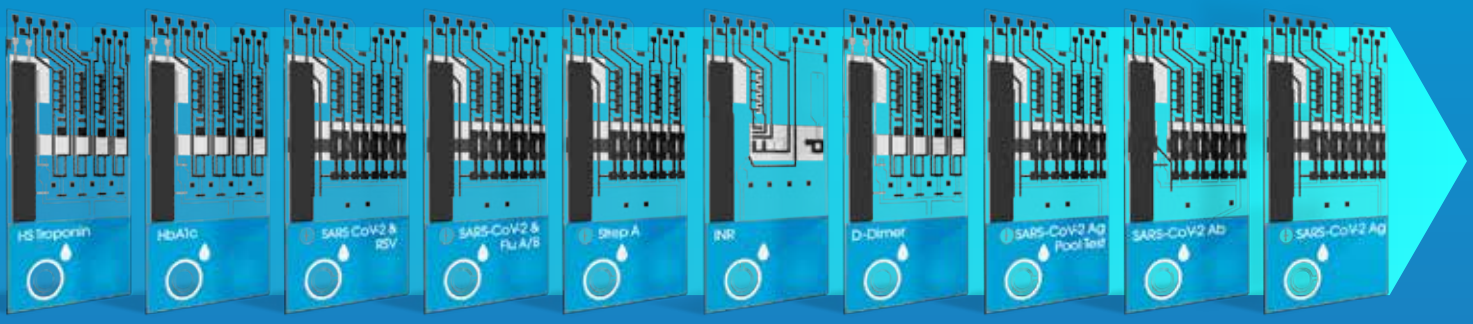

Development test strip designs are for illustrative purposes only. Not an exhaustive list of pipeline assays.

HS Troponin	HbA1c	SARS-CoV-2 & RSV	SARS-CoV-2 & Flu A/B	Strep A	INR	D-Dimer	SARS-CoV-2		
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*The LumiraDx SARS-CoV-2 Ag test and the LumiraDx SARS-CoV-2 Ab test have not been cleared or approved by FDA. The LumiraDx SARS-CoV-2 Ag test has been authorized by FDA under an EUA only for the detection of SARS-CoV-2 nucleocapsid protein. The LumiraDx SARS-CoV-2 Ab test has been authorized by FDA under an EUA only for detecting the presence of total antibodies to SARS-CoV-2. They have not been authorized for use to detect any other viruses or pathogens. The tests are authorized in the United States for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostic tests for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

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"There are pitfalls in the tools we use, and there has been a movement for more than the past two decades to try to find better ways to diagnose patients."
—Jay Koyner

and sometimes it progresses and it's not, so patients will need dialysis, he said, adding that "differentiating between those possibilities can be quite challenging."

Diagnosing AKI by changes in creatinine or urine output alone relies on "antiquated, functional markers of the kidney," said nephrologist Jay Koyner, MD, a professor of medicine at the University of Chicago. "Creatinine has been around and known to be associated with kidney function for 160 years plus, so it is ubiquitous. It's cheap, it's easy, and like most things that have been around for that long, it's imperfect. It's delayed, it's not always sensitive, and it is a bronze standard from my perspective."

Likewise, urine output is easy to measure—if a patient is catheterized. But that's less common now with hospitals targeting reduced catheter use as one way to reduce infection. "There are pitfalls in the tools we use, and there has been a movement for more than the past two decades to try to find better ways to diagnose patients," Koyner said.

LOOKING TO THE FUTURE

So what does the future hold as AKI diagnosis continues to evolve?

"I definitely think there is a role for automated alerts, and decision support around the care of patients with AKI," Koyner said, "but the data around it is a little bit muddied, and there are studies that have shown if you don't provide guidance, you can do harm. We need to be thoughtful about it. It's not a yes or no, one-box flowsheet. It's a complicated thing that takes expertise and varies from patient to patient."

Koyner's group is studying machine learning to see if they can predict who is at risk for AKI, using data in their electronic health record. It's possible that combining these technologies with urine output or biomarker measures could identify a high-risk population who may benefit from early nephrology consults and intensive, kidney-focused care, or from novel prophylactic or therapeutic treatments for AKI, he said. Additional biomarkers such as NGAL (neutrophil gelatinase-associated lipocalin), LFABP (liver fatty acid binding protein) or proenkephalin used in other countries also may prove helpful, he said.

But to be effective, Yeo cautioned, any new tests would have to be automated or have a short turnaround time, and there shouldn't be special handling requirements for samples.

Good evidence and a concerted effort by working groups may be needed to effect significant change, Lieske said.

"We know a lot more about AKI now than we did 10 years ago, but practically speaking, what's going to be the big advance is probably more going to relate to recognizing people at risk and intervening early and trying to resuscitate people very quickly," he said.

Koyner is a consultant for and receives research funding from Astute Medical and BioPorto Diagnostics A/S.

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The Lab + Beyond at the 2021 AACC Clinical Lab Expo

With more than 400 companies exhibiting and hundreds of new products, innovations, and services to experience, the 2021 AACC Clinical Lab Expo is the premier global laboratory medicine exposition. In addition to the breakthroughs and upgrades exhibitors are preparing to share, favorite opportunities for exhibitor-led learning are also back for 2021, including:

- Product Showcase: Be the first to learn about exciting products being presented at the meeting. Explore the latest lab solutions in interactive digital exhibits while in Atlanta. Products are also featured in each issue of the *CLN Daily*, the official publication of the meeting.
- Lecture Series Presentations: Learn about the latest technologies and services in convenient, 20-minute presentations. These highly attended presentations will include hot topics such as launching SARS-CoV-2 testing in small and nontraditional labs and lessons from the pandemic in advancing lateral flow immunoassay technology.
- Industry Workshop Theaters and Hotel Industry Workshops: Engage in learning about new diagnostic breakthroughs and critical topics in laboratory medicine such as: point-of-care testing, advances in infectious diseases assays, and population health management. These presentations will be held in the Exhibit Hall Theater, conveniently located on the Clinical Lab Expo show floor. Additional presentations will take place at select hotels near the Georgia World Congress Center.
- An opportunity to participate in AACC-led research: The AACC COVID-19 Immunity Study is planning to examine immune responses to SARS-CoV-2 vaccination or prior infection in a large, diverse cohort of volunteers, with the goal of gaining insight into how long the currently available SARS-CoV-2 vaccines will protect against the virus. Blood samples for the study will be collected September 28–30 in the Clinical Lab Expo hall.

Know Before You Go: Stay Updated on AACC's Health and Safety Plan

To ensure the health and safety of all attendees, AACC and the Georgia World Congress Center will strictly enforce COVID-19 safety protocols. As of August 6, AACC announced that all attendees must wear masks, regardless of vaccination status, and proof of COVID-19 vaccination or a negative coronavirus test will be required to enter the building. AACC has also developed a unique meeting logistics plan designed to prevent crowding and also to disperse crowding should it occur. Learn more about the plan at meeting.aacc.org/about/aacc-covid19-health-and-safety-plan.

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SPOTLIGHT ON THE LAB

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Nova POC Creatinine/eGFR Method is More Accurate than Laboratory Method: Large Medical Center Study

In a 670 patient study funded by the International Society of Nephrology, the South Africa Medical Research Council and the University of Witwatersrand, Johannesburg, South Africa, the Nova POC StatSensor Creatinine/eGFR meter was more accurate than the central laboratory IDMS-traceable Jaffe methodology in estimating GFR when both methods were compared to MEASURED GFR (iohexol).[1]

- StatSensor measurements showed less proportional and constant error than respective IDMS Jaffe measurements when compared to iohexol measured GFR (mGFR).[1]
- StatSensor showed better accuracy than the IDMS Jaffe methodology at identifying patients with mGFR's <90 mL/min/1.73 m^2.[1]
- Of particular interest in the study, StatSensor showed better accuracy than the laboratory Jaffe methodology in the 60-89 mL min/1.73 m^2 range, where individuals with early disease may benefit renal protective measures.[1]

Nova Biomedical StatSensor Creatinine Meter

1.George J et al. Evaluating chronic kidney disease in rural South Africa: comparing estimated glomerular filtration rate using point of care to iohexol measured GFR. CCLM 2021.

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Regulatory Roundup

CDC Planning to Withdraw Request for EUA of SARS-CoV-2 PCR Test

After December 31, 2021, the Centers for Disease Control and Prevention (CDC) will withdraw its request to the Food and Drug Administration (FDA) for emergency use authorization (EUA) of the CDC 2019-Novel Coronavirus Real-Time RT-PCR diagnostic panel. CDC is announcing this in advance so that any clinical laboratories that are using this test have adequate time to select and implement one of the many FDA-authorized alternatives.

CDC first introduced this assay for detection of SARS-CoV-2 in February 2020. Now, however, the agency has decided to voluntarily withdraw its request for EUA primarily because "hundreds of SARS-CoV-2 [polymerase chain reaction (PCR)] tests have received EUAs and are widely available," said AACC President Stephen R. Master, MD, PhD, FAACC. This means that "CDC's test is no longer needed to fill an unmet testing need."

As laboratories look for an alternative to CDC's test, the agency encourages labs to consider adopting a multiplexed method that detects and differentiates between SARS-CoV-2 and influenza viruses. This will facilitate a more cost-efficient approach to testing once flu season arrives, according to Master. CDC actually has a separate EUA for such a test—one that detects and distinguishes between SARS-CoV-2, influenza A, and influenza B—that it will be maintaining. Moving forward, CDC and other public health laboratories plan to use this multiplex test so they can simultaneously monitor flu activity in addition to SARS-CoV-2.

FDA GRANTS EUA TO ROCHE FOR PCR-BASED SARS-COV-2 POINT-OF-CARE TEST

Roche has earned Food and Drug Administration emergency use authorization for the cobas SARS-CoV-2 nucleic acid test for use on the cobas Liat system. According to Roche, this singleplex test is the first real-time reverse transcriptase-polymerase chain reaction test that identifies SARS-CoV-2 infection within 20 minutes, and that is authorized to screen both symptomatic and asymptomatic persons at the point of care. It also offers broad SARS-CoV-2 strain coverage as monitored by Roche's ongoing variant surveillance program. The cobas Liat system fully automates the testing process and features a simplified workflow that enables healthcare professionals to perform this test with minimal training. The cobas SARS-CoV-2 nucleic acid test is intended for use at a wide range of point-of-care settings, including emergency and primary care settings, physician offices, and other SARS-CoV-2 screening locations. It is also available in markets accepting the CE mark.

PROMEGA RECEIVES FDA CLEARANCE FOR LYNCH SYNDROME SCREENING TEST

The Food and Drug Administration has cleared Promega's OncoMate MSI Dx analysis system, which determines microsatellite instability (MSI) status in colorectal cancer tumors. High-frequency MSI is an indication that patients and their family members should be referred for further genetic testing for Lynch syndrome, an inherited condition that increases the risk of developing colorectal and other cancers. Promega's OncoMate

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MSI Dx is based on the company's research-use-only fluorescent, multiplex polymerase chain reaction-based fragment-sizing technology, which has been used to test for MSI status in clinical research for more than 15 years and is supported by more than 140 peer-reviewed publications. The OncoMate MSI targets five mononucleotide repeat markers that align with guidelines such as the National Cancer Institute's "Revised Bethesda Guidelines for Hereditary Nonpolyposis Colorectal Cancer (Lynch syndrome) and Microsatellite Instability." From sample collection to result, the test takes 10 hours, and it can be performed using a single formalin-fixed paraffin-embedded section.

FDA CLEARS INOVA'S DIGITAL MULTI-ANALYTE SYSTEM, CELIAC DISEASE TEST

Inova Diagnostics has received 510(k) clearance from the Food and Drug Administration for its Aptiva system and Aptiva Celiac Disease IgA assay, both of which previously received the CE mark in August 2020. The Aptiva is a fully automated, high-throughput digital multi-analyte system. It features 150-sample rack capacity, which reduces the number of daily interventions, and a 6.5-hour consumable walkaway time. It also uses a particle-based multi-analyte technology (PMAT) that processes multiple analytes simultaneously from a patient sample. PMAT enables Aptiva to deliver up to 720 results per hour using a 12-analyte test cartridge, thereby allowing the laboratory to complete its workflow in a single shift. On the Aptiva system, Inova eventually plans to include tests for seven additional autoimmune disease states that detect more than 60 analytes, with the goal of closing the seronegative gap, e.g., identifying autoimmune disease states in patients who would normally test negative for them.

QIAGEN EARNS CE MARK FOR HUMAN ADENOVIRUS TEST

The CE mark has been granted to Qiagen for its NeuMoDx HAdV Quant assay, which is designed to identify and quantify human adenovirus (HAdV) DNA and runs on the NeuMoDx 96 and 288 molecular systems. Qiagen developed this new assay in partnership with Sentinel Diagnostics. The test uses Qiagen's automated, three-step NeuMoDx solutions, which extract DNA from blood or urine to isolate the target nucleic acids and then conduct real-time polymerase chain reaction to target conserved sequences in the HAdV genome. The NeuMoDx HAdV Quant assay is part of the NeuMoDx transplant assay menu, which also includes CE-marked tests for cytomegalovirus, Epstein-Barr virus, and BK virus viral load monitoring. These tests are all intended for the management of immunocompromised patients, such as those who have undergone organ transplantation.

JAPAN APPROVES AMOY DIAGNOSTICS' LUNG CANCER CODIAGNOSTIC PANEL

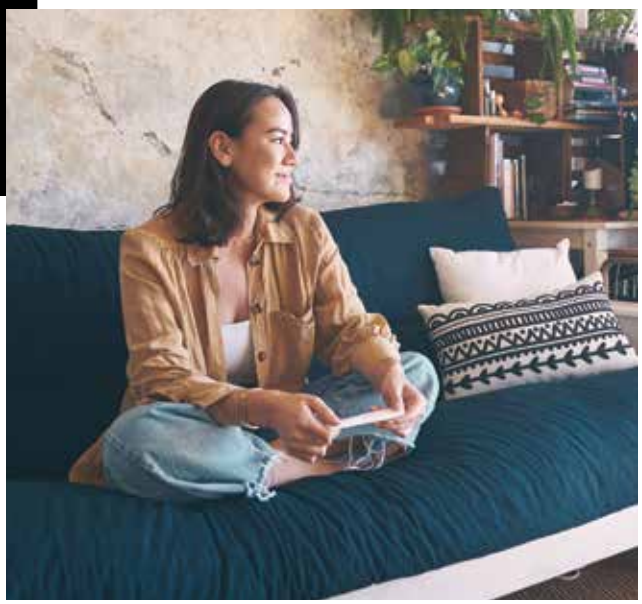
Amoy Diagnostics has received approval from Japan's Ministry of Health, Labour, and Welfare (MHLW) to produce and market the AmoyDx Pan Lung Cancer (PLC) polymerase chain reaction panel in Japan. Developed in collaboration with Riken Genesis and Precision Medicine Asia, this test is intended for use as a companion diagnostic for multiple cancer therapeutics. It can be performed on formalin-fixed paraffin-embedded tissue and fresh frozen tissue in which the presence of tumor cells has been confirmed, and it can simultaneously evaluate the presence of up to 11 driver genes: *EGFR*, *ALK*, *ROS1*, *KRAS*, *BRAF*, *HER2*, *RET*, *MET*, *NTRK1*, *NTRK2*, and *NTRK3*. So far, the MHLW has approved the detection of four of these genes (*EGFR*, *ALK*, *ROS1*, and *BRAF*) with the AmoyDx PLC Panel for nine associated targeted therapies for non-small cell lung cancer. These therapies include gefitinib, erlotinib hydrochloride, afatinib maleate, osimertinib mesylate, crizotinib, alectinib hydrochloride, brigatinib, and combined administration of dabrafenib mesylate and trametinib dimethyl sulfoxide.

Industry Playbook

At-home, Personalized Fertility Test Launches in U.S.

A newly developed at-home fertility test, Inito, has launched on the U.S. market. The test aims to help users better understand hormone and ovulation information. The monitoring device can be paired with a smartphone app for quick access to data.

Inito works by measuring hormone values for estrogen and luteinizing hormone levels to predict fertile days, then measuring progesterone to confirm ovulation, ultimately assisting patients through the conception process. The test requires a patient to dip a strip into urine, attach the monitor to a smartphone, insert the strip into the monitor, then review results on the app. Compared with to traditional ovulation tests currently on the market, Inito says it can provide detailed and more accurate results with faster turnaround times.



According to the company, Inito has the ability to customize to a patient's unique hormone levels to better work with regular and irregular menstrual cycles, identify six fertile days in a patient's cycle, and even remind a patient when to test based on personalized hormone variations.

In addition to the launch of the device, Inito also is introducing a feature in the app titled Hormone Charts for users to better understand their hormone levels and to have the option to share the data with their doctor.

"Abnormalities such as frequent anovulatory cycles, shorter luteal phase, and low levels of progesterone can easily go unnoticed without monitoring with expensive and invasive lab tests," said Kim Langdon, MD, advisor to Inito.

"We started Inito to provide couples with a more accurate look at what's happening with their unique cycle and actionable data to help them get pregnant faster," added Varun AV, cofounder of Inito.

Currently, Inito has collected over 1 million hormone values from patients in Asia.

QIAGEN, VEROGEN PARTNER FOR NGS AND HID SOLUTIONS

Aiming to improve human identification (HID) workflows in laboratories, Qiagen and Verogen have teamed up to advance the use of next-generation sequencing (NGS) in the forensics field. Through the partnership, Qiagen will expand its established work in the forensics market while also commercializing Verogen's sequencing and analysis products for HID.

Currently, Qiagen's work in forensics focuses on sample collection and preparation, genetic testing analysis, and workflow automation. By obtaining the rights to Verogen's HID solutions, Qiagen will not only broaden its portfolio but will also expand the reach of Verogen's lineup, which includes the Verogen ForenSeq assay, the Verogen MiSeq FGx Sequencing System, and its Universal Analysis Software. Both partners also plan to develop a menu of forensically validated workflows for NGS that combine Verogen's library-prep products with Qiagen's QIAseq products, automation solutions, and expertise.

"This partnership with Qiagen will make it easier for laboratories to provide more impactful answers. By combining Verogen's industry-leading NGS-based product portfolio with Qiagen's gold-standard extraction, assay, and automation solutions, we will accelerate adoption and use of NGS in forensics," said Brett Williams, CEO of Verogen.

THERMO FISHER LAUNCHES RAW SALIVA TESTING KIT FOR SARS-COV-2

To improve research on and surveillance of SARS-CoV-2, Thermo Fisher Scientific announced their newly developed testing kit, SpeciMAX Saliva Collection Kit.

Thermo Fisher describes the SpeciMAX Saliva Collection Kit as an easy-to-use self-collection kit designed to provide a widely available, cost-effective solution for

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raw saliva collection. According to Thermo Fisher, each kit delivers clean saliva transfers, reduces the risk of cross-contamination when paired with liquid handlers, and fits seamlessly into viral RNA extraction and direct-to-PCR downstream automation workflows for high throughput surveillance testing.

"With SpeciMAX, labs will be able to capture raw saliva with minimal workflow disruption and minimal manual processing, enabling more efficient SARS-CoV-2 research and surveillance," said Ellie Mahjubi, vice president and general manager of sample preparation at Thermo Fisher Scientific.

Each kit includes one barcoded collection tube, a funnel, and a cap, and requires only 1 mL of saliva, as well as less refrigeration, incubation, and storage space than other collection kits currently on the market.

LIGHTDECK RECEIVES $35.1 MILLION IN FUNDING FROM DOD

In collaboration with the Department of Health and Human Services (HHS), the Department of Defense (DOD) awarded a $35.1 million contract to LightDeck Diagnostics to increase its manufacturing capacity in its Colorado production facility.

The DOD specifically granted the funding for LightDeck's COVID-19 Ultra-Rapid Antigen and Total Antibody tests, which are are currently being developed for regulatory approval. According to LightDeck, its multiplex waveguide immunoassay platform has the ability to return results in just 5 minutes due to the special laser-based technology that enables rapid signal development and reduces background noise that could cause interference. LightDeck plans to market both the platform and testing assays to healthcare facilities across the U.S. before expanding to a worldwide network. Its target settings include traditional healthcare facilities as well as nontraditional environments such as prisons. With the awarded money, the parties expect LightDeck to be able to produce 1 million tests per month, as opposed to its current limit of 50,000 tests per month.

Drazen Zigic / iStock; image courtesy of LightDeck

TWIST BIOSCIENCE ACQUIRES IGENOMX FOR $35 MILLION

Twist Bioscience, a synthetic biology and genomics company, announced acquisition of iGenomX, a company offering multiplex library preparation tools for next-generation sequencing (NGS) workflows.

Twist CEO Emily Leproust said that the acquisition of iGenomX will allow customers to convert from single nucleotide polymorphism microarray to an NGS-based approach.

"The iGenomX team built a robust PCR-like workflow for ultra-high throughput library construction," Leproust said. "We anticipate this technology, together with our leading NGS product line and worldwide commercial infrastructure, will drive adoption of Twist NGS workflow solutions into fields that run large volumes of samples with shallow sequencing."

According to Twist, using an NGS-based approach will be more cost-effective and allow for customization with iGenomX's automated library prep system.

The $35 million deal includes an initial $500,000 cash payment and $29.5 million in Twist stock. The agreement also includes an additional $5 million in Twist shares if certain milestones are met starting 6 months after the close of the deal.

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Ask The Expert

Using Free Antiepileptic Drug Levels for Therapeutic Drug Monitoring

EXPERT
Adam J. McShane, PhD, DABCC (CC, TC), FAACC

When is therapeutic drug monitoring (TDM) of antiepileptic drugs indicated for clinical management of epilepsy?

A: TDM of antiepileptic drugs (AEDs) may prove useful when initializing or adjusting treatment, establishing a personal therapeutic range after desired clinical response is reached, or when assessing or managing toxicity. TDM also might be needed when there is persistent seizure activity despite typical dosing, an AED formulation change, unexpected clinical response, question of AED compliance, and for patients with variable pharmacokinetics.

When is the free AED level clinically useful?

Labs can measure either the total or non-protein-bound (free) AED level. In most clinical situations, total AED measurement is adequate for TDM due to a relatively constant relationship between the free and protein-bound fractions. Analytically, the total AED level is less cumbersome, less costly, and less time-consuming to measure. Nevertheless, the free fraction most accurately reflects the active component of AEDs, and can be of clinical utility in certain scenarios.

Measurement of the free fraction is most useful with extensively bound AEDs. Examples of highly protein-bound AEDs include carbamazepine (~75% bound), phenytoin (~90%), and valproic acid (~90%). When the protein binding of these AEDs is disturbed, the free concentration may reflect the pharmacologically active concentration with greater accuracy than the total. This can occur in a variety of common situations, such as when patients are experiencing hepatic disease, renal disease, pregnancy, hypoalbuminemia, and uremia.

Another common reason to measure free AED levels is to assess potential toxicity and guide AED reintroduction. The free fraction is particularly useful in this scenario due to the fact that toxicity is often caused by factors that disrupt protein binding, such as drug-drug competition for available plasma protein binding sites or protein site displacement. For example, the percent of protein-bound valproic acid is dependent on saturation of available protein-binding sites. However, saturation can be reached unexpectedly if a patient is taking multiple AEDs or other medications—and once available plasma protein sites are saturated, the free fraction of valproic acid rises rapidly. This leads to a scenario where the total valproic acid concentration may be therapeutic, but the free (or pharmacologically active) fraction is starkly elevated and indicates possible toxicity to the clinician.

How are AED levels measured in the laboratory?

Labs use a variety of techniques to measure AED levels, including immunoassays, gas chromatography, liquid chromatography, and chromatography interfaced with a mass spectrometer. Immunoassays are typically performed in core hospital laboratories on automated chemistry analyzers or immunoanalyzers. Generally, they do not offer the analytical specificity or analyte multiplexing ability afforded by the other techniques listed. However, an advantage of immunoassays is their decreased turnaround time due to the 24/7 operations of a core laboratory with random access instrumentation. Short turnaround times are especially valuable in cases of suspected toxicity.

In order to measure the free fraction specifically, labs must separate out the non-protein-bound AED prior to analysis. Two techniques to accomplish this task are equilibrium dialysis or ultrafiltration. Both utilize a membrane with pores that are small enough to keep the protein-bound AED from passing through. Ultrafiltration also has the advantage of speed (it typically takes 20–40 minutes) due to the process being aided by centrifugation. After the non-protein-bound fraction is separated, it is collected for subsequent analysis. If a free AED assay is not offered by a chemistry analyzer vendor, labs can use a total AED assay to measure the free fraction. However, this may require optimization (e.g., increased sample volume and lower concentration calibrators) due to the lower concentrations of free versus total AED.

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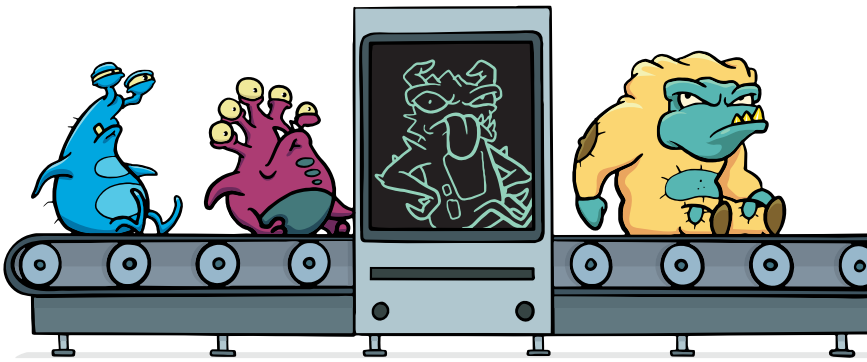

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1. Cybulski R, Bateman A, Bourassa L, Bryan A, Beail B, Matsumoto J, Cookson B, Fang FC; Clinical impact of a Multiplex Gastrointestinal PCR Panel in Patients with Acute Gastroenteritis. 2018. Clinical Infectious Diseases, ciy357, https://doi.org/10.1093/cid/ciy357.
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OVERHAULING POCT STRATEGY

70%

Increase in clinician response to improved POCT alerts

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Interdisciplinary Teams Show Tenacity in the Pursuit of Quality

BY KIMBERLY SCOTT

Clinical laboratorians are taking the lead in more than just SARS-CoV-2 testing. Across the globe, laboratory medicine professionals are finding ways to amplify their powerful data and expertise as part of integrated healthcare teams.

One area where laboratorians are gaining visibility is in engineering healthcare systems for high quality care. Within the laboratory, quality usually means avoiding and correcting internal errors. However, the quality problems with the largest effect on patients often happen in the pre- and postanalytical phases of testing. Such arenas are ripe for the scientific insight and medical data laboratorians have to offer, and they present unique opportunities for collaboration with clinical colleagues.

Multiple teams have been recognized by AACC, Abbott, and other leading healthcare organizations through the UNIVANTS of Healthcare Excellence program for quality, patient-focused achievements, five of which are profiled in this issue. From reducing inpatient daily blood draws to increasing detection of acute myocardial infarction in women to optimizing detection of thyroid dysfunction in pregnant women, the initiatives profiled below have achieved measurable, innovative impact within their health systems.

REDUCING DAILY INPATIENT BLOOD DRAWS

After noticing that many patients had daily blood tests conducted without a stop date, a team at St. Paul's Hospital in Vancouver, British Columbia, decided to investigate further. They analyzed 2 years of inpatient laboratory data and found that 1,575 patients in the 500-bed system had experienced daily blood test runs of 14 days or more. Chart reviews revealed that 30% of patients had months of identical daily testing that was not contributing to their care and showing only expected homeostatic fluctuations.

In 2019, the team developed a guideline that any order written as "daily" would last only 3 days and then require reassessment by the ordering physician. This policy change led to a demonstrable decrease in core lab workload and the elimination of extended runs of daily blood draws except when specifically ordered by physicians.

28%

Reduction in the number of patients undergoing daily phlebotomy for more than 10 consecutive days

$4,500

Monthly savings in supplies and phlebotomy time

St. Paul's Hospital, Vancouver

The guideline reduced the number of patients undergoing daily phlebotomy for more than 10 consecutive days by 28%, reported Janet Simons, MD, medical director of pre- and post-analytics in the pathology and laboratory medicine department and co-medical director of clinical informatics at Providence Health Care.

In a country with publicly funded universal healthcare, opportunities to reduce healthcare costs are paramount, Simons noted. This initiative, recognized with distinction by the UNIVANTS of Healthcare Excellence program, is estimated to save $4,500 a month in supplies and phlebotomy time at St. Paul's Hospital alone. Other hospitals in the region have since adopted similar protocols, adding to the savings for the province. Compounding the benefits, the team also found that this shrinks the need for downstream follow-up testing, reducing iatrogenic anemia and the need for transfusions.

"Doctors don't often think about bloodwork as being invasive or a big deal, but for patients, especially when they get poked every day for the whole hospital stay, bloodwork can be the worst part of their day and can really negatively affect their hospital experience," Simons said. "If we have to put patients through that, it should be because the information we are getting really matters to their care."

INCREASED DETECTION OF ACUTE MYOCARDIAL INFARCTION IN WOMEN

Improving the quality of care often means that clinical laboratorians approach problems from a population-based level. For example, sex differences are common across multiple aspects of cardiovascular care, including diagnosis, treatment, and outcomes. Large, multi-center randomized clinical trials have shown that women are under-recognized for acute myocardial infarction (AMI) and consistently have higher fatality rates compared to men, even adjusting for age and comorbid conditions. Women tend to have atypical symptoms when presenting to emergency departments (EDs) and tend not to be recognized for experiencing AMI without male-patterned chest pains symptoms.

A greater awareness of this disparity is behind guidelines recommending implementation of sex-specific upper reference limits (URLs) into clinical pathways for patients that present to the ED with suspected acute coronary syndrome. In fact, research suggests the differences between sexes in the URLs of seemingly healthy individuals can be as high as 50%.

Recognizing that poorer outcomes for women post-intervention may result from delayed diagnosis, and with the full appreciation that some men may be more aggressively treated based on use of lower URLs that lack sex discrimination, the Biochemistry and Immunology Department at Kokilaben Dhirumhai Ambani Hospital & Medical Research Institute (KDAH) investigated moving from an overall URL for high-sensitive troponin I (hsTnI) to sex-specific URLs consistent with guideline-based care.

Before the initiative was implemented in 2018, the previous threshold for both men and women was 26ng/L. After implementation, the cutoff threshold value of hsTnI for women was set at 16ng/L and for men, 35ng/L. Implementation of sex-specific URLs at the hospital identified an additional 14% of at-risk women with potential acute myocardial infarction during a 6-month period from October 2018 to March 2019. This in turn also decreased the number inappropriately diagnosed with acute myocardial infarction by 3%. The initiative was recognized with achievement by the UNIVANTS of Healthcare Excellence program.

In the evaluation of chest pain, the standard recommendation for serial troponins is 0, 3, and 6 hours for conventional troponin I and 0 and 3 hours for hsTnI. For cTnI, the team considered testing in compliance to protocol if a minimum of two serial tests were done, which occurred only 7% of the time. With hsTnI, however, the team could accomplish the prescribed two serial tests in 93% of cases.

Changes in the chest pain protocol have allowed emergency clinicians to diagnosis acute coronary syndrome (ACS) faster with a 3-hour protocol. Other changes KDAH made included skipping the immediate ED assessment and directly taking the patient for an electrocardiogram (ECG). If the ECG showed no new ischemic changes, hsTnI was tested at 0 hours and 3 hours, skipping the sixth hour testing necessary in serial protocols with cTnI, speeding the rule-in and rule-out of ACS.

Every unnecessary procedure and/or hospitalization that can be eliminated helps to reduce costs across the health ecosystem, noted Barnali Das, MD, a consultant in the biochemistry and immunology department at KDAH. With average length of hospital stay in patients with suspected ACS now reduced by 43%, the resources and costs associated with that time were also reduced, she said.

"The average emergency department length of stay is 7 hours for cTnI and 4 hours for hsTnI," she explained. "This time-effective testing protocol has better acceptance by patients as well as ED physicians. Since a majority of patients in our hospital pay out of pocket, their acceptance and compliance to the hsTnI-based chest pain protocol markedly improved."

STRATEGIC ACTIVATION OF POINT-OF-CARE TESTING

Point-of-care (POC) testing can offer substantial benefits to patients in specific settings but must be strategically controlled and integrated into high-quality clinical care pathways to ensure accurate and timely results.

When POC testing was first implemented at the Aga Khan University hospital in Nairobi, Kenya, it was not through an integrated team. Test results were not standardized nor was the equipment maintained under a quality system. This led to substantial gaps in care with avoidable discrepancies, risks, and medical errors. Specific areas of concern included quality control (QC), manual transcription errors in patient reports, and mismatched result reporting/patient identification.

A cross-functional leadership effort at the Aga Khan University hospital invested in an overarching, patient-centric POC strategy that was lead and implemented by laboratory medicine in partnership with various departments.

According to John Waigwa, laboratory quality coordinator for the hospital, the collaborative overhaul radically changed internal processes, as well as patient flow, enhancing care at the hospital.

"Ultimately, the point-of-care strategy expanded to 33 additional sites," Waigwa said. "In all cases, the accuracy and timeliness of point-of-care testing improved, ensuring high-quality results for our patients, as well as increasing the confidence of the clinicians."

Altogether, there was a five-fold reduction in total medical errors, including elimination of mis-matched patient results, mitigation of pre-analytic confounders (20% reduction) and substantially enhanced compliance with routine QC. In addition, improved flagging of critical/panic values on POC testing devices resulted in a 70% increase in actions associated with alerts.

Substantial improvement in data capture and associated documentation/billing processes resulted in reduced revenue loss of KES 19,109,800 ($177,400) from June to December 2019. The initiative was recognized with distinction by the UNIVANTS of Healthcare Excellence program.

"Medical errors can have catastrophic effects on patients, resulting in potential medication errors, injury, and possible death," said Majid Twahir, chief of staff and associate dean of clinical affairs for the hospital. "With medical errors being 20 times more likely in Africa compared to developed countries, a five-fold reduction has profound impact on mitigating preventable adverse outcomes and downstream costs."

OPTIMIZED DETECTION OF THYROID DYSFUNCTION DURING PREGNANCY

Thyroid dysfunction during pregnancy (both hyper- and hypothyroidism) can be associated with increased risk of adverse outcomes for mothers and offspring. Optimal detection and management of thyroid disfunction can decrease potential complications. But too often, thresholds used for diagnosis of hypothyroidism during pregnancy are not set correctly, leading to over- and underdiagnosis. To optimize the assessment of thyroid dysfunction, measurement method and regional factors (such as iodine intake) should be considered, according to guidelines. Determination of anti-thyroid peroxidase-antibody (Anti-TPO AB) is also recommended, as higher rates of complications are seen during pregnancy in women with Anti-TPO antibodies and increased thyroid-stimulating hormone (TSH).

To reduce complications in pregnant women, an integrated clinical care team at Hospital Virgen de la Luz in Cuenca, Spain, established improved reference ranges for TSH and improved the accuracy of diagnosis for thyroid dysfunction during pregnancy, avoiding misclassification of hyper- and hypo thyroidism. Prior to 2019, pregnancy screening within the first trimester used the same reference interval as a healthy adult population (TSH from 0.35 to 4.94 mU/L). After a comprehensive review of records and pregnancy outcomes, the team established a new reference interval of 00.064 to 3.50 mU/L.

9.2%

Increase in pregnant women accurately classified as euthyroid instead of hyperthyroid

12,800 euros

Savings within first year of implementation

Hospital Virgen de la Luz

The results of this program were significant for pregnant patients. Of the 794 pregnancies after implementation of outcome-based ranges, 9.2% were more accurately classified as euthyroid when they previously would have been classified as hyperthyroid, noted Enrique Prada de Medio, head of laboratory medicine and pathology at the hospital. As every diagnosis of hyperthyroidism requires follow-up visits with the endocrinology department, 73 pregnant women (9.2% of 794) had more streamlined care while avoiding extra costs.

"Optimized detection and treatment of thyroid disorders enables better patient management, reducing complications and lowering overall cost of care," de Medio explained. "Mitigating these costs of 176 euros per visit per patient results in annualized savings of more than 12,800 euros for the first year of implementation."

The thyroid dysfunction initiative was recognized with achievement by the UNIVANTS of Healthcare Excellence program.

REDUCING POST-OPERATIVE COMPLICATIONS IN CARDIAC SURGERY PATIENTS

Perioperative coagulopathy and postoperative bleeding are the most common complications in patients

14%

Increase in at-risk women identified with potential acute myocardial infarction

43%

Reduction in average length of stay in patients with suspected acute coronary syndrome

Kokilaben Dhirumhai Ambani Hospital & Medical Research Institute

undergoing cardiac surgery, especially when the cardiovascular surgery is associated with cardiopulmonary bypass (CPB). Approximately 20% of patients present with significant postoperative bleeding after cardiovascular surgery, and 5% of these patients require unplanned re-exploration (up to 7% in valve surgery).

Often, managing the bleeding associated with CPB leads to excessive use of allogeneic blood products and hemostatic pharmacological agents. Blood transfusion is associated with increased morbidity (cardiac and non-cardiac adverse events), hospitalization cost, and mortality. Early diagnosis and targeted and effective therapy of perioperative and postoperative coagulopathy are critical.

Some studies suggest that implementation of visoelastic POC tests, such as rotational thrombo-elastometry, in conjunction with a specific algorithm for coagulation management in cardiac surgery, allow for better control of hemostatic pathology.

A clinical care initiative implemented by the Hospital Virgen Macarena in Sevilla, Spain, used pre- and post-implementation comparison of transfusion rates, the main associated cardiac surgery complications rates, and other clinical outcome parameters to assess the impact of visoelastic POC tests with algorithm-based coagulation management in cardiac surgery with cardiopulmonary bypass.

The POC initiative reduced the length of stay in the intensive care unit (ICU) from 6.0 days to 5.3 days, and the incidence of cardiac complications in the ICU decreased (57.8% to 55.8%), especially acute postoperative pericarditis (3.6% vs. 1.2%), according to Isabel Rodríguez Martin, MD, PhD, a physician in the clinical biochemistry department.

"We observed a lower rate of ICU admissions for visoelastic testing patients – 4.6% versus 2.7%, a decrease in total hospital stay, and a decrease in hospital mortality associated with cardiac surgery, from 4.5% to 2.4%," she said. "Reducing readmissions to the ICU saves the system money, allows optimal resource utilization, and reduces poor patient outcomes."

Although the cost of POC visoelastic testing was higher than conventional laboratory coagulation tests (52.30 euros vs. 22.70 euros), the overall cost of blood products plus laboratory testing was less in the visoelastic testing group (20,803 euros vs. 31,059 euros). Costs associated with hematological complications also decreased significantly in patients who underwent cardiac surgery after the implementation of visoelastic testing.

The cardiac surgery initiative was recognized with distinction by the UNIVANTS of Healthcare Excellence Program.

4.5% to 2.4%

Reduction in hospital mortality associated with cardiac surgery

31,058 euros – 20,803 euros

Reduction in cost of blood products plus laboratory testing

Hospital Virgen Macarena

THE SECRET WEAPON FOR TOPPLING QUALITY BARRIERS

Each of these initiatives demonstrates how when clinical laboratorians get involved with care teams outside the laboratory, overall care quality and outcomes improve. Beyond simply providing test results, laboratorians are finding success taking leadership roles in helping diagnose health conditions earlier when they can be treated most effectively. Not only are these laboratories performing crucial testing, they also are helping to develop integrated care practices that are improving current standards of care across the healthcare enterprise.

To learn more about these and other 2020 UNIVANTS winners, visit univantshce.com.

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UNIVANTS 2020 Teams Recognized in This Issue

Reducing Medical Errors and Enhancing Patient Care through Pathology Lead Strategic Activation of Point-of-Care Testing in an Emerging Market | Aga Khan University Hospital | John Waigwa, Serafino Gatwiri, Samuel Ng'aaru, Gregory Muruga, Nancy Kunyiha, and Daniel Maina

Optimized Detection and Management of Thyroid Dysfunction During Pregnancy for Improving Maternal and Offspring Outcomes | Hospital Virgen de la Luz | Enrique Prada de Medio, Dulce María Calderón Vicente, Andrés Moya Plaza, Vanesa Martínez Madrid, and Sandra Serrano Martínez

Reduction of Inpatient Daily Blood Draws With Data Science and Clinical Collaboration | St. Paul's Hospital | Janet Simons, Deborah Shaw, Mirjana Besir, Astrid Levelt, and Camille Ciarniello

Increased Detection of Acute Myocardial Infarction in Women Using Sex-Specific Upper Reference Limits in Clinical Pathways for Patients Presenting With Suspected Acute Coronary Syndrome | Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute | Barnali Das, Jamshed Dalal, Sanjay Mehta, Prashant Nair, and Santosh Shetty

Reducing Post-Operative Complications in Cardiac Surgery Patients | Hospital Virgen Macarena | Isabel Rodríguez Martín, Jesús Villanueva Mena-Bernal, Francisco Javier González Fernández, Juan Galán Páez, and José Garnacho Montero