November 2020

CLN Clinical Laboratory News

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37.4%/44.6%

Cumulative mortality in patients with diabetes after 1-time cTn I/cTn T measurement ≥90th percentile

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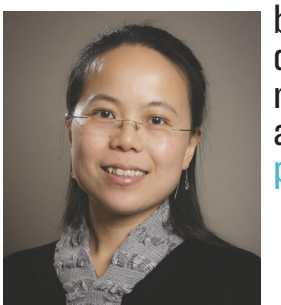

Although drug-induced liver injury (DILI) is clearly defined as being caused by drugs, the correlation between DILI and drug administration may not be clear in actual cases.
p36

Federal Insider

Laboratory Groups Seek Transparency on SARS-CoV-2 Testing

AACC and five other laboratory groups wrote to Vice President Mike Pence asking that the White House Coronavirus Task Force provide transparency into the allocation and availability of laboratory supplies needed to respond to COVID-19. "Our organizations stand ready and willing to partner on any efforts to facilitate the release and dissemination of this information," the letter says. A lack of transparency into the federal government's acquisition and distribution of testing supplies to states and private laboratories is compounding the problem of insufficient reagents, personal protective equipment, and other supplies, according to the letter.

The organizations urge the White House Coronavirus Task Force to lead a coordinated federal effort to transparently communicate information on the availability of SARS-CoV-2 testing supplies and to do everything possible to encourage the production of sufficient testing supplies. Relying on one test platform or two or three large manufacturers isn't enough to increase testing capacity, the letter notes.

"We urge the Task Force to take bold action to encourage the manufacturing of COVID-19 test supplies and to transparently share information on the availability of supplies among the entire laboratory community," the letter adds. "Until the federal government takes action, these shortages will persist, future surges in the pandemic will occur, and patients will continue to suffer."

In a separate letter to leaders of Congress, AACC revealed new evidence of continuing supply shortages in laboratories. AACC's most recent survey, completed in September, found that 68% of labs had trouble obtaining test kits, up from 48% of respondent laboratories in May. The same percentage of laboratories also had trouble getting reagents. The survey did show improvement in the ability to obtain swabs: 36% of laboratories reported this problem, versus 62% in May.

CMS PEGS PAYMENTS TO SPEED FOR SARS-COV-2 TESTING

After nearly doubling payment for high-throughput SARS-CoV-2 tests from about $51 per test to $100 per test in April, the Centers for Medicare and Medicaid Services (CMS) beginning January 1 is cutting those rates back to $75 for clinical laboratories that do not turn around results within 2 days. Medicare will pay $100 only to laboratories that complete high throughput tests within 2 calendar days of the specimen being collected.

The plan works by cutting the high-throughput SARS-CoV-2 diagnostic test reimbursement rate to $75. To get a $25 add-on payment that will bring the total back up to $100, laboratories would have to do two things: complete the test in 2 calendar days or less and complete the majority of their SARS-CoV-2 tests in 2 calendar days or less for all of their patients (not just their Medicare patients) in the previous month. CMS is implementing the change under an amended administrative ruling (CMS-2020-1-R2) and coding instructions for the $25 add-on payment (HCPCS code U0005).

Laboratory groups are speaking up against the payment change. Most experts see supply shortages and other constraints as the cause of slow turnaround times, not a lack of financial incentive.

GOVERNMENT CRACKS DOWN ON CLIA RULES RELATED TO COVID-19

The Centers for Medicare and Medicaid Services (CMS) is focusing on making sure that clinical laboratories' CLIA certifications are up to date. After a recent record check, CMS issued 171 cease and desist letters since August 2020 to facilities that did not have proper CLIA certifications in place.

In a statement, CMS underscored that any facility that conducts SARS-CoV-2 testing is considered a laboratory and must be certified under CLIA. To make certification more efficient, CMS implemented an expedited review process at the beginning of the public health emergency and recently released a quick start guide that helps laboratories with the application process.

According to the agency, of the 171 cease and desist letters issued, 34% went to facilities conducting laboratory testing without a CLIA certificate and 66% were issued to laboratories performing SARS-CoV-2 testing outside the scope of their existing CLIA certification.

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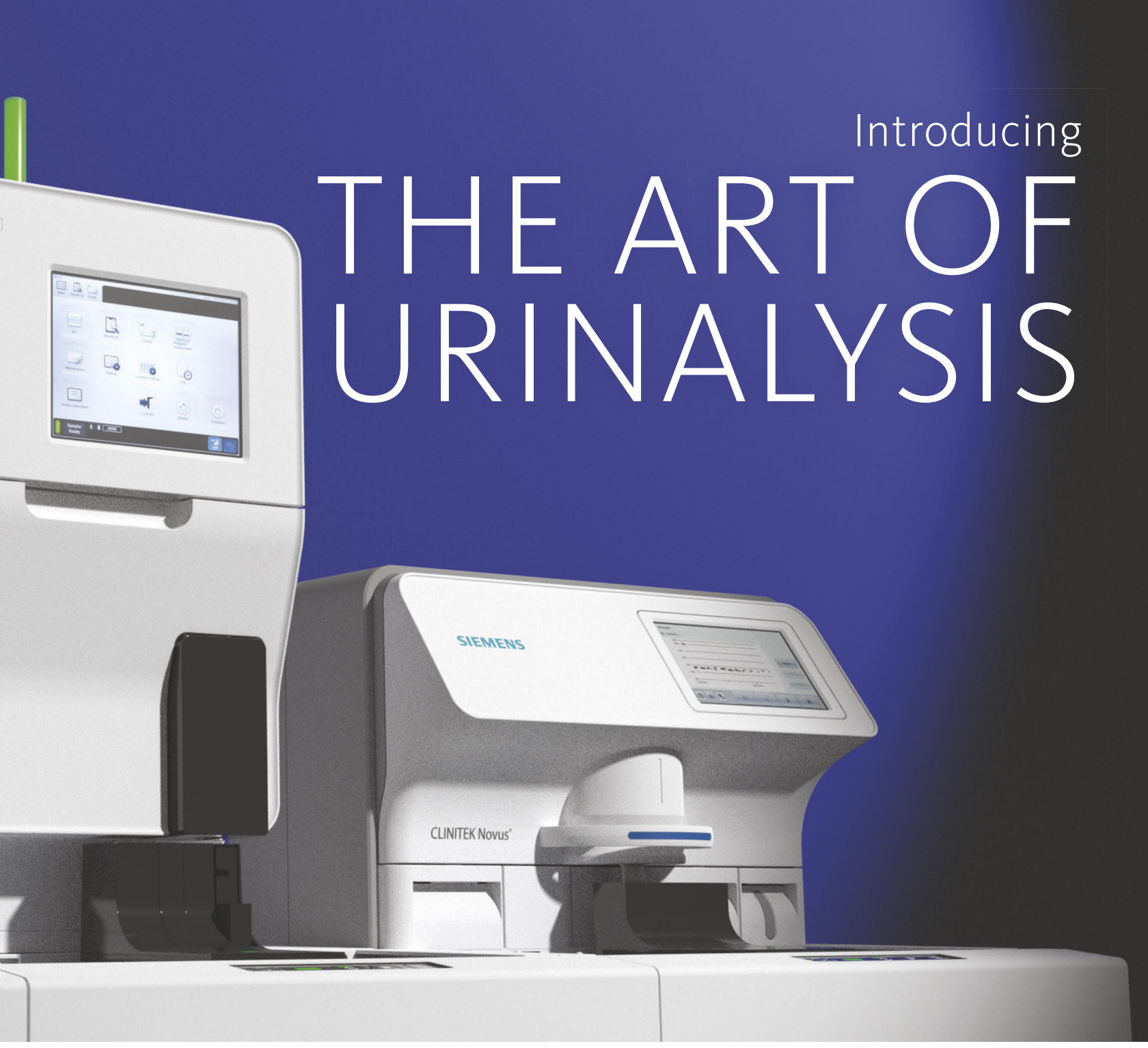

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Bench Matters

From Routine Analytes to Cytokines:

Diagnosticians Deliver Value to COVID-19 Diagnosis, Management, and Risk Assessment

Barnali Das, MD, DNB, PGDHHM

Diagnosticians are working alongside clinicians in supporting optimal care for patients with COVID-19. Routine laboratory markers provide key insights into this illness, contributing to patient admission protocols, guiding treatment, and assessing patients' risk of severe disease. Here at Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute in Mumbai, India, we have undertaken a study evaluating routine laboratory biomarkers in COVID-19 patients admitted with positive SARS-CoV-2 test results by real-time reverse transcriptase polymerase chain reaction (rRT-PCR).

Our study involved 528 subjects—370 males (70%) and 158 females (30%)—with a median age of 61 years, ranging from 12 to 93. We performed serial measurements of at least 22 routine laboratory biomarkers, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein (CRP), procalcitonin (PCT), cardiac troponin measured with a high-sensitivity assay (hs-cTn I or T), and lactate dehydrogenase (LDH).

In COVID-19 cases versus controls, we found significant increases in mean values of AST, ALT, total bilirubin, creatinine, CRP, PCT, LDH, interleukin-6 (IL-6), ferritin, lactate, hs-cTn I, and N-terminal pro B-type natriuretic peptide and decreases in mean values of albumin, saturated oxygen, and neutrophil lymphocyte ratio. We applied a receiver operating characteristic (ROC) curve to discriminate the case population more precisely than the control population.

Because severe COVID-19 has been linked to raging cytokine storm syndrome, we also performed serial measurements of analytes that might offer insights into this condition, including not only CRP, D-dimer, and ferritin but also cytokine tests, particularly IL-6.

SEVERE ILLNESS IN TWO CASES

Not every country has sex-specific data, but a clear trend has emerged in some places, including at our institution where we have seen not only a higher percentage of male patients but also a higher percentage of men experiencing more severe illness. The disease distribution also varies according to ethnicity. To explain the role of routine laboratory parameters in COVID-19 disease monitoring, we present below two cases involving an elderly female and an elderly male patient. Both cases also show that cytokine storm can affect both men and women.

CASE 1: A WOMAN WITH HYPERTENSION

An elderly female with a history of hypertension presented to the hospital complaining of breathlessness and fever for 2–3 days, along with generalized weakness. She did not have a history of recent travel or SARS-CoV-2 contact but was confirmed for COVID-19 through rRT-PCR testing. Her ECG showed changes in ST waves and T waves, in anterior and lateral leads. High-resolution CT scanning detected bilateral subpleural ground glass opacities, associated with small consolidations and crazy paving mainly in the right lobe, typical of viral infection.

This patient's laboratory findings supported the diagnosis of severe COVID-19 illness with elevated levels of ferritin (389.7 ng/mL), IL-6 (9.83 pg/mL), D-dimer (1,555.94 ng/mL), creatinine (1.34 mg/dL), hs-cTn I (130.6 ng/L), and CRP (3.33 mg/dL) (Table 1).

CASE 2: A MAN WITH DIABETES

An elderly male with diabetes, hypertension, and chronic kidney disease on maintenance hemodialysis presented to the hospital complaining of very high-grade fever for 3 days along with breathing difficulty and generalized weakness. The patient had no recent travel or SARS-CoV-2 contact history. He tested positive for SARS-CoV-2 by rRT-PCR from a nasopharyngeal swab, and his chest X-ray showed bilateral lung infiltrates.

This patient's routine laboratory findings supported the diagnosis of severe COVID-19 illness with elevated levels of IL-6 (650.5 pg/mL), CRP (17.3 ng/mL), PCT (2.02 ng/mL), hs-cTn I (45.9 pg/mL), D-dimer (3,298.31 ng/mL), ferritin (>40,000 ng/mL), LDH (745.2 U/L), creatinine (4.5 mg/dL), blood urea nitrogen (29.5 mg/dL), neutrophil count (85.7%), absolute neutrophil count (11 X 10^3/µL), lactate (3.3 mmol/L) and decreased levels of albumin (3.62 g/dL), total protein (6.3 g/dL), saturated oxygen (85.2%), lymphocyte count (6.2%), absolute lymphocyte count (0.8 X 10^3/µL), and platelet count (132 X 10^3/µL).

AN INSIGHT INTO IL-6

In individual cases and in our study overall, we have found IL-6 measurements to be particularly useful in discerning worsening COVID-19. For example, in a third case involving a

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T1 Trend Analysis of Routine Laboratory Markers in Case 1

Parameters	Reference Interval	Report Values												
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13
SARS-CoV-2		Detected												
IL-6 (pg/mL)	0-7										650.5			
CRP (ng/mL)	below 0.5	0.479				17.3	10.5	11.1	8.4	6.4	10.5	21.9	15.9	
PCT (ng/mL)	below 0.5	0.34				2.02	2.32	2.35	1.75	1.45			3.01	
AST (U/L)	10-50	14.1										35.0		
ALT (U/L)	below 41	20.2										37.5		
Total Bilirubin (mg/dL)	0.3-1.2	0.4										0.31		
D-dimer (ng/mL)	below 500	503.37							39948.6		3298.3	2230.5	2705	
Ferritin (ng/mL)	21.8-274.66	4268										>40000		>40000
LDH (U/L)	135-225	297.2									745.2	672.8	614.7	
Creatinine (mg/dL)	0.67-1.17	11	3.78			4.5		2.77	4.7	2.9	4.4	3.2		
BUN (mg/dL)	6-20	85.3	15.7			29.5		19.7	47.7	29.2	53.6	66.5		
SpO2%	95-98	95.60			25.2	74.3	80.9	85.0			72.1	73.2		72.8
Lactate (mmol/L)	0.7-2.5	1.3			1.4	1.4	2.4	2.0	2.0	3.3	2.9	3.9	3.9	
WBC Count (10^3/µL)	4-11	8.26		6.91	7.29	9.6	10.85	6.83	6.67	9.39	12.86	8.84	21.71	14.7
Neutrophil (%)	40-80	71.2		71.4	77.6	89.1	93	85.8	89.6	87.9	85.7	87.2	93.1	98
Absolute Neutrophil (10^3/µL)	2-7.5	5.9		4.9	5.7	8.6	10.1	5.4	6.0	8.3	11.0	7.7	20.2	13.2
Lymphocytes (%)	20-40	15.9		12.3	12.3	5.8	3.3	7.8	6.1	6.5	6.2	7.8	2.3	4.0
Absolute Lymphocyte (10^3/µL)	1-3	1.3		0.9	0.9	0.6	0.4	0.5	0.4	0.6	0.8	0.7	0.5	0.7
Platelet Count (10^3/µL)	150-410	132		101	86	81	78	77	87	102	144	112	86	53

BUN: blood urea nitrogen; SpO2: saturated oxygen; WBC: white blood cell

severely ill patient, a trend analysis of IL-6 found this analyte reaching a trough of 524 pg/mL 2 days after admission from a baseline of 2,766 pg/mL, then rebounding over the next 2 days to 1,056 pg/mL, while other markers of inflammation such as PCT, CRP, and D-dimer steadily declined. Ferritin joined IL-6 in an unfavorable trajectory, rising from a baseline of 4,097 ng/mL to 5,828 ng/mL 3 days later.

An ROC analysis to discriminate between COVID-19 cases admitted to intensive care versus healthy subjects found the ROC for IL-6 to be 1.0 with 95% confidence interval and a *P*-value <0.0001. In box plots of the IL-6 data from the case group, the first quartile (25th percentile) and third quartile (75th percentile) were 33.56 pg/mL and 295.15 pg/mL, respectively, with an interquartile range of 261.58 pg/mL, a median of 76.86 pg/mL, and whiskers to 7.24 pg/mL and 679.1 pg/mL. This illustrates the important role cytokines play in inflammatory and immunological response regulation.

The COVID-19 pandemic has notably underscored the essential role that we as diagnosticians play not only in identifying SARS-CoV-2 infections but also in supporting clinicians working strenuously to effectively manage patients with COVID-19 who exhibit a considerable spectrum of illness.

Barnali Das, MD, DNB, PGDHHM, is a consultant in laboratory medicine at Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute in Mumbai, India. She also is an executive member of the scientific division of the International Federation of Clinical Chemistry and Laboratory Medicine and chair of AACC's India section.
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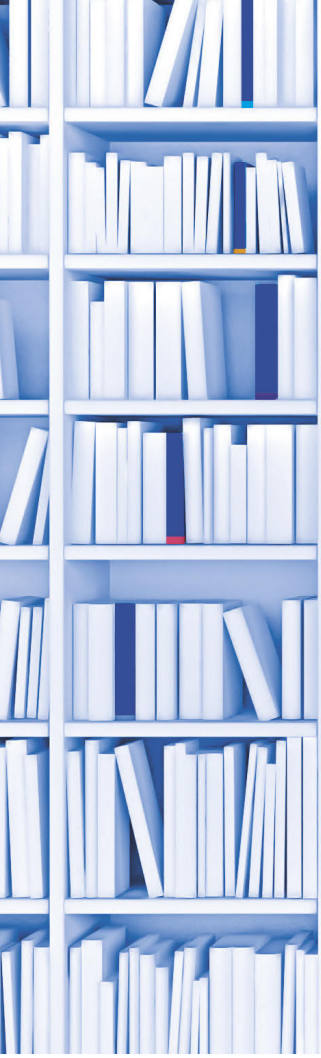

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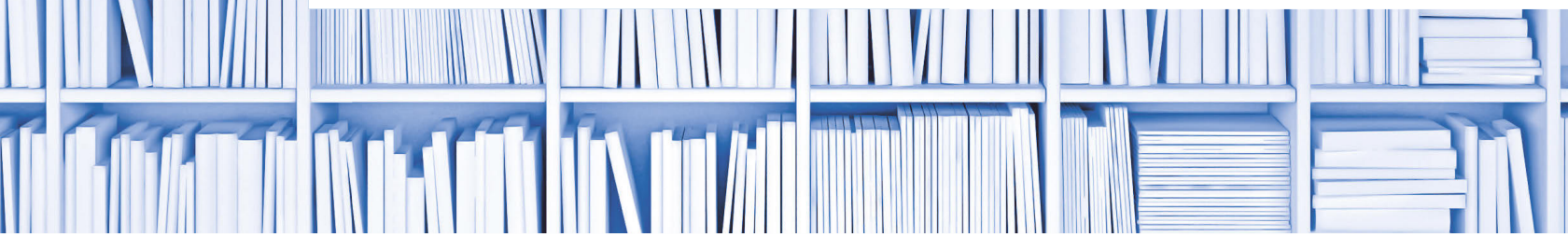

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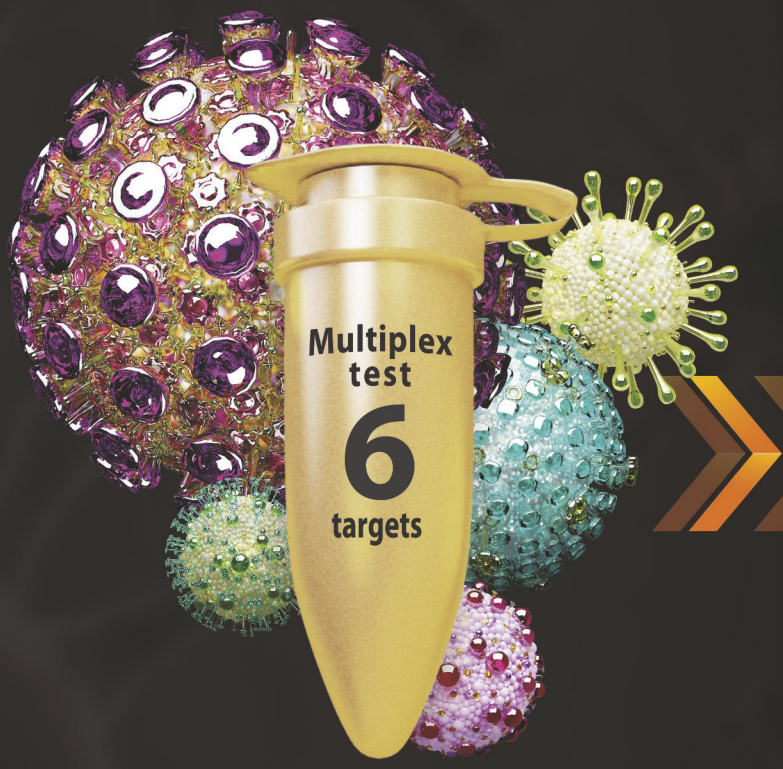

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The Sample

4 Lab Values Among Key Predictors of Worsening COVID-19

A COVID-19 Inpatient Risk Calculator (CIRC) based on 24 variables known to be associated with COVID-19 found that four lab measurements at admission—absolute lymphocyte count, albumin, cardiac troponin, and C-reactive protein—were among the inputs most predictive of in-hospital disease progression (Ann Intern Med 2020; doi:10.7326/M20-3905). Other highly predictive variables included age, nursing home residence, comorbid conditions, obesity, respiratory systems, respiratory rate, and fever. This information could help hospitals make important decisions about planning and resource allocations for COVID-19 care, according to the researchers.

Researchers at Johns Hopkins University developed CIRC based on data from patients with confirmed SARS-CoV-2 infection at five Johns Hopkins Medicine hospitals in Maryland and Washington, D.C. The study involved 832 consecutive patients admitted from March 4, 2020, to April 24, 2020, with data on their hospitalizations fed into JH-CROWN, a COVID-19 registry, which utilizes the Johns Hopkins precision medicine analytics platform.

The authors sought to determine the factors at admission most predictive of severe disease or death from COVID-19, as categorized by the World Health Organization disease severity scale. CIRC incorporated demographic data, comorbid conditions, vital signs, presenting symptoms, and 20 laboratory values.

Overall, 16% of patients died, while 63% had mild-to-moderate disease, and 20% had severe disease. Of patients admitted with mild-to-moderate disease, 38% progressed to severe disease or death, 60% within 2 days and 79% within 4 days.

CIRC had an area under the receiver operating characteristic curve to predict in hospital admission of 0.85, 0.79, and 0.79 at day 2, 4, and 7, respectively. Different combinations of risk factors predicted disease or death probabilities ranging from more than 90% to 5%.

The authors noted several lab-related limitations about the study. First, collection of key lab values was not standardized across Johns Hopkins Medicine or at individual hospitals, contributing to missing data. In addition, testing challenges might have resulted in not all COVID-19 cases being captured. Finally, respiratory virus panel testing was not available on all patients, so the model does not account for co-viral infections that might have altered patients' disease trajectories.

CIRC is available online to support providers in assessing their patients' risk of worsening disease: https://rsconnect.biostat.jhsph.edu/covid_predict/.

TARGETED GENETIC TESTING FOUND COST-EFFECTIVE IN NEWLY DIAGNOSED GIST

Targeted genetic testing is cost-effective for patients newly diagnosed with metastatic gastrointestinal stromal tumors (GIST) (JAMA Network Open 2020;3:e2013565). This finding supports widespread adoption of genetic testing for GIST, according to the authors.

Though still rare, GIST is the most common sarcoma, according to the investigators. Oncologists tend to prescribe imatinib for all patients with metastatic GIST, but this small molecule therapy provokes variable responses depending on patients' *KIT* variations. Patients also develop primary and acquired secondary resistance to imatinib. Guidelines recommend genetic testing for *KIT* variants in GIST to ensure imatinib therapy starts with the optimal dose; however, just 15% to 33% of patients actually undergo such testing, perhaps due to concerns about its cost and utility.

The authors developed a Markov model to compare the cost-effectiveness of targeted gene testing and variation-directed first-line therapy, versus empiric imatinib therapy. They explored outcomes for three genomic populations: *KIT* exon 11, *KIT* exon 9, and all other variations. The model also simulated treatment outcomes associated with first-line, second-line, and third-line therapies.

The authors determined the cost of targeted gene therapy based on

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Medicare claims data for multigene next-generation sequencing diagnostic tests.

Aside from cost, the other primary outcome was quality-adjusted life years (QALYs). The authors deducted 0.12 QALYs for each disease progression, represented by first-line, second-line, or third-line treatments, but did not deduct QALYs for any toxic effects from imatinib or sunitinib therapy. The model incorporated a willingness-to-pay threshold of $100,000 per QALY, with treatments less than this threshold deemed cost-effective.

The investigators determined that targeted gene therapy would increase QALYs by 0.10 at a cost increase of $9,513 compared with empiric imatinib therapy, for a $92,100 incremental cost-effectiveness ratio. A therapy-directed approach would remain cost-effective until genetic testing costs amounted to $3,730. A probabilistic sensitivity analysis found that this approach would be cost-effective 70% of the time.

I-TIME CARDIAC TROPONIN TEST USEFUL IN ASSESSING MORTALITY, CARDIOVASCULAR DISEASE RISK IN PATIENTS WITH DIABETES

Subclinical levels of cardiac troponin I and T measured with high-sensitivity assays (hs-cTn I/T) in a middle-aged population of people with diabetes are "robustly associated" with long-term mortality and cardiovascular disease (CVD) risk (Diabetes Care 2020;43:e144-6). These findings suggest that a single measurement of either analyte in middle-aged patients could be used to risk-stratify these individuals to help guide their clinical management, according to the investigators.

The authors included data from 1,704 participants in the Atherosclerosis Risk in Communities (ARIC) study, who were between the ages of 54 and 75, attended ARIC visit 4 (between 1996 and 1998), and had diabetes, as reported by physician diagnosis, medication use, or blood glucose level ≥126 mg/dL (fasting) or ≥200 mg/dL (nonfasting).

The investigators measured cTn I or cTn T from stored plasma drawn during ARIC visit 4 and examined incident CVD events through the last date of follow-up in 2018. They found 1,102 deaths in this cohort, of which 443 were CVD-related. The cumulative mortality was 37.4% and 44.6% in patients with hs-cTn I ≥90th percentile and no CVD, and hs-cTn T ≥90th percentile and no CVD, respectively. Meanwhile, the cumulative mortality was 43.1% in participants who had preexisting CVD.

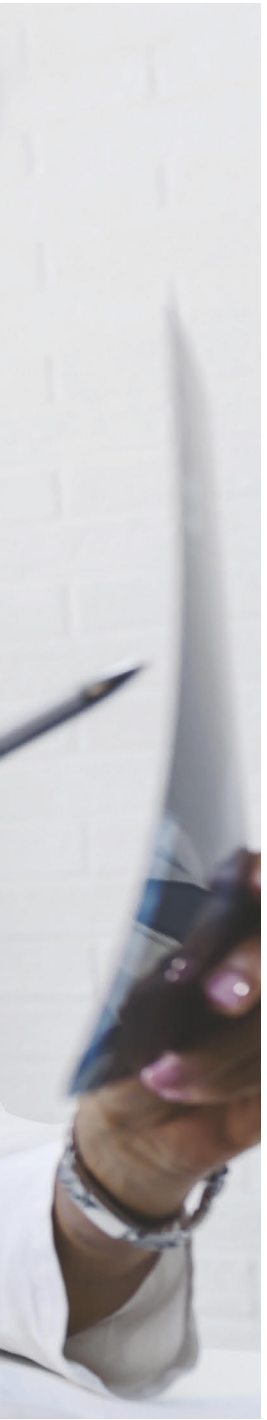
After they adjusted for traditional risk factors, the authors found both cTn I and cTn T were "independently associated with and significantly improved model discrimination" for all-cause and CVD-related mortality risk.

A NEW ERA FOR LIQUID

With approvals of 2 next-generation sequencing assays, lab insights about test performance, interpretation will be vital

BY DEBORAH LEVENSON

BIOPSY



Tissue biopsies—standard care for diagnosing cancer—can be invasive, risky, and painful. Some patients cannot have tissue biopsy because of tumors' locations, multiple metastases, or other health conditions. Liquid biopsy poses an alternative. Compared to tissue biopsies, this type of testing is less invasive, easily repeated, quicker, and more useful when a tumor's location makes tissue biopsy unfeasible.

Usually performed on blood, liquid biopsies analyze DNA from whole circulating tumor cells (CTCs) or cell-free DNA (cfDNA) from tumors. Many tests specifically target a type of cfDNA called circulating tumor DNA (ctDNA), most of which comes from cells in the bed of the tumors. Until recently, oncologists had at their disposal only two Food and Drug Administration (FDA)-approved liquid biopsy tests, and they targeted single genes. However, liquid biopsy entered a new era in August with FDA's approval of two tests that use next-generation sequencing (NGS) to target many genes in advanced cancer patients, including mutations for which there are targeted drugs, and to profile any solid tumor. These new tests are Guardant Health's Guardant 360 CDx assay, and FoundationOne Liquid CDx, marketed by Foundation Medicine.

"These tests allow oncologists to focus care on the molecule of origin rather than the cell type," said William G. Cance, MD, chief medical and scientific officer of the American Cancer Society. "Approval of these tests is another step in the pathway to precision medicine and targeted therapeutics."

While both tests represent a major advance in cancer diagnostics, their use involves several considerations, experts said. These issues include questions about the tests' sensitivity, potential for false positive results, and how to use negative results and information about mutations in genes for which there are no targeted therapeutics.

COMPANION DIAGNOSTICS AND MORE

Guardant 360Dx uses NGS to detect mutations in 55 tumor genes from circulating cfDNA in the blood. The test is approved both to provide information on multiple biomarkers of advanced solid tumors and as a companion diagnostic to identify specific *EGFR* mutations in patients who might benefit from treatment with osimertinib (Tagrisso) for a form of metastatic non-small cell lung cancer (NSCLC).

FoundationOne Liquid CDx targets 324 genes using circulating cfDNA in advanced cancer patients. This test also is indicated for use as a companion diagnostic, for assessing *BRCA1* and *BRCA2* mutation status in patients with metastatic, castration-resistant prostate cancer who might benefit from rucaparib (Rubraca), and for detecting *EGFR* exon 19 deletions or exon 21 L858R substitutions in patients with NSCLC for whom gefitinib (Iressa), osimertinib (Tagrisso), or erlotinib (Tarceva) might be effective.

FoundationOne Liquid CDx helps identify patients who might benefit from immunotherapy, including those whose tumors have cancer cells with a high degree of microsatellite instability (MSI), which affects proper repair of DNA inside cells and might respond to certain medications, said Nickolas Papadopoulos, PhD, professor of oncology and pathology at Johns Hopkins University in Baltimore. The test detects genomic signatures that include MSI.

Tumors with high mutational burden might also respond to immunotherapy. FoundationOne Liquid CDx provides information about the quantity of mutations within a tumor, added Christian Rolfo, MD, PhD, MBA, professor of medicine at University of Maryland School of Medicine in Baltimore.

PROS AND CONS

Answers from liquid biopsy are quicker than those for tissue biopsy, which involves scheduling and a procedure, in addition to lab work. Generally, the entire process for both the Guardant and FoundationOne tests takes 1 to 2 weeks, versus at least 2 to 4 weeks for standard biopsy, said Maximilian Diehn, MD, PhD, associate professor of radiation oncology at Stanford University in Stanford, California.

Tests can also be used for real-time monitoring to see if therapy is working, added Papadopoulos. Additionally, liquid biopsies can be repeated easily to see whether tumor cells or cfDNA are disappearing from the blood. When results—back quicker than those of standard biopsy—show treatment failure, "it's easy to pivot to another drug," added Cance.

Oncologists also could use the new liquid biopsy tests to monitor patients for emerging new mutations that could be treated with a therapy included in the FDA approval or another drug, noted Richard L. Schilsky, MD, chief medical officer and executive vice president of the American Society of Clinical Oncology.

The new tests' advantages must be balanced with their limitations. No guidelines directly address the newly approved tests, but 2019 National Comprehensive Cancer Network (NCCN) guidelines say for several reasons that older liquid biopsy tests should not replace tissue biopsy (nccn.org; ebulletin 1536). First, the guidelines point to low sensitivity and high false negative rates for tests that existed as of 2019. Meanwhile, no standards address analytical performance or recommend performance characteristics for cfDNA.

cfDNA testing can identify alterations that are unrelated to a lesion of interest, the NCCN guidelines add. For example, cfDNA testing could find clonal hematopoiesis (CH) of unknown potential. CH occurs when a hematopoietic stem cell develops into blood cells with the same genetic mutation, giving them a different genetic pattern than the rest of the blood cells. In rare cases, CH might lead to blood cancers.

Cance added that tumors are heterogenous, so it is impossible to know whether a liquid biopsy test analyzes DNA that represents a fraction of the tumor mutations or all mutations.

The FDA approvals call for use of Guardant 360Dx and FoundationOne Liquid CDx in conjunction with tissue biopsy, just as both the NCCN guidelines and a 2018 International Association for the Study of Lung Cancer (IASLC) statement did for older liquid biopsy tests that target single genes (Crit Rev Oncol Hematol 2020;150:102978).

Experts agree. "The tests may miss mutations because the tumor isn't shedding enough DNA into the blood," explained Diehn. "Just because these tests don't find a mutation doesn't mean it's not there. Therefore, doctors should consider a tissue test if the blood test is negative." Conversely, he added, sometimes liquid biopsy picks up mutations biopsy misses. "It may be advantageous to do both. Sometimes there's low tumor content in a biopsy specimen and tumor heterogeneity can lead to missing mutations. So using both tests could identify more candidates to target with particular therapies."

The NCCN guidelines do suggest that liquid biopsy alone can be considered in patients who are not healthy enough for biopsy or who cannot provide sufficient tissue samples, Diehn pointed out.

New liquid biopsy tests are "not as accurate as looking at tissue. . . However, the technology is getting more sensitive," added Papadopoulos.

Rolfo, first author of the 2018 IASLC statement, is working on an updated version that will comment on the use of Guardant 360Dx and FoundationOne Liquid CDx and other recent innovations in the field.

INTERPRETING RESULTS

In the meantime, oncologists will need education about the new liquid biopsy tests. Clinical laboratory professionals can help, Schilsky said. In particular, laboratorians would do well to explain liquid biopsies' sensitivity and specificity and what negative results might mean, as well as advise on how to navigate next steps. Oncologists will ponder their next steps after a negative result: accept that this finding means a patient truly has no cancer, repeat the test, or proceed to a tissue biopsy, if one hasn't already been performed.

Due to the tests' complexity, a molecular tumor board should interpret and assist treatment decisions, maintained Rolfo. Liquid biopsies detect both driver mutations that promote cancer development and passenger mutations that do not directly contribute to the cancer phenotype but could impact a treatment's success. "For example, responses to anti-*EGFR* drugs can be different, according to the presence of other mutations in the tumor," Rolfo said.

"Interdisciplinary molecular tumor boards should comprehensively analyze results in the context of the tumor and passenger, and their relationship to one another," added Umberto Malapelle, PhD, assistant professor in the department of public health at University of Naples (Italy) Federico II and a co-author with Rolfo of the 2018 IASLC statement.

THE ROAD AHEAD

Experts pointed to potential future uses for the newest breed of liquid biopsies. For example, even if new tests do not identify a mutation with a targeted therapy right now, they could qualify more patients for clinical trials, Schilsky noted. "For most trials, patients need measurable disease on imaging studies. If imaging doesn't find disease, patients are excluded from trials. If ctDNA level can be used as a validated end point for responding to treatment, you can have a baseline measurement and follow to see if ctDNA levels decline. It's like when you scan and see a tumor has shrunk as a response to treatment."

The tests might also monitor how patients do on treatment. "If the ctDNA level fails to decrease on treatment, the oncologist might have reason to switch treatment if there's a good backup drug. Test results that show a spike in ctDNA or whole cells may be a sign of recurrence," Schilsky added.

While these uses by themselves would be welcome, all eyes are on the day when liquid biopsy can be employed to spot cancer early. "The blood-first approach is almost here," Rolfo said. He predicted that liquid biopsy will be a tool not only for screening, but also for finding minimal residual disease and targeting processes that lead to cancer formation.

Having FDA approval for tests built on NGS means that FDA understands how to evaluate and regulate similar tests, added Papadopoulos. "The trials on which FDA based approvals say the assays are safe. Ongoing trials will show if they are useful."

For example, another Guardant test called Lunar, now available for research use only, is being evaluated for screening and detecting disease recurrence. Research is also determining whether Signatera, a Natera test that uses ctDNA, can monitor treatment and assess molecular residual disease. Life sciences company Grail is developing an early detection test for multiple cancer types. PapGene is engineering another early detection test that uses ctDNA and protein biomarkers to find cancer in average-risk, asymptomatic patients over age 65.

"Liquid biopsy will be part of routine care one day," Schilsky predicted. "Research needs to determine what type of cancer someone has and where in the body it's located. It needs more tissue specificity than we have today."

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Diehn, Malapelle, Papadopoulos, Rolfo, and Schilsky report disclosures. A full list of these relationships is available in the online version of this article, at aacc.org/cln

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The Hunt for a KIDNEY TROPONIN

Like its cardiac counterpart, a world-class, highly specific biomarker for acute kidney injury would be a game changer for diagnosis and clinical management

BY JOE M. EL-KHOURY, PHD, DABCC, FAACC

Acute kidney injury (AKI) is a common and serious syndrome affecting up to 15% of hospitalized patients and up to 50% of patients in the intensive care unit (ICU) or undergoing cardiac surgery, oncology treatment, or transplantation (*1*). Early diagnosis is critical so that clinicians can start appropriate management and avoid irreversible damage to the kidneys that can lead to chronic kidney disease or death.

Current criteria for diagnosing and staging AKI rely on a rise in serum creatinine or drop in urine output as described in the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines (Table 1) (*2*). However, patients' urine output is rarely measured, and serum creatinine is slow to react, taking 24–40 hours to increase in response to kidney injury (*3*). In addition, most forms of AKI do not involve the glomerulus but rather the renal tubular epithelium, so a decrease in glomerular filtration rate (GFR), as measured by creatinine or cystatin C, is not a sensitive indicator (*3*).

These limitations have fueled a search for a better AKI biomarker, which ideally would rapidly and specifically detect occurring kidney injury, measure prognosis, guide treatment, and improve patient outcomes. Over the last decade, several new AKI biomarkers have gained regulatory approval for human testing in different countries (Table 2), but only combined measurement of tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) [TIMP-2]×[IGFBP7] is authorized by the Food and Drug Administration (FDA) for clinical use in the United States.

Moreover, adoption of these AKI biomarkers into clinical practice has been slow due to a number of factors, leading to disparities in AKI care around the globe (*4*). This article will review the clinical utility of currently approved AKI markers listed in Table 2 and briefly highlight emerging approaches for the early detection of AKI.

NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN

Perhaps the most studied AKI biomarker is neutrophil gelatinase-associated lipocalin (NGAL), a 25 kDa protein that was first discovered in granules of neutrophils (*3*). It plays important roles in the kidneys, such as induction of the genesis of tubular epithelium. NGAL also is anti-inflammatory and antiapoptotic and as a transport protein is involved in iron-trafficking.

NGAL is upregulated and released into the urine following injury to the renal tubules. We now know that NGAL is not exclusive to the kidneys: It can also be found in lungs and large intestines, and its plasma levels can also increase due to hepatic production.

Two recent meta-analyses involving more than 2,500 patients each demonstrated moderately strong areas under the curve (AUC) of 0.72–0.82 for predicting AKI (*3*). NGAL's performance was stronger in studies involving children, yielding a pooled AUC of 0.90 (*5*). Among several biomarkers investigated in children, urine NGAL had the fastest rise postoperatively in those who developed AKI, peaking at 6 hours and remaining elevated (*5*).

Researchers have also investigated the predictability of long-term outcomes. Increased levels of urinary NGAL in patients with AKI were associated with 2-fold to 3.2-fold increased risk of mortality in a multicenter international study involving 1,199 adults who underwent cardiac surgery (*6*). On the other hand, age, female sex, urinary tract infections, and chronic kidney disease are also reported to increase urinary NGAL levels and might affect the specificity of the test (*3*). In addition, the availability of multiple assays and lack of standardization imply that different cutoffs are needed for every NGAL assay.

The largest barrier against implementing NGAL measurement in the U.S. is that there are currently no FDA-approved assays for this analyte. A few vendors might be selling these for research use only, which require additional considerations for validation and clinical use as laboratory developed tests.

LIVER-TYPE FATTY ACID-BINDING PROTEIN

Liver-type fatty acid-binding protein (L-FABP) is a 14 kDa member of the lipid-binding proteins superfamily and plays a crucial role in fatty acid uptake and its transfer between extracellular and intracellular membranes (*3*). Similar to NGAL, L-FABP is found in a variety of tissues other than the liver, like the intestine, lung, stomach, and kidney, and it is detectable in urine.

A meta-analysis of clinical studies evaluating L-FABP's ability to predict AKI after cardiac surgery showed poor to moderate AUCs between 0.52 and 0.85 (composite AUC = 0.72) (*3*). Also similar to NGAL, L-FABP performed better in children with studies reporting AUCs of 0.78–0.85, but it rises later and in studies performed best when measured 12 hours post-cardiopulmonary bypass surgery (*5*).

Outcome studies are much more limited for L-FABP than for NGAL. However, a recent study evaluated L-FABP's ability to predict long-term adverse outcomes in 1,119 patients being treated in a (nonsurgical) cardiac ICU and found that increased urine L-FABP (≥ 9.0 ng/mL) correlated with increased risk of all cause of death or progression to end-stage kidney disease (*7*). There are no FDA-approved assays

AKI and COVID-19

COVID-19 illness caused by SARS-CoV-2 has affected more than 39 million patients and caused more than 1 million deaths worldwide since its emergence in December 2019. The incidence of acute kidney injury (AKI) among patients admitted with COVID-19 is as high as 28% in some U.S. cities, with a staggering 60% of the AKI cohort requiring renal replacement therapy and a 50% in-hospital mortality rate.

A clear explanation for the link between the high incidence and mortality rates of AKI in COVID-19 patients is still lacking because "sepsis-related" pathways have not been firmly established. Recent evidence supports a direct viral attack theory due to the binding of COVID-19 with angiotensin converting enzyme 2, expressed in the proximal tubules, to gain entry into the host cells and directly damage the kidney tubules.

for L-FABP in the U.S., limiting its adoption in clinical practice.

TIMP-2 AND IGFBP7

TIMP-2 and IGFBP7—both cell-cycle regulators—are considered second-generation AKI biomarkers because they were derived using a rigorous discovery process rather than starting from a model system (*3*). Both markers are measured together in urine and reported as a product of both levels, [TIMP-2]×[IGFBP7], with $(ng/mL)^2/1000$ as the unit.

This combined measurement method was the first FDA-approved test for assessing the risk of developing AKI. It was approved in 2014 for predicting the development of moderate to severe AKI (KDIGO stage 2 and 3) within 12 hours from sample collection. At the present time, standardization is not a problem, because Astute Medical (now owned by bioMérieux) is the only company that produces and markets this test under the name NephroCheck with the result labeled AKIRisk.

In early validation studies, urinary [TIMP-2]×[IGFBP7] outperformed all other markers—including urinary and plasma NGAL, plasma cystatin C, and urine L-FABP—for the development of moderate to severe AKI within 12 hours, with an AUC of 0.80. This test has since been studied in over 1,800 critically ill patients in different settings with promising outcomes (*8*).

However, the performance of the test in studies has varied widely depending on the cutoff, testing time, and diagnostic criteria used. First, the recommended 0.3 $(ng/mL)^2/1000$ cutoff had poor specificity and generated a significant number of false positives, while a threshold of 2.0 $(ng/mL)^2/1000$ yielded almost 100% specificity but poor sensitivity. This is not surprising considering that the thresholds fall within the reference intervals, which were reported to be 0.04–2.22 $(ng/mL)^2/1000$ from 750 subjects by a large multi-center study (*9*). Second, the AUCs were best when measured 3–12 hours from cardiopulmonary bypass surgery, ICU admission, chemotherapy administration, or other procedures with high risk for AKI development.

Lastly, studies that evaluated the performance of [TIMP-2]×[IGFBP7] for the development of Stage 1 AKI—for which the test was not approved—reported poorer performance, as expected. However, urinary [TIMP-2]×[IGFBP7] has not been studied as well in pediatric populations, and clinical labs are cautioned against implementing this test in patients with low risk for developing AKI due to its suboptimal specificity (*8*). Therefore, optimization of different cutoffs and collection times for specific populations is needed prior to implementation.

Overall, lack of widespread adoption might be attributed to this test's suboptimal specificity at the recommended 0.3 $(ng/mL)^2/1000$ cutoff, limited performance studies outside of ICU or perioperative settings, and lack of positive impact on patient outcomes. Clearly [TIMP-2]×[IGFBP7] is no kidney troponin, and future studies should examine if combining it with clinical examinations, symptoms, or other biomarkers will improve its diagnostic accuracy.

Nevertheless, this test's clinical utility has been demonstrated in very specific populations and is already recommended for use in certain practice guidelines, most notably for perioperative care in cardiac surgery (*4*). However, both the National Institute for Health and Care Excellence (NICE) in the U.K. and the AACC Academy in the U.S. *(in press)* state that there is not enough evidence to recommend its routine use (*10*). They recommend additional research to assess [TIMP-2]×[IGFBP7]'s clinical effectiveness as part of care bundles and its effect on clinical outcomes.

NOVEL MARKERS AND TOOLS

The clinical utility of other AKI biomarkers can be further subclassified into biomarkers of tubular injury, tubular function, kidney inflammation, and adaptive repair and fibrosis (*11*). A detailed discussion on these research markers is beyond the scope of this article, but interested readers will find an excellent summary by Zhang et al. (*11*).

While some of these other markers hold promise, notably their performance in clinical trials has varied significantly. This variability might trace back to the use of research assays from different vendors and the lack of sufficient information in reported studies on the assay used or the epitope of antibody targets, among other reasons (*12*). Therefore, researchers and assay manufacturers need to provide in their reports detailed assay information, validation data, and preanalytical data.

Another exciting development in this space came from a collaboration between clinicians and machine-learning researchers from a Google subsidiary in the U.K. called DeepMind. This research, reported

T1 KDIGO 2012-based Definition of Acute Kidney Injury

Diagnostic criteria for AKI	
• Increase in serum creatinine by ≥0.3 mg/dL (26.5 µmol/L) within 48 hrs; or • Increase in serum creatinine to ≥1.5 times baseline, known or presumed to have occurred in the past 7 days; or • Urine volume <0.5 mL/kg/h for 6 hours	
AKI Staging	
AKI Stage I	• Increase ≥0.3 mg/dL (26.5 µmol/L); or • Increase to 1.5-1.9 times from baseline; or • Urine volume <0.5 mL/kg/h for 6-12 hours
AKI Stage II	• Increase to 2.0-2.9 times from baseline; or • Urine volume <0.5 mL/kg/h for ≥12 hours
AKI Stage III	• Increase to ≥3.0 times from baseline; or • Serum creatinine ≥4.0 mg/dL (≥354 µmol/L); or • Initiation of renal replacement therapy; or • Decrease in eGFR to <35 mL/min/1.73m² in patients <18 years; or • Urine volume <0.3 mL/kg/h for ≥24 hours; or • Anuria for ≥12 hours

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by Tomasev et al. in *Nature*, leveraged data from more than 700,000 individuals across 1,239 healthcare facilities in the U.S. Veterans Affairs database to create a computational model that predicts the development of AKI in 48 hours (*13*). The reported AUC was 0.92, eclipsing the best performing blood and urine biomarkers studied thus far.

This research effort employed an algorithm with impressive complexity, including 620,000 variables as inputs to the model. A major downside is that any one of these inputs can "break" easily, as can happen when, for example, a test name is changed or a lab migrates laboratory information systems (*14*). As a result, thorough validation and quality management plans are desperately needed before artificial intelligence can be safely implemented in clinical medicine (*15*).

CONCLUSION

Over the last decade, we have seen a rise in the number of AKI biomarker assays gaining regulatory approval for clinical use, with some even making it into clinical practice guidelines. Current research is still focused on understanding the different roles that current and emerging biomarkers play in AKI diagnosis, management, and prognosis.

Alas, the hunt for the elusive kidney troponin continues. If recent reports are any indication, then perhaps it has always been in front of our eyes. We just lacked the "intelligence" to recognize it.

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T2 Urine Biomarkers Approved for Clinical Use by Region or Country

Urine Biomarker	Regulatory Approval for Clinical Use (Year)
NGAL	European Union (2009) Canada Korea Israel
L-FABP	Japan (2011)
[TIMP-2]×[IGFBP7]*	United States (2014) European Union (2012)

NGAL, neutrophil gelatinase-associated lipocalin
L-FABP, liver-type fatty acid binding protein
TIMP-2, tissue inhibitor of metalloprotease 2
IGFBP7, insulin-like growth factor binding protein 7
*Currently marketed as NephroCheck test and result referred to as AKIRisk Score

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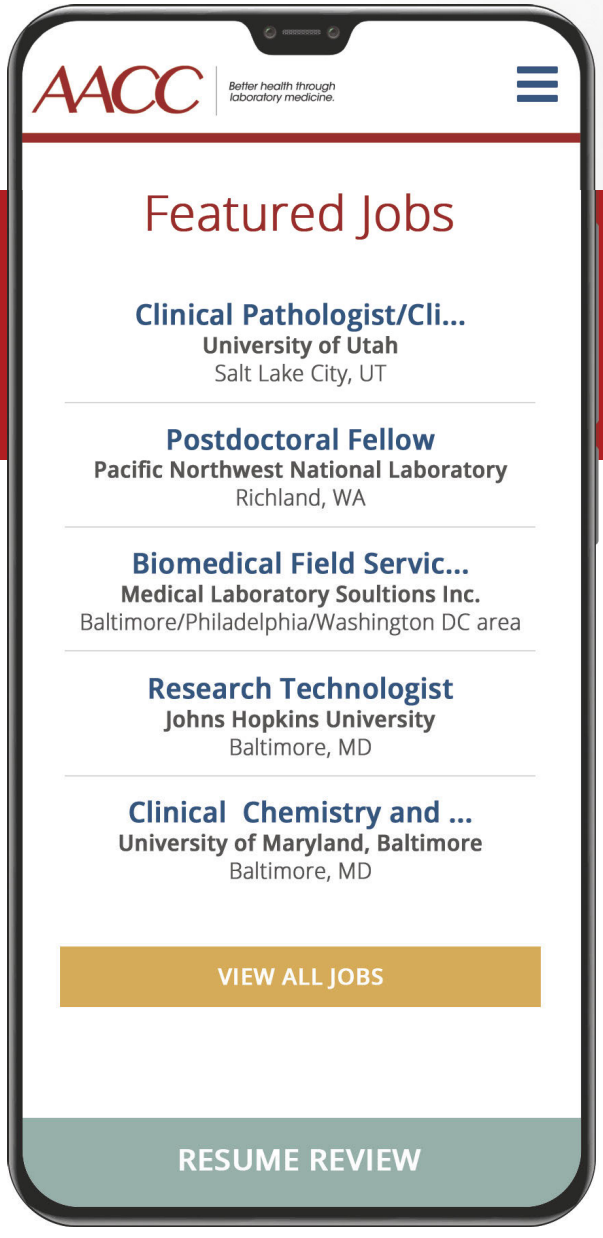

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HHS Decision Raises Questions About FUTURE OVERSIGHT OF ALL LDTS

While framed as regulatory relief during the COVID-19 pandemic, the action could have a broader impact

BY KIMBERLY SCOTT

The Department of Health and Human Service's (HHS) recent announcement that the Food and Drug Administration (FDA) will not require premarket review of laboratory developed tests (LDTs) absent notice-and-comment rulemaking has raised new questions about future oversight of LDTs.

At the beginning of the COVID-19 pandemic, FDA first required laboratories to obtain emergency use authorization (EUA) before using LDTs to detect SARS-CoV-2. After pushback from AACC and other laboratory groups, FDA announced a policy under which clinical laboratories still need an EUA, but they could begin using LDTs immediately pending FDA review. While FDA typically has not required such premarket review for LDTs, the agency has maintained that it has the authority to require such review.

This change, detailed in an August 19 notice, first indicated that clinical laboratories may still voluntarily seek EUA for LDTs, but they are not required to do so. On October 7, FDA posted another update that it would no longer review EUA requests for LDTs. "FDA continues to prioritize review of EUA requests for POC tests, home collection tests, at-home tests, tests that reduce reliance on test supplies, and high-throughput, widely distributed tests," the agency posted on its website.

Laboratories that offer such LDTs without premarket authorization will not be eligible for liability protection under the Public Readiness and Emergency Preparedness Act. Clinical laboratories that have already obtained an EUA or other marketing authorization for an LDT are not affected by the announcement.

While the notice referenced LDTs to test for SARS-CoV-2, the implications of this change are much broader, affecting all LDTs. In a frequently asked questions (FAQs) document posted shortly after the announcement, HHS said the notice is broadly applicable to all LDTs, regardless of what they are testing for.

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"The decision means FDA will have to take a step back and go through the appropriate channels in order to regulate LDTs," said Patricia Jones, PhD, DABCC, FAACC, clinical director of the chemistry and metabolic disease lab at Children's Medical Center of Dallas and chair of AACC's Policy and External Affairs Committee. "The notice doesn't say FDA can't regulate LDTs; it just says the agency can't do it without formal rulemaking. It gives labs a bit of a breather."

FDA's jurisdiction to regulate LDTs under the medical device provisions of the Federal Food, Drug, and Cosmetic Act has long been the subject of debate. FDA for years has asserted that it has legal authority over LDTs but has chosen to exercise "enforcement discretion" not to regulate such tests in most situations. The clinical laboratory community disagrees and maintains that tests developed in clinical labs for use only in those labs should not be subject to FDA oversight.

FDA several times has tried to define just what its role should be in overseeing LDTs. In October 2014, the agency issued a controversial draft guidance proposing a framework for regulatory oversight of LDTs, including, among other things, phasing in premarket review of most LDTs. In November 2016, FDA then said it would not finalize this guidance document. But in January 2017, the agency issued a "discussion paper" regarding another proposed framework for LDTs that included, among other things, premarket review.

Congress has also tried to tackle the thorny issue of LDT oversight, though efforts in the past have failed. Sen. Rand Paul (R-Ky.) tried again this year, introducing the Verified Innovative Testing in American Laboratories (VITAL) Act, which would accelerate test approval during public health emergencies by codifying that current federal regulations place oversight of LDTs under CLIA. AACC, which endorsed the VITAL Act, has long held that LDTs are already regulated under CLIA and do not need an additional layer of oversight from FDA. The VITAL Act was referred to committee, but no action has yet been taken on it.

Another measure, the Verifying Accurate and Leading-Edge IVCT Development (VALID) Act, also was introduced this year. This legislation attempts to set out a regulatory framework for in vitro clinical tests (IVCTs), which would cover an array of clinical tests, including LDTs and in vitro diagnostics (IVDs) sold to laboratories by manufacturers. AACC opposes the VALID Act, arguing that giving FDA new, expansive powers to regulate LDTs would result in decreased patient access to essential medical tests.

NOTICE ONLY APPLIES TO PREMARKET REVIEW

HHS's announcement does not question FDA's long-standing position that it has the statutory authority to regulate LDTs as medical devices and that its LDT policies have been grounded in enforcement discretion, notes Greg Levine, an attorney with Ropes & Gray in Washington, D.C. Nor does the announcement deal with any aspect of FDA regulatory oversight other than "premarket review."

The HHS FAQs specifically state, "Although FDA has asserted the authority to do so, [the premarket review] requirement has in fact almost never been enforced. It was only being enforced during public health emergencies, and we are simply reverting to the same level of regulatory requirements that were in place during all other times."

The announcement does, however, acknowledge that FDA could, at least theoretically, seek to impose premarket review requirements for LDTs through notice and comment rulemaking, though Levine noted that FDA's efforts to assert its regulatory authority over LDTs have stalled in recent years, and FDA appears to have resigned itself to waiting for congressional action.

"It is possible HHS's announcement could spur Congress to take such action," Levine said. "However, in an election year, the passage of LDT legislation by the current Congress, such as the VALID Act, remains unlikely."

HHS FACES CRITICISM

While the laboratory community has largely praised HHS's August 19 notice, Scott Gottlieb, FDA commissioner from 2017 to 2019, has criticized the decision, saying that it could hinder FDA's ability to protect public health. In a series of tweets shortly after the notice was announced, Gottlieb argued the HHS decision will have potentially dire consequences for the nation's response to COVID-19.

"For the last 6 months, FDA's device center worked effectively with labs to advance hundreds of tests for COVID," he wrote. "A new policy that extricates FDA from this work—and goes further, by removing any FDA role over any lab developed test—could put this work at risk."

Gottlieb also said the decision means FDA might not be able to provide critical advice to test developers or take needed enforcement actions against bad tests. "We'll see

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Disclaimer: AACC collected 60 mL of blood from volunteer donors attending the AACC Annual Meeting in Atlanta, GA in order to establish the 99th percentile for cardiac troponin in a healthy population. After collection, the blood was processed on site, divided into equal sample sizes and then transported to CDC for storage at -80°C. Samples were de-identified and no test results will be provided to donors. Sets of donor samples are being offered to IVD manufacturers of cardiac troponin assays for purchase. AACC has undertaken this activity as part of its mission to further scientific research. THE DONOR SAMPLES ARE PROVIDED "AS IS". AACC DISCLAIMS ALL WARRANTIES INCLUDING IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE.

a plethora of [direct-to-consumer] COVID tests enter the market, where tests ship directly to consumers and are processed in a central lab operating outside FDA oversight," he tweeted.

Levine, however, emphasized that the notice does not take away FDA's ability to crack down on test developers who make false claims. While FDA will not be able to pursue enforcement for failure to comply with premarket review requirements, false and misleading labeling and promotion claims will continue to be fair game for FDA, the Federal Trade Commission, Department of Justice, and state regulators under applicable consumer protection and fraud statutes, he said.

However, Jeff Gibbs, an attorney with Hyman, Phelps & McNamara and contributor to the FDA Law Blog, believes there is some ambiguity on this point, noting that FDA's previous actions against labs whose tests were considered unsafe or misbranded were based on the agency's position that it has the authority to regulate LDTs.

"HHS's announcement, while short on specifics, apparently takes the position that FDA can't regulate LDTs absent rulemaking," he said. "Given that, it is difficult to see the legal basis that FDA could assert to support action against a lab, even if FDA deemed a test to be unsafe or the lab's claims to be false. FDA has no general mandate to regulate laboratory developed tests."

DEVELOPING A COMMON REGULATORY FRAMEWORK

Two senior managers at FDA also pushed back against the decision not to require premarket review for SARS-CoV-2 LDTs. In an editorial published September 9 in the *New England Journal of Medicine*, Jeff Shuren, MD, JD, and Timothy Stenzel, MD, PhD, wrote that they believe FDA has a role in overseeing clinical tests, whether they are developed by commercial manufacturers or by laboratories, especially during a public health emergency. Shuren is director of FDA's Center for Devices and Radiological Health, and Stenzel is director of the Office of In Vitro Diagnostics and Radiological Health.

Whether developed by an IVD company or a clinical laboratory, diagnostic tests should undergo thorough review, according to Shuren and Stenzel. "We need common approaches to validating test design and performance, regardless of whether there is an emergency," they wrote. "Our experience with COVID-19 highlights the need for a common legislative framework to ensure that all clinical tests are accurate and reliable."

Jones agrees that a regulatory framework is necessary, but she believes the basic framework already exists in CLIA. "CLIA does need to be updated, but I don't think we need to create a new regulatory structure under FDA. We already have the structure in place."

Kimberly Scott is a freelance writer who lives in Lewes, Delaware.
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Regulatory Roundup

OralDNA Labs Gets EUA for First Oral Rinse SARS-CoV-2 Test

The Food and Drug Administration (FDA) has granted an emergency use authorization to OralDNA Labs for the OraRisk COVID-19 RT-PCR test, which is the first FDA-authorized test for SARS-CoV-2 that uses a saline oral rinse sample. OralDNA Labs hopes that this type of sample collection will reduce exposure of front-line healthcare professionals to the virus by shortening collection time, in addition to helping with supply chain bottlenecks by reducing the need for swabs. Oral rinse sample collection also avoids the difficulty some individuals have in providing sufficient saliva for direct saliva testing. To collect an oral rinse sample, patients gargle for 30 seconds with a saline solution. Samples are then viable for up to 72 hours and do not require cold pack transportation. Laboratories can also use the OraRisk COVID-19 RT-PCR test with nasopharyngeal swab and nasal swab specimens collected in universal transport media, and nasal swabs collected in oral saline rinse.

OralDNA Labs

FDA GIVES EUA TO BECKMAN COULTER FOR IL-6 TEST FOR COVID-19 PATIENTS

Beckman Coulter has received Food and Drug Administration emergency use authorization for its Access Interleukin-6 (IL-6) assay. Access IL-6 is a fully automated immunoassay designed to detect IL-6 levels in serum and plasma, and is intended to help physicians identify severe inflammatory response in COVID-19 patients and to determine the likelihood that a patient will need intubation with mechanical ventilation. Preliminary studies have shown that IL-6 levels are elevated in patients with severe COVID-19 and that IL-6 may contribute to the severe inflammatory response, also known as cytokine storm, that leads to acute lung injury, pneumonia, or acute respiratory distress syndrome. Testing for IL-6 could enable physicians to treat patients before they need ventilators, which could reduce the number of patients on ventilators and improve outcomes.

ASSURE TECH RECEIVES EUA FOR FIRST POINT-OF-CARE TEST FOR SARS-COV-2 ANTIBODIES

The Food and Drug Administration (FDA) has issued an emergency use authorization (EUA) to Assure Tech for the first point-of-care SARS-CoV-2 serology test, a 15-minute lateral flow assay called the Fastep COVID-19 IgG/IgM rapid test device. FDA first authorized this test in July 2020 for emergency use by certain labs to help identify individuals with antibodies to SARS-CoV-2 that indicate recent or prior infection. With this latest EUA, FDA is expanding its initial authorization of the test to include point-of-care testing using fingerstick blood samples. This means that healthcare professionals can now use this device to test for SARS-CoV-2 antibodies in doctors' offices, hospitals, urgent care centers, emergency rooms, and other patient care settings operating under a CLIA Certificate of Waiver, Certificate of Compliance, or Certificate of Accreditation. Assure's test is also authorized for use with venous whole blood, serum, and plasma.

ROCHE GETS EXPANDED FDA APPROVAL FOR CERVICAL CANCER TRIAGE TEST

The Food and Drug Administration (FDA) has approved expanded use of Roche's CINtec Plus Cytology, the first biomarker-based triage test for women whose cervical cancer screening results are positive for high-risk types of human papillomavirus (HPV). This test is designed to support clinical decisions about which of these women will benefit most from immediate follow-up, and was initially approved by FDA in March 2020. This new approval allows labs to use the CINtec Plus Cytology in conjunction with Roche's cobas HPV test.

The CINtec Plus Cytology test detects the simultaneous presence within a single cell of two biomarkers, p16 and Ki-67. This abnormality is associated with HPV infections that are transforming and can, if left

untreated, progress to pre-cancer or cancer. A positive result of these two biomarkers in a single cell therefore signals that a woman is at significantly higher risk for disease. On the other hand, women with negative dual stain results are at significantly lower risk for cervical disease and can be given more time to clear the HPV infection on their own.

FDA PROPOSES RECLASSIFYING CERTAIN CYTOMEGALOVIRUS DNA TESTS

The Food and Drug Administration has issued a proposed order to reclassify certain cytomegalovirus (CMV) quantitative tests intended for transplant patient management. The agency hopes that this proposed order, when finalized, will provide patients with more timely access to these tests by reducing the regulatory burdens currently associated with them. The order will reclassify certain CMV DNA quantitative assay devices from class III to class II, which means that manufacturers will no longer be required to submit a premarket approval application for these tests, and will instead only have to submit a premarket notification and obtain 510(k) clearance. The order will also rename these devices to "quantitative CMV nucleic acid tests for transplant patient management" and provide special controls that, in addition to general controls, will provide a reasonable assurance of safety and effectiveness for these types of tests. This proposed order will not impact CMV tests that are not based on the detection of CMV DNA.

CE MARK GRANTED TO PROCISEDX FOR POC TESTS FOR MONITORING IMMUNOSUPPRESSIVE DRUGS

ProciseDx has received the CE mark for its infliximab and adalimumab point-of-care drug level tests, which are called the Procise IFX and Procise ADL, respectively, and are designed for use on the ProciseDx system. Standard tests for monitoring these biologic drugs take up to 1 week to return results, which can delay dose adjustment for 2 to 6 weeks. ProciseDx's new point-of-care tests, on the other hand, deliver therapeutic drug monitoring results in less than 5 minutes using blood from a finger-prick. The company hopes this will improve treatment for patients using infliximab and adalimumab (also known as Remicade and Humira) by enabling immediate decisions on drug dose adjustments at the time of infusion. Infliximab and adalimumab are both immunosuppressive drugs that block the immune regulatory protein tumor necrosis factor-alpha. They are used to treat a number of autoimmune conditions, including a few different types of arthritis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis.

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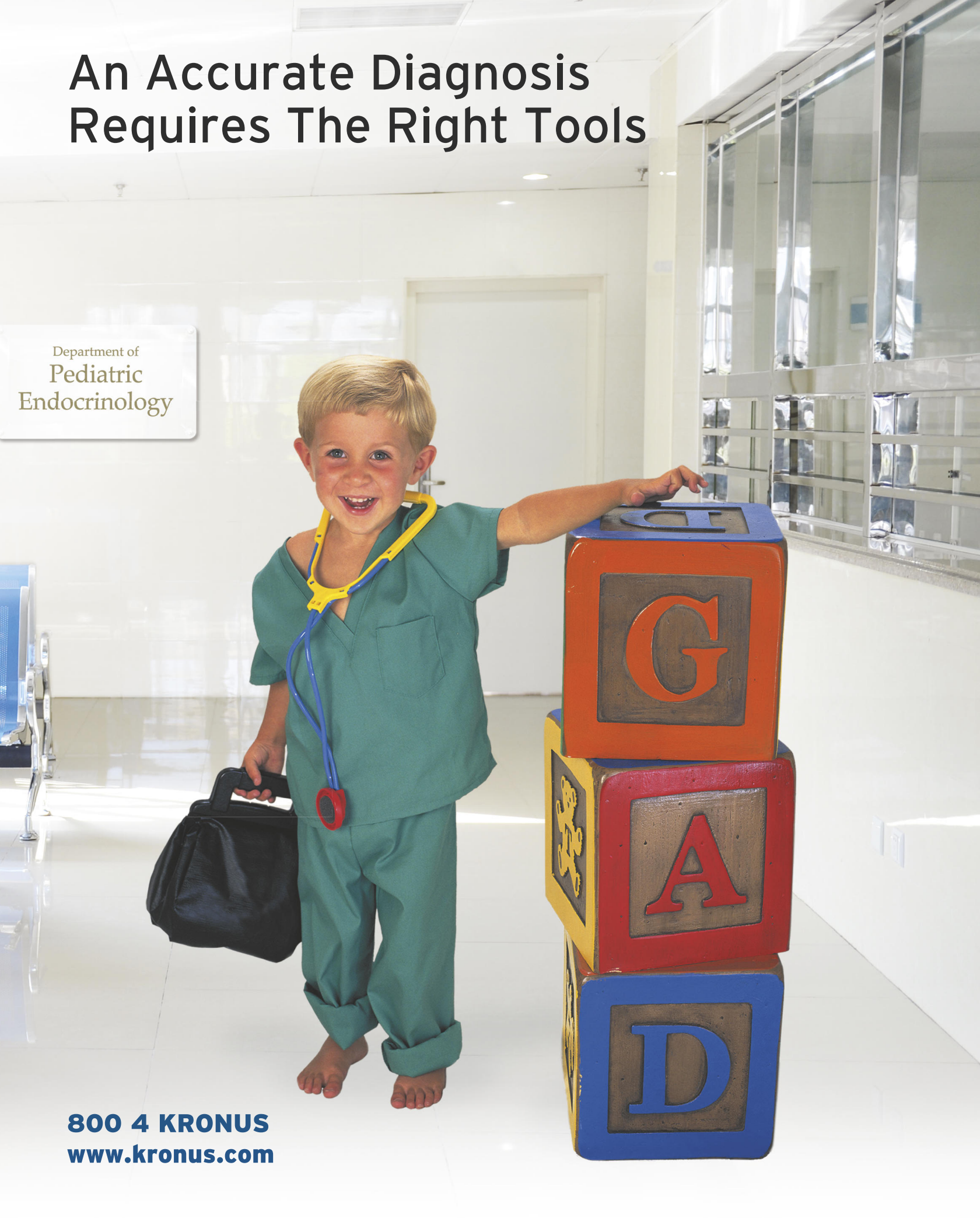

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Building a Digital Adventure

The laboratory medicine community is gearing up for the first all-virtual AACC Annual Scientific Meeting & Clinical Lab Expo, December 13–17, 2020

This year's unique, all-virtual 2020 AACC Annual Scientific Meeting & Clinical Lab Expo will be an energizing platform for attendees to share their labs' stories, hear about others' experiences, and—importantly—catch up with the evolving science around not only SARS-CoV-2 testing but also all other areas of lab medicine.

Many disciplines outside infectious diseases have made notable strides to provide excellent patient care during the pandemic. Clinical laboratorians continue to improve and refine the tools clinicians need to ride a wave of innovation and fulfill technology's promise in healthcare.

The meeting will also be a time away from the unsteady pace and buzzing distractions that have defined a volatile period in healthcare and in the world. If ever there was a time to step back and take in the big picture of laboratory medicine—from exciting developments in data analytics to new assays and instruments—this is it. The 2020 AACC Annual Scientific Meeting & Clinical Lab Expo also will be an opportunity to make the meaningful connections that encourage, inspire, and sustain attendees in the face of the unyielding demands they deal with every day in labs worldwide.

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Here are *CLN*'s top tips for making the most of this year's meeting:

1 Take the time needed for professional growth and refreshment

It can be tempting to try and cram a virtual conference into one's regular weekly schedule. Don't. Treat this time the same as if traveling to a meeting for an in-person event. Even if it's not possible to take several days off work, block off a number of hours over the week for uninterrupted learning and networking.

2 Plan the experience based on personal needs and goals

Just like planning time for an in-person conference, getting the most out of a virtual event takes a thoughtfully prepared schedule that considers specific goals. This way sessions, exhibits, and events will match your needs. The event platform is big—full of hundreds of sessions, exhibitors, and other special content. Navigating with a purpose in mind will help you to stay focused and make the best use of time.

Fun and networking events are also built into the program. Networking and socializing will be different in the virtual domain, but remember that professional development encompasses cultivating relationships and engaging in activities that bring much-needed encouragement and a sense of belonging.

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3 Get into the right mindset

First-time virtual conference attendees might find they face some of the same challenges as people do when they're working from home instead of an office, such as missing the normal cues that their work has begun or ended. Part of making a schedule should include a plan for starting and closing each day. Attendees who will be joining the meeting from home will do well to carve out a comfortable space that's a little separate from where their usual downtime activities occur so they can focus.

Many sessions will be available on-demand both during and after the official meeting dates, enabling attendees to take in more sessions than during a face-to-face meeting when it's not possible to attend sessions scheduled simultaneously. But this emphasizes the importance of a good plan: Putting off attending a session for later without a specific time for doing so might mean never getting to it.

Need to focus on a specific area of laboratory medicine at the 2020 AACC Annual Scientific Meeting? Chart a course based on your needs and interests first, then add other sessions that might be outside your comfort zone to freshen your skills.

Novel Coronavirus

Pandemic Preparedness: The Role of Clinical Laboratories and Public Health in Controlling Outbreaks Representing a Global Health Threat

SARS-CoV-2: Virology and Evolving Diagnostic Paradigms

Vaccine Basics for SARS-CoV-2

Antibody and Antigen Testing for SARS-CoV-2: Where Are We Now?

Data Analytics

Practical Examples of Predictive Analytics: Leveraging Data Science to Solve Problems in Your Laboratory

Data-Driven Quality Assessment

How Should We Collaborate to Realize the Value of Real-World Evidence for IVD?

Integrating Technology, Data Analytics, and the Laboratory Value Pyramid for High-Value Patient Outcomes

Point-of-Care Testing

Point-of-Care Testing Boot Camp

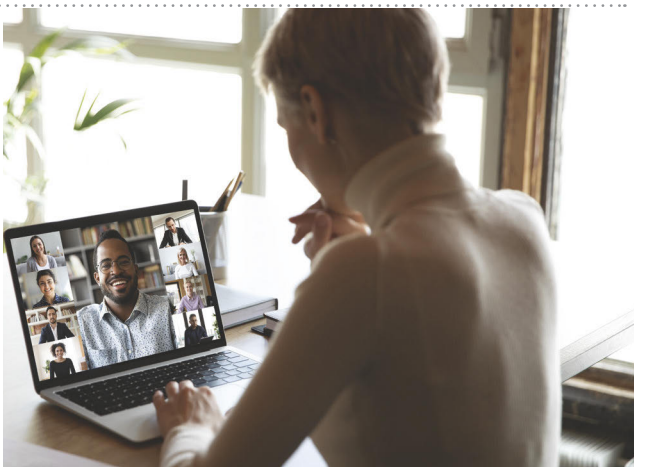
Governance in the Increasingly Complex World of Point-of-Care Testing

The Total Testing Process: Collaboration Between Laboratory Medicine and Emergency Medicine to Ensure Quality Testing

Management of Point-of-Care Testing: An AACC Academy Laboratory Medicine Best Practice Guideline

Emerging Diagnostics

Emerging Applications of Multi-omic Mass Spectrometry



Current Landscape of Clinical Diagnostics and Emerging Technologies in the U.S. and China

The Future Is Near: Blood Tests for Alzheimer's and Related Neurodegenerative Diseases

Stroke Biomarkers: From Discovery to Diagnosis, Prognosis, and Guidance of Therapy

Genomics

Tumor Mutation Burden: A Potential Novel Biomarker for Therapeutic Selection

If at First You Don't Succeed: An Interactive Case-Based View of Emerging Molecular Technologies

Transform Passive Laboratory Testing to Active Consultation in Clinical Pharmacogenomic Service

Laboratory Automation in Molecular Diagnostics for Infectious Diseases and Oncology

Toxicology/TDM

Is Therapeutic Drug Monitoring for Organ Transplantation on the Bleeding Edge?

Fentanyl and Fentanyl Analogs: From Overdose, to Outbreaks, to Laboratory Detection

More Than Opioids: New Trends in Adolescent and Young Adult Substance Abuse Testing

A Tale of Using Seized Drugs, DUID, and Postmortem Cases to Keep the Laboratory at the Front Line

HOW TO REGISTER

Members recieve significant savings on both early and advanced registration, but everyone saves by registering before November 13. **https://meeting.aacc.org/register**

Industry Playbook

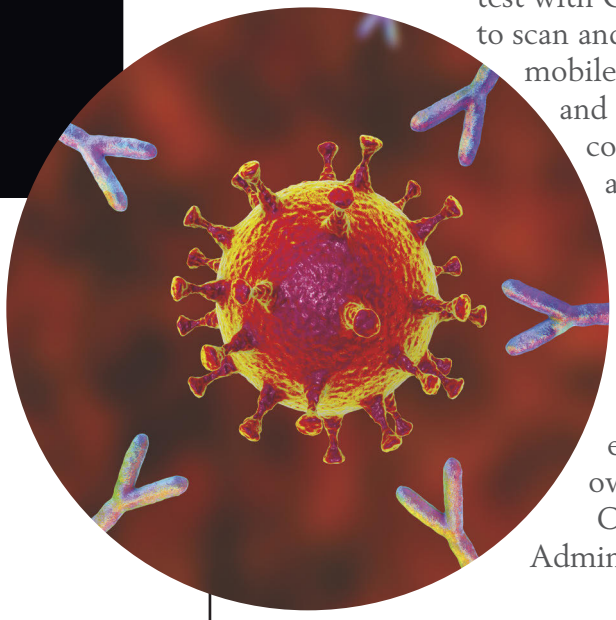
Gauss and Cellex Partner for First At-Home SARS-CoV-2 Antigen Test

To improve at-home SARS-CoV-2 testing, Gauss, a healthcare computer applications company, and Cellex, a biotechnology company specializing in point-of-care testing, have teamed to develop the first-ever rapid, at-home and point-of-care SARS-CoV-2 antigen test. The test would be the first of its kind that allows users to perform the test themselves and receive results at home.

Cellex is currently in the midst of clinical trials for its rapid antigen test that detects the nucleocapsid protein found on the SARS-CoV-2 virus from nasal swab samples. Results from clinical trials show this test has nearly 90% sensitivity and 100% specificity. The partners plan to combine Cellex's antigen test with Gauss' new artificial intelligence mobile application to allow patients to scan and receive test results themselves by using their smartphones. Gauss' mobile app provides users with video instructions on collecting the sample and performing the test to receive results in seconds. According to the companies, the app will also contain an automated feature for patients and healthcare professionals to share medical data.

"The integration of Cellex's accurate, at-home rapid antigen test with Gauss's mobile app offers a scalable solution to significantly reduce transmission of COVID-19 and help society mitigate the impacts of the pandemic until a vaccine is widely available," said Siddarth Satish, Gauss founder and CEO. "By embedding advanced computer vision algorithms within a thoughtfully designed user experience, we can enable consumers to perform a rapid test in their own homes simply by using their smartphone cameras."

Currently, the partners are working to receive Food and Drug Administration emergency use authorization for the test.



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ILLUMINA, GRAIL ANNOUNCE $8 BILLION DEAL FOR EARLY CANCER DETECTION

In an $8 billion deal, Illumina announced its planned acquisition of Grail, a healthcare company that specializes in early detection of cancer. Grail was founded by Illumina in 2016 and launched as its own company to further research on cancer detection, diagnosis, and monitoring.

As a stand-alone company, Grail has successfully enhanced its research and technology to develop Galleri, a multi-cancer screening test set to launch in 2021. According to Grail, Galleri detects early cancer signs through cell-free DNA analysis and has proven its success in detecting over 50 cancer types. Through the acquisition, the partners expect to improve blood-based screening of cancer, which can lead to better treatment options for patients at a lower cost.

Additionally, the deal will allow both companies to expand their platforms and commercialization opportunities. By acquiring Grail, Illumina will be able to enhance its portfolio to include cancer care. In return, Illumina will provide Grail with commercialization opportunities across the globe. The agreement also allows Illumina to advance its work in clinical genomics by not only providing its next-generation sequencing platform, but also positioning itself as the main distributor of clinical tests.

The deal is expected to close in 2021 and includes upfront cash and stock transactions.

NIH GRANT PROVIDES FUNDS FOR SCANWELL AT-HOME CKD TEST

Scanwell Health, developer of at-home lab tests, announced that it received a $1.6 million National Institutes of Health Small Business Innovation Research (SBIR) grant to further production of its at-home test for chronic kidney disease (CKD).

The CKD test designed by Scanwell will allow patients to rapidly screen their own urine for excess protein, a potential symptom of the disease. Currently, researchers at

healthcare centers across the country are performing studies using the test. Patients receive urine testing kits through the mail, and through the Scanwell mobile app, scan the urine sample to quickly view results. With the SBIR grant, Scanwell will be able to further studies before submitting the test for approval to the Food and Drug Administration.

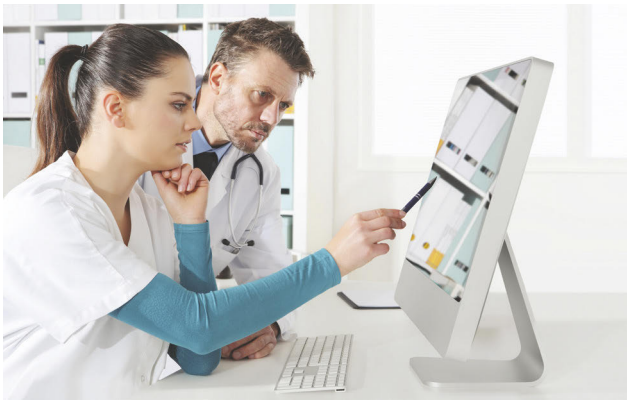
Research shows that most Americans diagnosed with CKD are asymptomatic. Though there are no current cures for the disease, experts have found that the earlier CKD is diagnosed, the better chance there is of survival. Through the rapid at-home test, Scanwell hopes to drive more timely diagnoses of CKD, which could result in improved early treatment options for patients.

SIEMENS AND NOVARTIS DEVELOP ASSAY FOR MULTIPLE SCLEROSIS

Siemens Healthineers and Novartis Pharma, a pharmaceutical company that focuses on neuroscience, have entered into an agreement to develop a serum neurofilament light chain (NfL) immunoassay for patients with multiple sclerosis (MS) and other neurological diseases. Through the partnership, the companies plan to further develop diagnostic tests that support Novartis' therapeutic infrastructure.

NfL, a biomarker for nerve cell injury, is measured through spinal fluid and blood. Research shows that blood NfL levels tend to vary with severity of neurological conditions. With the agreement, Novartis will benefit from Siemens' specialization in clinical diagnostics and testing platforms, such as the Advia Centaur and Atellica. Serum NfL would expand Siemens' Laboratory Diagnostics Neurology test menu.

"We are looking forward to our collaboration with Novartis as it promises to yield innovative diagnostic solutions to address critical unmet clinical needs," said Deepak Nath, PhD, laboratory diagnostics president at Siemens. "Our initial focus on blood-based diagnostic solutions for MS patients is another example of Siemens Healthineers' commitment to shape the future of precision medicine."



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PATIENT DATA PROVIDES ANSWERS IN NEW COVID-19 QUESTION PORTAL

A new healthcare platform aims to provide patients and healthcare experts with new research on COVID-19 using patient record data from hospitals. The program, Reliable Response Data Discovery (R2D2), will allow individuals to submit COVID-19-related questions through an online portal, covid19questions.org.

According to R2D2, each submitted question will be translated into codes for participating hospitals to run on their own patient medical records, maintaining privacy for patient identity. The computer system will collect the most relevant information from patient data to then post a response back to the website. The program can obtain information from over 45 million patients and includes hospitals ranging from large metropolitan areas to smaller community health centers for diverse results.

"No single hospital alone has treated enough patients with COVID-19 to be able to see reliable patterns emerge and use that information to guide the direction of new studies. That's why we formed the R2D2 Consortium," said Lucila Ohno-Machado, MD, PhD, chair of the Department of Biomedical Informatics at University of California San Diego Health and head of R2D2.

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Ask The Expert

What Labs Need to Know About Drug-induced Liver Injury

EXPERT
Yu Zhang, MD, PhD

What is drug-induced liver injury (DILI)?

A: DILI is caused by either prescription or over-the-counter medications, herbal and dietary supplements, or other xenobiotics that result in abnormalities in liver tests or in hepatic dysfunction that cannot be explained by other etiologies. DILI is the most common cause of acute liver failure in the U.S. and one of the two most frequent reasons for clinical trial failure and drug withdrawals.

What are the challenges associated with diagnosing DILI?

Although DILI is clearly defined as being caused by drugs, the correlation between DILI and drug administration may not be clear in actual cases. Some drugs cause intrinsic hepatotoxicity in a dose-dependent manner, while others lead to idiosyncratic hepatotoxicity, which is dose-independent and unpredictable. Additionally, in some cases, liver injury might only become apparent weeks or months after a drug has been administered. Therefore, the diagnosis of DILI is mainly one of exclusion, i.e., abnormal liver function with other liver disease excluded. Monitoring a patient's liver function after discontinuing the suspected causative drugs and/or after re-exposing a patient to these drugs can provide supporting evidence for a diagnosis of DILI. However, when considering this approach, the potential delay in patient response should still be kept in mind.

Complicating diagnosis even further are factors such as preexisting disease, drug-drug interactions, and other drug side effects. For example, the breakdown of damaged skeletal muscle known as rhabdomyolysis occurs commonly in patients taking illicit substances. In such cases, labs should not base a DILI diagnosis on tests for the standard hepatotoxic markers alanine aminotransferase (ALT) and aminotransferase (AST), because abnormal ALT/AST results could be due to muscle injury, liver injury, or both.

What can labs do to detect and monitor DILI?

First of all, laboratory tests for liver function are paramount for diagnosing hepatic injury, which includes DILI. These tests include ALT and AST to evaluate hepatocellular injury, alkaline phosphatase (ALP), γ-glutamyl transferase, and bilirubin for cholestasis, and albumin and prothrombin time for hepatic protein synthesis. The criteria for DILI diagnosis using these tests include either: ALT ≥ 5 x upper limit of normal (ULN); ALP ≥ 2 x ULN; or ALT ≥ 3 x ULN and total bilirubin ≥ 2 x ULN (this last criterion is also known as Hy's law).

Secondly, drug screening and therapeutic drug monitoring can identify potential culprit drugs and quantify their concentrations. Immunoassays or spectrophotometric methods can qualify the most common hepatotoxic drugs. Liquid chromatography mass spectrometry (MS)-based assays can screen for common pharmaceutical drugs, illicit substances, and their metabolites to identify potential causative agents. Labs can also engage quantitative MS methods to evaluate drug concentrations accurately, which is vital for properly assessing DILI severity and guiding antidote therapy, if available.

Additionally, researchers are exploring and developing novel biomarkers for liver injury, which include microRNA(miR)-122, high mobility group box1, cytokeratin 18, and glutamate dehydrogenase, among others. MiR-122 in particular is an ideal DILI biomarker candidate, as it is predominantly and specifically expressed in the liver and makes up approximately 70% of total liver miRNA content.

Studies have verified that miR-122 is reliable and sensitive to liver injury compared to standard tests such as ALT, AST, and liver biopsy. Recent research also indicates that miR-122 increase precedes by approximately 8 hours the elevation of ALT and AST. This significantly shifts forward the detection window for DILI and could improve patient outcomes in cases where an antidote needs to be administered rapidly, such as when acetaminophen is the cause of DILI. Acetaminophen accounts for approximately 37% of acute liver failure cases in the U.S., but its antidote, N-acetyl-cysteine, is almost 100% effective if administered before hepatotoxicity sets in.

As technical advances simplify the process of testing for miR-122 via reverse transcription polymerase chain reaction, miR-122 and other similar biomarkers likely will soon be introduced in clinical practice to improve the diagnosis of DILI.

Jada (Yu) Zhang, MD, PhD, is a clinical chemistry and toxicology fellow at Zuckerberg San Francisco General Hospital and the University of California, San Francisco.
+EMAIL: yu.zhang3@ucsf.edu

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