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FEBRUARY 2020 ■ Vol 52 ■ No 2

CE Implementing hs-cTn assays into the clinical practice

Top takeaways from Lab Director's Summit

Diagnostic tests aim to fight spepsis

The future of molecular pathology

LAB INNOVATOR

Billie Whitehurst
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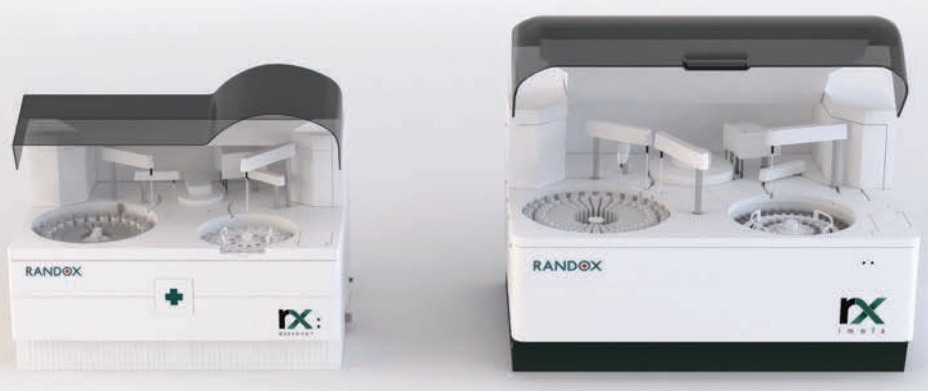

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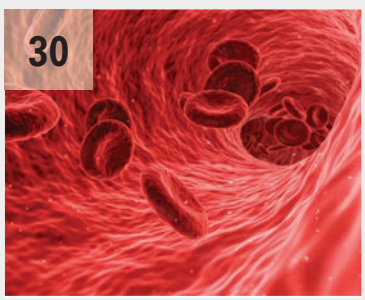

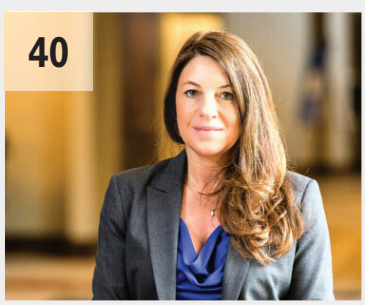

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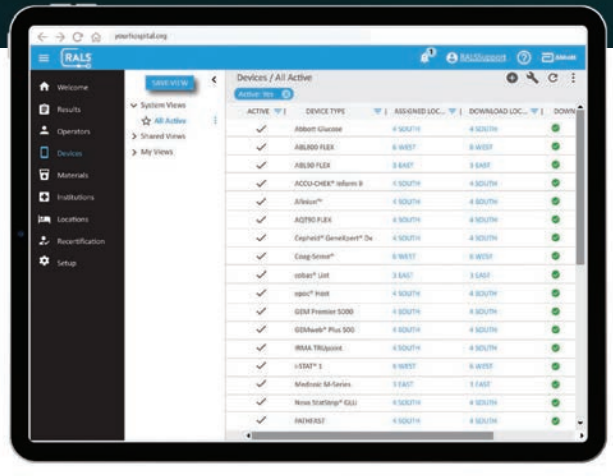

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The heart of the matter

By Brenda Silva
Senior Editor

According to L. Frank Baum, "hearts will never be practical until they can be made unbreakable," and with each cardiovascular advance in laboratory diagnostics, it seems we move closer to making this ideal a reality (of sorts). As the result of new tests and clinical trials, today's cardiovascular disease (CVD) is no longer discovered only at autopsy after a patient dies, but rather, through routine yet specific blood tests designed to find CVD biomarkers early, while the patient is very much alive.

In this month's *Medical Laboratory Observer (MLO)*, we take a closer look at CV biomarkers with "Implementation of high-sensitivity cardiac troponin into clinical practice" on page 8 and learn why cTn has been "the preferred biomarker for diagnosis and rule out of acute myocardial infarction (AMI)" for almost a decade. In related troponin news, researchers in the U.K. recently analyzed data of 250,000 non-MI patients who had minor spikes in troponin levels. The results of the analysis showed a ten-fold increased risk of death among people 18-29, with the same risk decreasing as ages increased. These results, and more like them, could lead to an increase in CV interventions at earlier stages, with a wider range of age groups affected globally.

Looking to the heart of the lab, *MLO*'s first Lab Director's Summit was held in December with success as one of the many takeaways the Summit offered attendees. Beginning on page 16, *MLO* Publisher Kristine Russell offers an insightful summary of current challenges faced by Lab Directors, who are at the heart of any efficient lab, and provides suggestions and solutions based on feedback and comments from speakers and attendees.

At another event-based session called "The future of molecular pathology," which was held at the most recent Association for Molecular Pathology (AMP) conference, panelists gave their industry predictions while acknowledging existing challenges. Clinical experts offered their forecasts and urged everyone from trainees to tenured lab professionals to take heart and embrace the changes on the horizon – read their suggestions and advice on page 36.

Even though heart disease continues to be the number one cause of death in the U.S, per numerous statistic-gathering online outlets, there are other current threats looking to surpass CVD for the same morbid distinction, including sepsis and antibiotic resistance. New research has also shown a relationship between cancer and autoimmune-related conditions and diseases. One statistic from the National Cancer Institute (NCI) asserts that between 10 percent and 30 percent of cancer patients have an autoimmune disease as well, further reiterating the need to study these patients more for immunotherapy treatments that address both diseases. Articles in this issue take a closer look at these diseases and how the industry is working to find solutions for them.

In the meantime, let's look outside February's heart-shaped box and see more than the potential for diabetes, obesity, dental issues and food allergies. We should keep our attention focused on the clinical laboratories of the near future, whose research and diagnostic advances will have us swooning and falling in love with our industry's perseverance all over again.

I welcome your comments, questions and opinions - please send them to me at Bsilva@mlo-online.com.

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2. Dispenzieri A, et al. International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. Leukemia 2009; 23:215-224.

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FAST FACTS

Cardiovascular Disease

1.1 million

Number of people in the U.S. that have a heart attack every year

460,000

Number of fatal heart attacks that happen every year

1 hour

Time when half of fatal heart attacks happen after symptoms begin

605,000

Number of people in the U.S. each year that have their first heart attack

200,000

Number of people in the U.S. who experience a recurrent heart attack

50 percent

Percentage of the American population affected by cardiovascular disease

650,000

Number of people who die in the U.S. every year from heart disease

17 million

Number of people who die every year worldwide from heart disease and stroke

• **Source:** American Heart Association – AHA; https://www.heart.org/en

Rare genetic variants predispose to sudden cardiac death

Sudden cardiac death affects 220,000 U.S. adults annually, most of whom have no prior symptoms of a heart issue. By identifying rare DNA variants that substantially increase risk of sudden cardiac death, researchers led by investigators at Massachusetts General Hospital (MGH) and the Broad Institute of MIT and Harvard have laid the foundation for efforts to identify individuals who could benefit from prevention strategies prior to experiencing symptoms.

The scientists also determined that such variants are present in approximately 1 percent of asymptomatic adults—corresponding to 3 million people in the U.S.

The findings are presented at the Scientific Sessions of the American Heart Association and published in the *Journal of the American College of Cardiology.*

The authors performed gene sequencing in 600 adult-onset sudden cardiac death cases and 600 controls who remained healthy—the largest such study performed to date and first to use a control group. A clinical geneticist reviewed all of the DNA variants identified, classifying 15 as clinically important pathogenic variants.

"Strikingly, all 15 of these pathogenic variants were in sudden cardiac death cases, with none in controls," said lead author Amit V. Khera, MD, cardiologist and associate director of the Precision Medicine Unit at MGH's Center for Genomic Medicine and the Broad Institute's Cardiovascular Disease Initiative. The prevalence of a pathogenic variant was found to be 2.5 percent in cases and 0 percent in controls.

Next, the investigators studied the genes of 4,525 middle-aged adults without any signs of heart disease, finding that 41 (0.9 percent) carried a pathogenic variant. These individuals have been followed for over 14 years, and those who inherited a pathogenic variant had a more than three times higher risk of dying from cardiovascular causes.

Based on these results, Khera and colleagues plan to conduct genetic sequencing tests for thousands of adult patients at MGH and affiliated hospitals who volunteered for a research program designed to understand how genetic and environmental factors impact risk of important diseases. They aim to find the one percent of individuals with rare genetic variants linked to heart disease. They plan to offer tailored prevention programs in a Cardiovascular Genetics Program or a new MGH Preventive Genomics Clinic that Khera is co-leading and is embedded within primary care.

Biomarker predicts heart failure patients with a higher risk of dying

A UCLA-led study revealed a new way to predict which patients with "stable" heart failure—those who have heart injury but do not require hospitalization—have a higher risk of dying within one to three years. Although people with stable heart failure have similar characteristics, some have rapid disease progression while others remain stable. The research shows that patients who have higher levels of neuropeptideY, a molecule released by the nervous system, are 10 times more likely to die within one to three years than those with lower levels of neuropeptides.

About half of people who develop heart failure die within five years of their diagnosis, according to an American Heart Association (AHA) report, but it hasn't been understood why some live longer than others despite receiving the same medications and medical device therapy. The researchers set out to determine whether a biomarker of the nervous system could help explain the difference. To date, no other biomarker has been identified that can so specifically predict the risk of death for people with stable heart failure.

The researchers analyzed blood from 105 patients with stable heart failure, searching for a distinct biomarker in the blood that could predict how likely a person would be to die within a few years. They found that neuropeptide Y levels were the clearest and most significant predictor.

The scientists also compared nerve tissue samples from patients with samples from healthy donors and determined that the neurons in the people who were at most at risk for dying from heart failure were likely releasing higher levels of neuropeptides.

The results could give scientists a way to distinguish very-high-risk patients with stable heart failure from others with the same condition, which could inform which patients might require more aggressive and targeted therapies.

REGULATORY HIGHLIGHTS—

CMS 2020 annual updates for clinical laboratory fee schedule and services

The Centers for Medicare and Medicaid Services updates their Common Procedural Technology (CPT) codes and guidelines by deleting codes, guidelines, or adding and revising codes to reflect current technologies, techniques, and services. Below is a summary from the current updates.

The annual update to the local clinical laboratory fees for CY 2020 is 0.90 percent. Beginning January 1, 2020, this update applies only to pap smear tests. For a pap smear test, Section 1833(h)(7) of the Act requires payment to be the lesser of the local fee or the National Limitation Amount, but not less than a national minimum payment amount. However, for pap smear tests, payment may also not exceed the actual charge. The CY 2020 national minimum payment amount is $15.12 (This value reflects the CY 2019 national minimum payment with a 0.9 percent increase or $14.99 times 1.0090).

The affected codes for the national minimum payment amount are: 88142, 88143, 88147, 88148, 88150, 88152, 88153, 88164, 88165, 88166, 88167, 88174, 88175, G0123, G0143, G0144, G0145, G0147, G0148, Q0111, Q0115, and P3000.

The annual update to payments made on a reasonable charge basis for all other laboratory services for CY 2020 is 1.6 percent (See 42 CFR 405.509(b)(1)).509(b)(1)). The Part B deductible and coinsurance do not apply for services paid under the CLFS.

CLFS data reporting delayed

• For Clinical Diagnostic Laboratory Tests (CDLTs) that are not Advanced Diagnostic Laboratory Tests (ADLTs), the data reporting is delayed by one year. CDLT data that was supposed to be reported between January 1, 2020, and March 31, 2020, must now be reported between January 1, 2021, and March 31, 2021. Labs must report data from the original data collection period of January 1, 2019, through June 30, 2019. Data reporting for these tests will then resume on a three-year cycle, beginning in 2024. (Section 105(a)(1) of the Further Consolidated Appropriations Act of 2020 (FCAA)).

• In addition, the statutory phase-in provisions are updated. For 2020, the rates for CDLTs that are not ADLTs or new CLDTs may not be reduced by more than 10 percent of the rates for 2019. There will be a 15 percent reduction cap for each of 2021, 2022 and 2023. (Section 105(a)(2) of FCAA).

Provider types affected

This MLN Matters Article is intended for clinical diagnostic laboratories that submit claims to Medicare Administrative Contractors (MACs) for laboratory services provided to Medicare beneficiaries.

Provider action needed

CR 11598 provides instructions for the Calendar Year (CY) 2020 Clinical Laboratory Fee Schedule (CLFS), mapping for new codes for clinical laboratory tests, and updates for laboratory costs subject to the reasonable charge payment. Make sure your billing staffs are aware of these updates.

The next data reporting period is January 1, 2020, through March 31, 2020, where laboratories report applicable information to CMS. CMS will use this data to calculate revised private payer rate-based CLFS rates effective January 1, 2021. Specific directions on data collection and data reporting are available at https:/www.cms.gov/Medicare/Medicare-Fee-for-ServicePayment/ClinicalLabFeeSched/PAMA-regulations.html.

Applicable laboratories

In 2019, CMS made two revisions to the regulatory definition of applicable laboratory:

1. Medicare Advantage plan revenues were excluded from total Medicare revenues (the denominator of the majority of Medicare revenues threshold).

2. Hospitals that bill for their nonpatient laboratory services may use Medicare revenues from the Form CMS 1450 14x Type of Bill (TOB) to determine whether its hospital outreach laboratories meet the majority of Medicare revenues threshold and low expenditure threshold.

The regulatory definition of an applicable laboratory is summarized below.

1. Is a laboratory as defined under the Clinical Laboratory Improvement Amendments(CLIA) regulatory definition of a laboratory (42 CFR 493.2)

2. The laboratory bills Medicare under its own National Provider Identifier (NPI) or

a. For hospital outreach laboratories -- bills Medicare Part B on the Form CMS 1450 under TOB.

3. The laboratory must meet a "majority of Medicare revenues" threshold, where it receives more than 50 percent of its total Medicare revenues from one or a combination of the CLFS or the PFS in a data collection period. For purposes of determining whether a laboratory meets the "majority of Medicare revenues" threshold, total Medicare revenues includes: fee-for-service payments under Medicare Parts A and B, prescription drug payments under Medicare Part D, and any associated Medicare beneficiary deductible or coinsurance.

4. The laboratory must meet a "low expenditure" threshold, where it receives at least $12,500 of its Medicare revenues from the CLFS in a data collection period.

Hospital outreach laboratories that met the definition of an applicable laboratory will be required to report applicable information to CMS during the next data reporting period, which is January 1, 2020, through March 31, 2020.

Additional sub regulatory guidance will be made available on the CLFS website under the PAMA regulations tab at https:/www.cms.gov/Medicare/Medicare-Fee-forService-Payment/ClinicalLabFeeSched/PAMA-regulations.html.

Advanced Diagnostic Laboratory Tests (ADLTs) effective January 1, 2020.

1. The ADLT DecisionDx-Uveal Melanoma owned and furnished by Castle Bioscience was assigned Proprietary Laboratory Analyses (PLA) code 0081U effective January 1, 2019. This code is being deleted effective December 31, 2019, and replaced by CPT code 81552, effective January 1, 2020. Short Descriptor: ONC UVEAL MLNMA MRNA 15 GENE. Long Descriptor: Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin embedded tissue, algorithm reported as risk of metastasis

2. Existing code 81538 is an ADLT and is priced at its median private payer rate.

3. For additional information regarding other ADLTs, see https://www.cms.gov/Medicare/Medicare-Fee-for-ServicePayment/ClinicalLabFeeSched/PAMA-Regulations#ADLT_tests.

Implementation of high-sensitivity cardiac troponin into clinical practice

By Alan H.B. Wu, Ph.D, Kara L. Lynch, Ph.D.

Since 2000, cardiac troponin (cTn) is the preferred biomarker for diagnosis and rule out of acute myocardial infarction (AMI).[1] This was reaffirmed with the recent Fourth Redefinition of AMI published in 2019.[2] Over the last 25 years, there have been significant improvements in assays for cTn with regards to analytical sensitivity and precision at low concentrations, the area where there is the most clinical value for this test.

High-sensitivity cTnT and cTnI assays have been approved by the Conformité Européene (CE) and commercially available for many years in countries outside the U.S.[3] In 2011, the Mitsubishi assay was approved as a near-patient troponin I assay using whole blood.[4] In January 2017, the first highly sensitive troponin assay was approved by the US Food and Drug Administration (5th-generation cardiac troponin T, Roche Diagnostics). In the summer of 2018, Beckman and Siemens received FDA approval for the hs-cTnI assay, followed by Abbott in October 2019.

It is appropriate to summarize the steps necessary for a successful launch of these assays with specific reference to clinical laboratories in the U.S. We reviewed the literature that has been generated since the launch of CE-approved assays by current users. Clinical laboratories implementing hs-cTn assays will need to decide on reference ranges, units of measure and assist their emergency department physicians and cardiologists in deciding the optimum frequency of blood collections for patients presenting with chest pain.

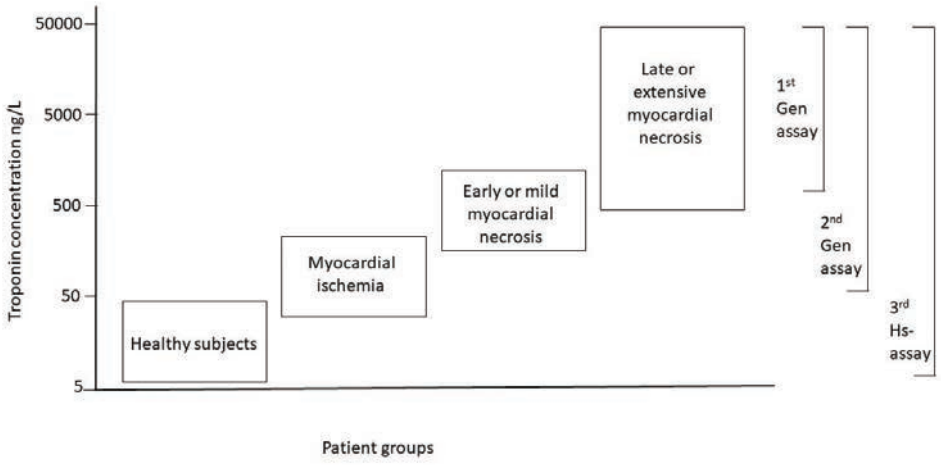

Figure 1. Influence of analytical sensitivity for cardiac troponin according to generations of assays. The first-generation assay was not able to detect low concentrations of troponin. The current or second-generation assay was able to detect injury earlier, but is not able to healthy subjects. High-sensitivity assays can reliably detect troponin in healthy subjects, and in patients with myocardial ischemia and early necrosis.

Earning CEUs

See test on page 14 or online at www.mlo-online.com under the CE Tests tab.

LEARNING OBJECTIVES

Upon completion of this article, the reader will be able to:

1. Recall the history of the troponin assay and the evolution towards a high-sensitive troponin (hs-cTn) assay.
2. Describe the laboratory considerations of the use of the hs-cTn including cutoff concentrations, reference intervals, reporting units and quality control materials..
3. Discuss clinical considerations of hs-cTn testing and the strategies developed for AMI rule out.
4. Describe physician concerns on adopting the use of hs-cTn in the use of diagnosing a cardiac patient correctly.

Laboratory Considerations

History of cutoff concentrations

Figure 1 illustrates the generation of troponin assays and the improvement in analytical sensitivity.[5] The cutoff concentration for cardiac troponin was initially determined through the use of receiver operating characteristic (ROC) curve analysis. Then, it was not possible to determine a traditional reference range from healthy subjects because these early assays were not sufficiently sensitive enough to detect troponin in their blood. Instead, the cutoff was selected that best separated ED patients with chest pain who ruled out for AMI from those who ruled in **(Figure 2)**.

Within a few years, it was recognized that troponin could be used for stratifying the short-term risk of mildly increased troponin. In order to capture these patients, the cutoff concentration was lowered to the value that was associated with an assay imprecision of ≤10 percent. With the release of more sensitive commercial cTn assays, the cutoff was further lowered to the 99th percentile of a healthy population. Thus, troponin evolved from a test to diagnose AMI to one that indicates myocardial injury. As such, the specificity for diagnosis of AMI declined with each generation of assays that demonstrated improved analytical sensitivity.

Today, a troponin assay is defined as "high sensitivity" if it can measure more than 50 percent of healthy patients above the assays limit of detection, i.e., the troponin value that exhibits a 20 percent imprecision.[6] In time, hs-cTnT and hs-cTnI will replace all older assays. Will there be a need to develop cardiac troponin assays with even more analytical sensitivity? It is not likely that an assay that can detect troponin below the reference range will produce clinical benefit. There are non-approved research assays that are more sensitive than FDA-approved assays, but the clinical advantages of these assays have not been demonstrated.[7]

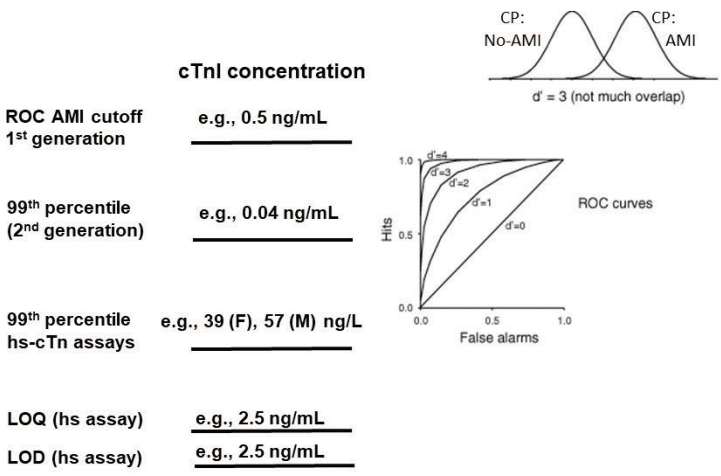

Figure 2. Evolution of cutoff concentrations for cardiac troponin assays. The cutoff for the first-generation assay was set to differentiate AMI from non-AMI from subjects presenting to the ER with chest pain using ROC curve analysis (right panel). The cutoff for the second-generation assay was set at the 99th percentile of a healthy population with an assay imprecision of ≤10%. Most of these have cTn below the LOD and LOQ. The cutoff for the hs-cTn assays were also set at the 99th percentile limit, with a change in the unit from ng/mL to ng/L. The majority of healthy subjects have values above the assay's LOD. Representative troponin values from the various generations of Siemens assays. M=males, F=females.

Sex-specific reference intervals

Reference range studies have shown that most hs-cTn assays produce different 99th percentile reference ranges between sexes, with males having higher results than females.[8] The FDA requires manufacturers of hs-cTn assays to list separate sex-specific cutoffs in addition to a combined cutoff that encompasses both. Lichtman et al. reported that women suffering AMI were more likely to perceive symptoms as anxiety rather than chest pain.[9] Using a lower cutoff value established for women will increase the AMI detection rate among women.

In contrast, experts argue that the treatment of women with mildly increased troponin results may not change, and the use of a combined cutoff at the female limit accomplishes the same goal.[10] Until there is international consensus, the clinical laboratory must decide if separate sex-specific reference intervals should be adopted at their institution. These clinical practice guidelines are silent regarding the appropriate cutoff values for transgender patients. If hormonal treatment (estrogens or androgens) does not affect skeletal or cardiac muscle mass, it may be appropriate to use the cutoffs for the individual's gender at birth.

Reporting units

The accepted reporting units for early generations of troponin is ng/mL. A typical cutoff concentration is 0.040 ng/mL. Use of hs-cTnI assays enable detection of values that are ten-fold lower. In order to minimize confusion for interpreting these low values, various international guidelines have recommended converting results to ng/L by multiplying results by 1,000, thereby producing whole numbers.[11] For example, a change in serial troponin values from 5 to 10 ng/L is more easily comprehended than reporting a change from 0.005 to 0.010 ng/mL.

Other than conventional troponin assays, there are no clinical laboratory tests where the majority of results are presented as decimals. Laboratories utilizing prior generation assays should retain the older ng/mL units. In this way, values reported in ng/L will necessarily denote the use of a high sensitivity assay. Use of the ng/L value instead of the equivalent pg/mL also conforms with the standards established by International System of Units (SI).

Value assignment for quality control materials

Given that the major advantage of hs-cTn assays is analytical sensitivity, the clinical laboratory must select and validate the appropriate quality control (QC) concentrations. The Academy of the American Association for Clinical Chemistry (AACC) has determined that the first control material should be above the assay's limit of quantitation and the lowest 99th percentile sex-specific cutoff. The second control material should be close to the highest 99th percentile sex-specific cutoff.[12] With this recommendation, the clinical laboratory will need to change the troponin control materials they are currently using, as they are likely to be set at too high of a value. A third control material should be higher to validate the assay's upper reportable range. This strategy will test medical decision limits for use of hs-cTn assays for rule out and rule in of AMI.

Clinical considerations

Serial troponin testing

The realization of the advantages of using hs-cTn will be to alter the frequency of serial blood collections. **Figure 3** illustrates the relationship between troponin assay sensitivity and serial blood collection protocols for AMI diagnosis. A blood collection strategy of zero, six and 12 hours was common with the use of older assays.

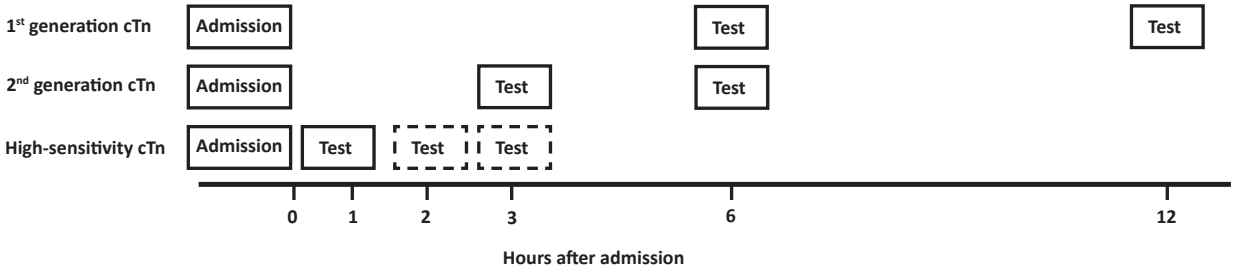

Figure 3. Frequency of serial testing as a function of assay sensitivity for cardiac troponin. The blood collection strategy with the use of hs-cTn assays is evolving. In addition to a baseline, some emergency departments may select one, two or three hours after baseline for the second draw. For patients who have very low baseline troponins, rule out could be made on the baseline concentration alone.

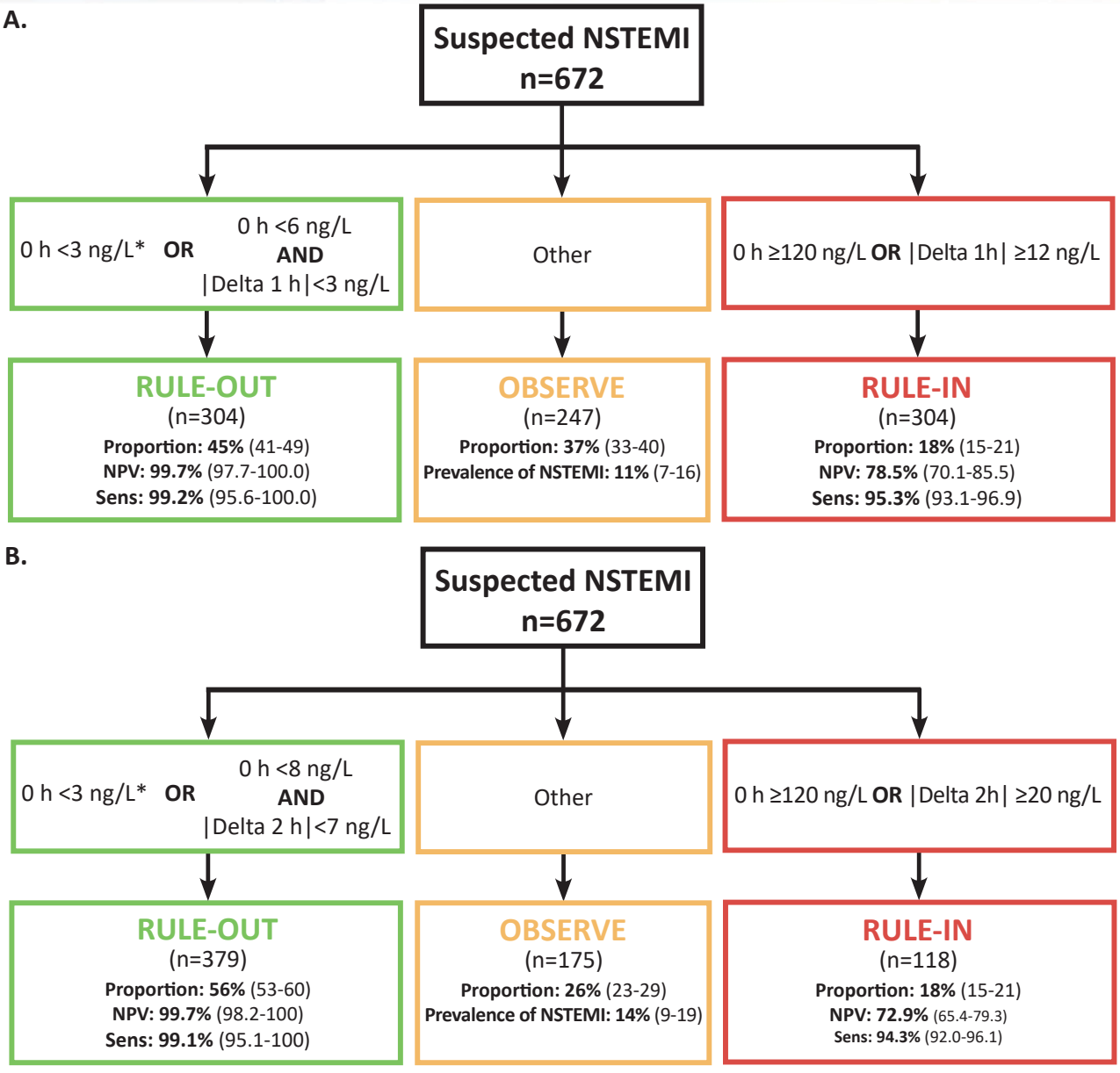

Figure 4. Rapid rule out of AMI using a 1-hour (a) and 2-h (b) serial blood collection protocol. The negative predictive value was 99.7 percent for both. Used with permission from *Clinical Chemistry* 2018;64(9):1347-1360

This was reduced to zero, three and six hours that is currently in place at many medical centers. With the use of hs-cTn assays, emergency departments are reducing the frequency to either zero and one or zero and two hours. It may be more difficult to implement the aggressive one-hour AMI rule out protocol in the U.S. because of the higher numbers of malpractice litigations that occur due to a missed diagnosis of AMI.[13]

The performance of this accelerated strategy has been demonstrated for a number of hs-cTn assays. **Figure 4** shows the specific cutoffs and results using the Siemens hs-cTnI assay (limit of detection 1.6 ng/L, limit of quantitation at 20 percent imprecision 2.5 ng/L). The APACE study was conducted in 12 centers across five European countries with enrollments of over 1,000 patients and had an adjudicated AMI rate of 18 percent.[14] Using an algorithm that collects blood at zero and one hour, and zero and two hours, the negative predictive value (NPV) was 99.7 percent with 50 percent of subjects that can be safely discharged. There are other studies demonstrating similar performance using other commercial assays for hs-cTnI and hs-cTnT.[15,16]

Single troponin testing for AMI rule out

The data on **Figure 4** shows that AMI rule out can be achieved with either serial testing using absolute (i.e., <8 ng/L) and delta change (i.e., <7 ng/L) cutoffs at two hours, or the results of a single low troponin value using a lower cutoff concentration (<3 ng/L).[14] The performance of using the admission sample troponin result alone has also been examined. In order to achieve comparable performance to the dual cutoff strategy, Body et al.[17] and Sandoval et al.[18] lowered the hs-cTnT and hs-cTnI cutoff concentrations at the assay's limit of detection (LoD) and reported high NPV for AMI rule out (>99th). The number of patients that could be ruled out was also comparable to the dual cutoff strategy. **Figure**

Issues/requirements	Opportunities
High sensitivity and analytical precision that matches the central laboratory assay performance	Reduced turnaround times for reporting results
Analyte/assay standardization against central laboratory platforms desired (enables proper interpretation of results even if testing is conducted on different platforms)	Whole blood analysis eliminates need for centrifugation
Small footprint of analyzer critical to success (handheld device optimal)	Improved sample delivery technologies available, e.g., microfluids
FDA clearance essential for U.S. implementation	Novel, high-sensitivity detection schemes available, e.g., surface plasmon resonance
Clinical trials demonstrating rapid AMI rule out performance	Reduction in quality control testing requirements
No troponin POCT devices that have achieved CLIA[1] "waived" status	Advancements in information technologies for reporting results
Lateral flow technology unlikely to be sufficient	Availability of better miniaturization of electronics and hardware components
More than two detection/capture antibodies desired	Improve medical practices for a common disease and a widely ordered test
Freedom from interferences (heterophile, HAMA,[2] autoantibodies, and biotin)	Education hurdle diminished for hospitals already using hs-cTn assays in the central lab
[1]CLIA, Clinical Laboratory Improvement Amendment	
[2]HAMA, human antimouse antibodies	

Table 1. Issues and opportunities for hs-cTn using point-of-care testing platforms.

4 shows the cutoff of <3 ng/L for discharge using the admission sample alone.

AMI rule out at the time of presentation is a very aggressive strategy, and few hospitals have adopted it worldwide. The risks of a missed AMI must be weighed against the improvement in emergency department patient workflow. The success can be improved if other important factors are considered when making early discharge decisions, e.g., the presence of low clinical risk scores such as thrombolysis in myocardial infarction (TIMI) or APACE,[19] the absence of any myocardial ischemia on the electrocardiogram or if history of chest pain onset from symptom onset is greater than three hours. In the U.S, the risk of a missed AMI is lower than in European countries, as the AMI rule in rate at 5-8 percent is lower than what is observed in other parts of the world. Unfortunately, the FDA does not permit clinical laboratories to report hs-cTn values down to the limit of detection. Therefore, this admission sample rule out strategy where the cutoff is at the LoD cannot be enacted today.

Issues for cardiologists

While there are major advantages for ruling out AMI earlier from the ED, there are real concerns by the cardiologists that adopting a lower cutoff concentration with cardiac troponin will lead to an increased admission of patients who have an increased hs-cTn result but are not suffering from an AMI. It is essential that ED physicians and cardiologists understand how to interpret increased hs-cTn values within the context of the history and presentation. The use of the hs-cTn assay will result in an increased number of patients having an abnormal level.

There are a number of etiologies for increased troponin, including heart failure, renal insufficiency, sepsis, cardiac and non-cardiac surgery and venous thrombosis. Each of these are serious medical conditions that warrant careful examination with possible hospitalization. In addition, risk stratification studies have consistently shown that patients with an increased cardiac troponin, outside of the context of acute coronary syndromes, are at higher risk for adverse cardiac events than patients with the same disease but without an abnormal troponin.[20]

Therefore, medical attention for these patients is warranted. However, it is not appropriate to send these individuals for acute revascularization (e.g., angioplasty). Some physicians may argue that some of these diseases do not fall under the jurisdiction of cardiology. The result of serial measurements is an essential criteria to determine if a patient with a positive troponin has active or chronic cardiac injury, with unchanging values favoring the latter. If a rising and falling pattern of troponin is observed, acute cardiac injury is suspected, but a diagnosis of AMI is not absolute. For example, acute exacerbation of heart failure can produce a transient troponin increase that is not caused by acute coronary syndromes.

Conclusions

In order to reap the benefits of hs-cTn assays, a medical practice must first, adopt the 99th percentile cutoff strategy and second, understand that diseases besides AMI will produce abnormal results. Prior to implementation, it is essential that members of the emergency department, cardiologists and clinical laboratory meet to discuss the ramifications of hs-cTn assays. There may be confusion with the change of units and use of sex-specific cutoff limits.

Past experience has shown that there will be an increase in unnecessary admissions of patients as the direct result of reporting low-level positive results. The objective of hs-cTn assays is to reduce the time for AMI rule out and improve the accuracy of AMI diagnosis and risk stratification for future adverse cardiac events in the short term. Therefore, it will be important to conduct audits of patient admission and discharge to determine appropriateness and to educate the staff making these decisions.

High-sensitivity point-of-care testing (POCT) assays represent the next frontier for troponin. Because some clinical laboratories are unable to meet the recommended one-hour reporting turnaround times for troponin results, a POCT device that tests whole blood and is implemented within the ED can reduce the time required for testing. **Table 1** lists the contemporary issues and opportunities for POCT. Unfortunately, there are no FDA-cleared, POC high-sensitivity troponin tests that use a handheld or small portable reader. There are several diagnostic companies who are developing POCT devices using novel sample handling and detection technologies for high sensitivity. When they become approved, it may change how troponin testing is conducted.

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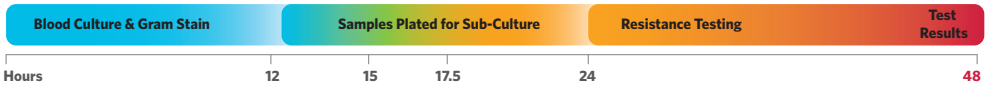

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* BC-GN will not distinguish *Escherichia coli* from *Shigella* spp. (*S. dysenteriae, S. flexneri, S. boydii,* and *S. sonnei*).

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TEST QUESTIONS

Circles must be filled in, or test will not be graded. Shade circles like this: ● Not like this: Ⓧ

1. **The preferred biomarker for diagnosis and rule out of acute myocardial infarction (AMI) is**
   - a. CK total
   - b. CK-MB
   - c. BNP
   - d. Cardiac Troponin (cTn)

2. **High-sensitivity troponin T (cTnT) and troponin I (cTnI) have been approved for many years in the U.S.**
   - a. True
   - b. False

3. **FDA approval was granted to hs-cTnI assays for two analyzers in**
   - a. 1980 and 1981
   - b. 1996 and 1998
   - c. 2005 and 2006
   - d. 2018 and 2019

4. **Implementing hs-cTn assays will require the clinical laboratory to make decisions regarding**
   - a. units of measure
   - b. reference ranges
   - c. frequency of blood collection for chest pain patients
   - d. all of the above

5. **Cutoff concentrations of troponin in early years of testing only determined**
   - a. patients with chest pain who ruled out for AMI
   - b. patients with chest pains who ruled in for AMI
   - c. a cutoff of healthy patients
   - d. all of the above

6. The higher sensitivity produced in newer generations of troponin assays have decreased the specificity for diagnosis of AMI.
   - a. True
   - b. False

7. **In order for a troponin assay to be defined as high sensitivity it must display**
   - a. 20 percent imprecision
   - b. 10 percent imprecision
   - c. more than 50 percent of healthy patients above the assay's limit of detection
   - d. a. and c.

8. **The FDA requires manufacturers to list specific cutoffs in reference to**
   - a. age
   - b. sex
   - c. diagnosis
   - d. all of the above

9. **Hs-cTnI assays are _____ than early generation troponin levels.**
   - a. ten-fold higher
   - b. ten-fold lower
   - c. one hundred-fold higher
   - d. one hundred-fold lower

10. **In order to interpret older generations versus high-sensitive troponin results, units for high-sensitive results should be reported in**
    - a. ng/L
    - b. ng/mL
    - c. ng/dL
    - d. ug/L

11. **Quality control (QC) materials that are used for early generations of troponin are suitable to use for hs-cTn**
    - a. True
    - b. False

12. **Older assays of troponin testing recommended blood testing at**
    - a. zero hours only
    - b. zero and six hours
    - c. zero, six and 12 hours
    - d. none of the above

13. **Which blood testing frequency strategy are emergency departments using with hs-cTn assays?**
    - a. zero hours only
    - b. zero and six hours
    - c. zero and two hours
    - d. zero, six and 12 hours

14. **Testing frequency that involves zero and one hour, and zero and two-hour blood collection has been shown to safely discharge**
    - a. 10 percent of patients
    - b. 20 percent of patients
    - c. 50 percent of patients
    - d. 80 percent of patients

15. **Studies that examined single troponin and dual troponin testing to rule out AMI have concluded that the number of patients that could be ruled out is comparable between the two strategies when cutoff levels on the single sample were lowered.**
    - a. True
    - b. False

16. **AMI rule out at the time of presentation isn't currently practiced in the U.S. because hs-cTn values cannot be reported down to the limit of detection, as ruled by the**
    - a. AAAC
    - b. FDA
    - c. CAP
    - d. JCAHO

17. **Etiologies for increased troponin levels include all but**
    - a. heart failure
    - b. venous thrombosis
    - c. lupus
    - d. sepsis

18. **Physicians must be educated on hs-cTn assays which can cause**
    - a. increased patients to have an abnormal higher level
    - b. decreased patients to have an abnormal higher level
    - c. increased patients to have an abnormal lower level
    - d. increased patients to have an abnormal lower level

19. **Unchanging values in serial measurements of hs-cTn typically indicates**
    - a. chronic cardiac injury
    - b. active cardiac injury
    - c. thrombosis
    - d. congestive heart failure

20. **The next step in improving cardiac diagnosis in the emergency department involves the development and approval of a point-of-care testing (POCT) assay for troponin.**
    - a. True
    - b. False

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   P ① ② ③ ④ ⑤ E
2. **To what extent was the article well-organized and readable?**
   P ① ② ③ ④ ⑤ E
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Top industry takeaways revealed at the MLO Lab Directors Summit

Expertise in abundance among speakers and attendees at inaugural lab event.

By Kristine Russell

The first annual Endeavor Lab Directors Summit, in collaboration with *Medical Laboratory Observatory (MLO)*, was held in December 2019 in Lake Las Vegas. The attendees were invited from the *MLO* subscriber audience of lab directors who are involved in daily laboratory operations via their managerial roles. As part of their extensive responsibilities, the lab directors oversee the selection and direction of lab systems, analyzers, automation and Laboratory Information Systems (LIS), as well as control inventory of supplies through purchasing and management.

The Lab Director Summit (LDS) program provided the attendees the opportunity to network and engage with senior-level decision-makers from healthcare labs that typically serve hospitals with 100 beds or more. The Summit is a unique way for attendees to learn from professionals who are in the in similar positions at their own facilities.

At the inaugural event, *MLO* was proud to host a wide range of Lab Directors and Pathologists from all walks of life from the most prestigious healthcare facilities to rural-location attendees, who were just as dedicated to the efficacy of their laboratory service and the test results they provide.

Before the Summit, *MLO* asked Laboratory Directors to tell us about their major concerns regarding operations, staffing, new technology adoption and visibility that affect their efficacy in delivering quality laboratory results. Based on this information, we created in-depth questions on topics and concerns that were mentioned most frequently by the attendees.

The meeting venue and schedule was designed to optimize the interaction between the attendees, as well vendor sponsors who had the chance to share meals and conversations with most of the attendees, if not all. The attendees had the opportunity to network at numerous roundtable discussions that *MLO* prepared, as well as meet with solution providers in the industry at Small Group Presentations, One-to-One meetings and multiple networking events.

The biggest difference between our meeting and any other is the ability and time for networking, which resulted in problem solving and information sharing between peers.

Top topics among attendees are listed below:

Strategies for recruiting and retaining quality staff

Are you having difficulty attracting and keeping highly qualified laboratory staff? What do lab professionals want and need to feel satisfied? If this is a pain-point for you, consider some small steps you could take right now to improve retention, as well as ideas that might need to be further developed into a formal policy requiring C-suite buy-in.

What are your solutions?

- Create Clinical Career Ladders at your facility. For example, cross-train phlebotomists to become lab assistants in MLS/MLT.
- Work with HR to offer sign-on bonuses, merit allowances and retention bonuses – Talk to HR about this step – most hospitals have this for other departments.
- Partner with local educational programs for Clinical Laboratory Scientists (CLS) Medical Laboratory Scientists (MLS) program–and offer internships at your lab with local nursing and science programs. You can also create a shadow program w/high schools and junior colleges in order to help build interest in the importance of the lab.
- Social media – Tweet out what your lab is doing in the community.
- Recruiters – Get rid of them. They don't tell applicants the right story about the job expectations nor do they screen potential employees properly. Get applications emailed to you directly so you can do the screening.
- Succession planning – Pick top performers in your laboratory and elevate their role to oversee certain processes and/or quality control. It will give them the opportunity to experience leadership Key Performance Indications (KPIs), and you can measure their successes.
- Offer perks such as free parking/public transportation/day care/on-site gym, etc.
- Employee recognition program – include passports to "events", PTO and/or education (aka association meetings).
- Have daily huddles and include peer recognition.

Are your reimbursements covering your costs?

An important first step in managing reimbursement cuts, whether from PAMA (Protecting Access to Medicare Act) or other payer programs, is to view the laboratory as a business — a commercial operation providing cost-effective healthcare through quality diagnostic results that drive medical decisions. Take steps toward achieving the following key business goals that are critical for any lab's success include: reducing costs, maximizing revenue and increasing volume.

What are your top concerns?

- How to survive outreach stresses–are immediate costs vs reimbursements not available as you build programs?
- Is Reference Lab usage delivering any cost savings?

"The Lab Director Summit helps build bridges and fill gaps from the larger community for the small world that we experience in our daily lives. It's a great opportunity to meet new people and engage in a greater discussion for patient care, where shared experience helps bring synergy to an ever-expanding field with new challenges and opportunities ahead. The Summit provided a great opportunity to meet people and gain resources, providing a fresh look at the same old problems."
-- Lab Director in New Jersey

- Is Administration Repository Directory (aka Supply Chain) asking for impossible reductions from vendors?
- Nursing homes and reimbursement issues on data capture and tests performed.

What are your solutions?

- Change staffing to 12-hour shifts
- Education of staff members to standardize processes
- Molecular testing as an effective increase for revenues
- Waste and efficiency studies to decrease overhead expenses
- Potential savings: review supply usage (i.e. tubes, butterflies)
- Health screen testing –bring testing in-house, use internal resources to save money
- Use analyzers that provide walkaway testing to reduce staffing in FTE hours.
- Reduce coding frustrations and modifications

Inventory control and consumable usage

Top areas for labs to focus on for cost-reduction strategies include operational efficiency, reagent efficiency and test utilization stewardship. Labs can leverage their suppliers' analytic capabilities to mine data from instruments and/or middleware to generate an analysis that provides detailed breakouts on how reagents are utilized, calibrations, quality control (QC), repeats and troubleshooting. The data should also provide insights on testing volumes, which can be leveraged to eliminate reagent waste for low-volume assays, improve inventory management of both reagents and consumables, and eliminate excess QC testing.

What are your solutions?

- Track supply utilization and keep records. Review reports on supplies ordered as compared to the number of invoiced tests.
- Utilization as not really lab issue but an organization issue. CMO helps to be able to educate peers on Lab Stewardship.
- Partner with Materials Management and get access to their electronic inventory tracking.
- Push for a 30-day inventory instead of 60-90 days – especially for consumables with expiration dates. This will also save time on rotating excess inventory.
- Consider vendor links or vendor-managed ordering. The data could potentially come from the analyzer or remote connect to the vendor.
- Contract agreements – lease without volume commitments
- Service contract – It is not preferred to outsource service contracts to a third party. Try to use in-house biomed for technical equipment.

Improving quality, efficiency and test utilization

Test volume information can be leveraged to kick-start a lab test utilization program to further cut costs by reducing or eliminating unnecessary testing, while ensuring that clinically relevant testing is performed. Key aspects of such a program tied to cost reduction include standardizing test ordering practices and formularies, eliminating obsolete tests from formularies, monitoring for duplicate test orders and leveraging reflex testing capabilities to run tests only when indicated.

What are your top concerns?

- What can you do about physicians that order a test that have to be processed as send-outs?
  - Implement a program that specifies pre-approvals on miscellaneous send-outs.
  - Track send-outs that result after discharge.
  - There are software tools that measure costly send-outs and the percentage of normalcy results and share the results with physicians.
  - Inform staff on test monitoring and cost analysis– (example for IP patient email chain includes pathologist, MRO and Lab Director to determine if needed).
- How do you notify physicians that testing is a send-out?
  - One solution is to add it to the check out list of tests when they fill out the orders.
- Would like to create a group to be interested in peer comparisons with like hospital labs.
- Some institutions have limitations on the number of tests ordered over a given time.

- Get evidence-based test utilization backed by data.
  (one source mentioned was Eugenio Zabaleta PHD- great resource for test utilization and how you get physicians to order correctly.)
- Quality Reference - use the 12 QSE's from "The Quality System Essentials (QSEs)", from CLSI. https://clsi.org/standards/products/quality-management-systems/companion/lqms
  1. Organization
  2. Process Management
  3. Customer Focus
  4. Document and Records
  5. Facilities and Safety
  6. Information Management
  7. Personnel
  8. Nonconforming Event Management
  9. Purchasing and Inventory
  10. Assessments
  11. Equipment
  12. Continual Improvement
- Also implement an operating structure known in manufacturing as a "quality management system" (QMS) to ensure the quality testing and services.

Equipment evaluation: How to prioritize needs and capital

Capital justification is a major process for you as a laboratory administrator. You must be able to decide the capital needs of your laboratory, and then be able to convince the financial department and others in the institution that your need is not only justifiable, but also more important than other requests for capital made by other department administrators.

Examples include:

- New technology needed to remain competitive.
- Save staff hours/cover shortages with automated equipment.
- Replacement equipment (broken or too expensive to repair).
- AHA Guidelines are a good source for determining life of equipment/instruments.
- Leasing of equipment needs to be budget neutral.
- Physicians determine need of new equipment based on their specialties.
- Work with supply chain connections to create RFPs.

Use of automation to develop the lab of the future

Clinical lab directors should expect the medical device industry to look at laboratory automation through a new paradigm and consider where the laboratory professional's workflow can be served by innovative ideas and approaches. Diagnostic laboratories have become such an integral part of the connected healthcare paradigm that methods for expanding their scalability, improving performance and managing data are critical to achieving the core objectives of meeting the needs of clinicians and patients. Improved efficiency and specimen traceability are achieved with automation.

Challenges – Develop best practices for adoption

- Designate a project manager who will coordinate with the vendor on immediate and long-term planning.
- Bring in or develop technical expertise.
- Develop a workflow/diagram/visual instrument placement in your facility.
- In space planning, analyze workflow processes and mapping – get IT involved early.

Create a future ready lab:

- Mobile remote testing
- Less staff/more technology equipment
- Less regulation
- Staff skill mix–licensed vs unlicensed
- Use of Artificial Intelligence (AI) in pathology
- Reimbursement

Bringing molecular and genetic testing to your lab

Many labs send test orders out for molecular testing if they don't have the MDx analyzers in-house. The decision to bring molecular tests into your lab should be based on the anticipated volume of tests, the skill level of personnel, the anticipated cost of performing the test in-house vs outsourcing and the need for your facility to remain competitive in your region. The wealth of information from genetic and molecular testing provides a means to more effectively administer drugs and treatments and provides enhanced patient efficacy in treatments.

Adoption of Molecular testing (MDx):

- Consider how it will be used–will it be the right fit?
- Consider who will run it–do they need training, what is their level of expertise?
- Cost–should it be laboratory developed test (LDT)?
- Is the right test being ordered for MDx use? What is the test utilization projected to be?
- Can we treat the result? Why would we need to know?
- Who has rights to the data to prevent it from being misused?
- Why is it important to have a molecular specialist on staff for test interpretation?

IT tools for clinical diagnostics

LIS/LIMS systems have grown from simple programs that handle the mechanics of laboratory billing to complete, end-to-end platforms that govern the entire business process and workflow of the laboratory. These IT systems are critical to the operation of a laboratory and must work in concert with instruments and automation for a laboratory to be successful. Decision support for these system choices can be found with vendors and associations.

What sources are needed to evaluate systems for your lab?

LIS evaluations can be found through the Association for Pathology Informatics. This organization's LIS Functionality Assessment Toolkit provides methodology for assessing the functionality of, and enabling comparisons among, competing LIS systems. The toolkit provides information about how to search for a new LIS among the systems available in the market, how to develop a request for proposal (RFP), which is commonly used to manage system selection, and how to plan live vendor demonstrations. You can access this resource at https://www.pathologyinformatics.org/lis_toolkit.php.

- Evaluate what tools are needed–auto-validation, middleware, outreach, etc.
- The biggest need is for data analytics and data mining from your LIS/LIMS.
- What are your corporate IT limitations? Establish a bridge from your lab staff to corporate IT, to evaluate needs at the corporate level and how to collaborate on goals.

New technology adoption and effective training practices

Your lab has installed new software which you hope will improve the quality and efficiency of its work. You want to

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-- Lab Director, NYC

get your staff up to speed as soon as possible so everyone can effectively use and benefit from the software without delay. But you find that your staff's learning curve is considerable. Training staff to use new software has inherent challenges.

How can training be made painless, quick, and successful?

- If the software is meant to be used by the majority of the lab's staff, then a mid- to large-sized laboratory could have dozens or even hundreds of trainees. These challenges can be met, however, with "train-the-trainer" sessions. In this approach, the software vendor trains a select group of "super-users," first.
- Have the IT department provide mandatory training for NEO (new employee orientation).
- Develop a lean process to create standard work and train staff.
- Create standard workflows with all stakeholders.
- Create "lunch and learn" training sessions.
- Follow up with vendor post-implementation.
- Send a lab person to LIS school.

Using metrics and Key Performance Indicators to drive successful outcomes

Describe the tools and other resources such as KPIs you use to gather metrics, measure performances and make effective decisions. What do your metrics reveal specifically - patient scheduling, patient care variations, test reruns, sample contamination rates, supply levels, compliance with regulations, etc.? How has the information helped you to improve lab efficiency and patient experience? What metrics would you like to be measuring better or differently? Have you gathered any data that you're not sure how to act upon?

Suggested solutions:

- Daily visual management board – staff with ideas for cost-savings process improvement.
- Review your list of Key Performance Indicators (KPIs) and ensure they are being met or revise them to cover pain points. Use them to measure performance and accountability.
- Senior leader makes weekly rounds and reports to their supervisor.
- Conduct daily safety huddles in hospital labs.
  - Do we need tools for data management?
  - Do we measure too much but do nothing about it?
  - Prioritize data – Red: Requires actions, Yellow: Caution, Green: Move threshold/discontinue analysis (complete).
  - Are we measuring the right things that impact patient care, safety, costs?
- Engage key stakeholders outside lab to make changes.
- Value moving and process education
- Create a culture that is inspection-proof using checklists and links to your policies and documentation; Set up a policy review and tracking system.

Effective strategies and tactics for reducing costs

Cost-containment efforts are a universal undertaking in healthcare systems everywhere, and efforts to reduce costs can be made in dozens of areas using a variety of best practices and technology. Where is spending highest in your Lab? Can you pinpoint what's causing it? What do you think is needed–and where is it needed–to curb unnecessary spending?

It's all about reviewing:

- Review reference labs costs and contracts; Develop a good relationship with reps.
- Repatriate for lab tests
- Instrument standardization
- Multi-year contracts: Instead of 1-3, go for 7 years and include service metrics, as well as a technology update clause.
- Individualized Quality Control Plan (IQCP) your instruments to reduce QC variations.
- Calculate savings on everything. For example, autoverification of lab tests can save $.14 each x volume of tests – it adds up quickly.
- Staff engagement – post their name and the amount saved due to their suggestion.
- Review contracts with vendors with mutual products/positions.
- Review savings opportunity utilization on schedules.
- Review any big volume changes within 30 days up or down.
- Leverage your labs abilities with neighboring hospital labs – turnaround time (TAT) , etc.
- Reduce blood culture contamination and other wastes.

In summary…

There were many more questions and discussions that covered outreach, safety and cleaning, as well as more molecular testing adoption concerns, just to name a few. The sponsors were happy with the quality of the interaction and in particular with their ability to have One-to-One meetings. One well-known vendor used their small group presentation lab participants as an evaluation team for their current products and practices. Our Second Annual Lab Directors Summit will be in October 2020.

Feel free to contact me for more information - krussell@mlo-online.com.

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The expanding role of point-of-care testing in patient care

By John Daly, MD

Over the past 50 years, we have witnessed a rapid evolution in the availability of point-of-care laboratory testing. Point-of-care (POC) testing is best defined as laboratory testing near the patient, which rapidly provides results for immediate patient care management. There are several reasons for growth in the near patient testing market:

- The advances in technology and informatics have enabled greater sophistication and miniaturization of testing devices.
- The growth of electronic medical records (EMRs) provides a central repository for all patient care information. This, in turn, has made the use of point-of-care technology more attractive in hospitals, offices, clinics, urgent care centers and emergency departments, because the information obtained at the various locations can be more widely available to multiple providers. In addition, today some patient devices used in the home can be downloaded into the electronic medical record.
- The ability to provide the clinician with data while the patient is being examined leads to more rapid and informed decisions for diagnosis and treatment of diseases, both acute and chronic. This, in turn, has an immediate impact on the quality of care. The tremendous growth in the number of analytes available via POC testing also has had an enabling role.
- The information provided by rapid availability of laboratory results guides the transition to a value-based reimbursement model rather than a volume-based reimbursement model of medical care delivery. Incentive reimbursement bonuses related to quality improvements are offered to offset the loss of fee for service reimbursement for laboratory testing.
- Consumerism has expanded in all areas of our lives, including medical care. Today, consumers expect answers immediately. This immediacy, partnered with the desire for one-stop shopping, highlights the value that laboratory testing at the time of medical examination can bring to the patient, as well as the clinician.

Advances in technology and instrumentation

Great change in laboratory medicine has occurred during the last 50 years. Laboratory devices available in the 1960s and 1970s were large, had limited menus, required considerable floor space and many technologists. Today, we have hand-held devices that can perform many of the same tests that are performed on larger analyzers, and there is less need to send a specimen for examination at a central laboratory. Witness the blood gas analyzers that were used in the 1970s and 1980s and compare their size with hand-held devices used today in many facilities to perform the same analyses. Today, in some emergency departments, we have multiplexed molecular testing for syndromic pathogens, and these allow accurate diagnosis in less than two hours. Point-of-service testing has come about as a result of improved technology and miniaturization of instruments.

Electronic medical records (EMRs)

Interfaces of the electronic medical record (EMR) with laboratory instruments, whether in a central laboratory or with smaller POC analyzers, enables all the laboratory testing performed on a given patient – even from multiple locations – to be complied into one record. In addition, the waived tests used every day at the point of care can be manually entered into the electronic record.

Today, patients are receiving care from multiple practitioners in diverse locations. The ability to store all the laboratory information being generated from these different facilities in one repository has the benefit of avoiding duplicate testing and associated cost. We now have available multiple wearable health-related devices. Results obtained and stored by these devices, can, in many instances, be downloaded into a central data bank for use across the whole spectrum of medical care.

Glucose testing is the most common point-of-care test performed, with the lion's share of it being performed in the home. The ability to download these results into the electronic record enables the practitioner to evaluate the patient's status, either in the recent past or over time, and to discuss the results and treatment plan in a more relevant timeframe.

Analytes available at the point of service

Currently, there are greater than 130 analytes that can be assayed by a waived point-of-care device and, in addition, other non-waived analytes that can be performed at the point-of-service due to the availability of smaller, robust instruments. This expansion in analyte availability via POC testing has afforded many different specialties the ability to perform testing during an office visit. So, while greater than 70 percent of CLIA certificates are issued for performance of waived tests, it is not just waived analytes that are being tested at the point of service.

It is well known that the U.S. is experiencing an opioid crisis. The ability to perform waived screening when the patient is meeting with the physician is critical to monitor patient compliance. Granted, the immunochemical testing that is available is not as definitive as mass spectrometry (MS) confirmatory testing, but it can provide useful guidance to the clinician during an office visit, particularly when the visit is for a prescription refill.

In multiple chronic illnesses, the ability to have monitoring tests performed at the time of the visit is crucial to quality patient care. I mentioned opioids, but equally important is the availability of Hemoglobin A1C for monitoring diabetics, as well as a variety of other testing performed at the point of service to monitor other chronic illnesses. With laboratory results in hand, the practitioner and the patient can have an informed dialogue. This will enhance the value of the testing, since two-way dialogue between the patient and clinician enables greater patient education and patient engagement in their own treatment plan.

When results are telephoned to the patient after an office, visit they may well be left on voice mail or, if someone other than the clinician telephones the results, the person calling may not be able to answer patient questions. Also, keep in mind some patients may not return for a follow-up visit and the results may never be communicated to the patient leading to delay in treatment.

We should not overlook the diagnosis of infectious diseases. The availability of immediate testing when the patient first presents for care potentially will lead to a shortening of recovery time because therapy can be rapidly initiated. This is witnessed

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in the diagnosis and treatment of group A Strep and influenza infection, among many others.

Volume-to-value reimbursement

Our healthcare systems are making a gradual transition from fee-for-service to a model of value-based care. Value, in turn, mirrors population health improvement with its emphasis on timely and preventive care. A basic example is the management of patients with diabetes. If the population of diabetic patients is effectively managed, and diabetic complications decrease, there will be a decreased overall cost for treatment of the diabetic population.

When this occurs, complication rates are improved, with decreased numbers of emergency department visits, decreased hospitalizations and decreased progression to cardiac disease to name a few promising outcomes.

In the value-based model, the cost of laboratory testing in the treatment of chronic illnesses becomes less a financial issue, as financial incentives are factored into reimbursement for achieving quality goals. Value-based care is more meaningful for the patient when they experience enhanced quality of life. Society benefits from the overall reduction in cost of medical care. In the end, the quality programs with the goal of timely, appropriate testing and treatment of patients with chronic illnesses make everyone a winner: the patient, the medical practice and society.

Role of consumerism

The role that consumerism plays in medical laboratory care today cannot be overstated. With the availability of "Dr." Google, patients seek to play a more active role in their healthcare, and prefer that testing be performed at the time of the face-to-face meeting with the provider so their questions can readily be answered and treatment plans developed based upon the most current information. Just consider the positive reception that online patient portals have received.

The experience of the American Association for Clinical Chemistry (AACC) website "Lab Tests Online" is very telling. This site provides patient information concerning the utility of several hundred laboratory tests and multiple disease conditions. Since its inception in 2001, over 325,000,000 views have been logged. Patients are consumers – they want information about their diseases, and they want one-stop shopping. There is immediacy in their desire for diagnosis and care. Online, they have access to learn best practices and to look for best practices in their providers. Point-of-care testing is certainly a best practice known to our patients.

With multiple analyzers available to perform testing of 130 different waived analytes, plus the availability of small instruments to perform moderately complex POC testing, we need to evaluate our patient populations for the commonly ordered laboratory tests currently sent to a reference laboratory. The available instrumentation and its cost, coupled with the realistic test needs of our patients, will assist in reaching a decision on the most practical approach to point-of-care testing in your facility.

John Daly, MD, has served as COLA Inc.'s Chief Medical Officer since 2011. He retired from Duke Medicine in 2009. Daly is certified by the American Board of Pathology in Anatomic, Clinical and Forensic Pathology, and is a member of the American Association for Clinical Chemistry (AACC), the College of American Pathologists (CAP) and the American Society for Clinical Pathology (ASCP).

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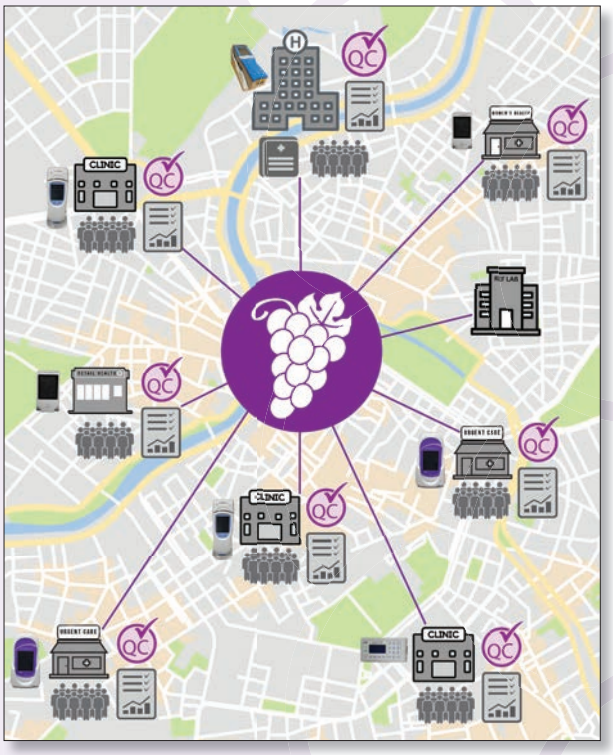

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The importance of diagnostics in responding to antibiotic resistance

By Jean B. Patel, PhD, D(ABMM)

We've all heard concerns about antibiotic resistance (AR). Messages coming from the doctor's office and even the mainstream press point to an increasing number of infections that don't respond to antibiotics because bacteria are becoming resistant. These infections are occurring in both outpatient and inpatient settings. Patients are cautioned that antibiotics may not be necessary for every infection, especially those that may be viral in origin, like ear infections or the common cold. Doctors are encouraged to hold off prescribing antibiotics to see if a minor infection resolves, or until diagnostics tests indicate that therapy is needed and, if so, which drugs are likely to be effective. Data from Centers for Disease Control and Prevention (CDC) indicate that as much as 50 percent of antibiotic prescriptions are inappropriate.[1]

However, antibiotics are essential, life-saving drugs for many patients with bacterial infections. Efforts to use antibiotics appropriately—better known as antibiotic stewardship—aim to ensure patients who need antibiotics get the right drug, at the right time and the right dose. Another stewardship goal is to avoid overuse of antibiotics. This reduces the selective pressure that drives new resistance and preserves a patient's natural microbiome, the healthy bacteria that populate a body and serve as protection from colonization with drug-resistant pathogenic bacteria. Antibiotic disruption of the microbiome is often a precursor to infections with resistant bacteria or with *Clostridium difficile*, a bacterium which is naturally resistant to many antibiotics and a cause of severe gastroenteritis.

While we have heard about AR, it is hard to understand what the threat is and how it might evolve in the future. The CDC *AR Threats Report* is an essential resource for understanding antibiotic resistance today.[2] This report ranks AR threats, reports national burden estimates for infections, and describes the epidemiology behind transmission. To understand how the threat of antibiotic resistance is likely to evolve, it is helpful to think about the evolution of antibiotic resistant *Enterobacteriaceae* over the past 30 years.

Enterobacteriaceae: A study in evolving resistance

Species of *Enterobacteriaceae*, like *Escherichia coli* and *Klebsiella pneumoniae*, are common causes of infections in outpatients and inpatients. Community-associated infections are usually urinary tract infections (UTIs). Healthcare associated infections (HAIs) include UTIs, respiratory infections and bloodstream infections. In the 1980s, extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* emerged as a cause of drug resistant HAIs.[3] ESBLs are plasmid-encoded enzymes that hydrolyze most beta-lactam drugs—including expanded-spectrum cephalosporins, the mainstay treatment for serious *Enterobacteriaceae* infections.

These bacteria are commonly resistant to other major classes of antibiotics as well. Carbapenems—broad-spectrum beta-lactam drugs—are recommended treatment for infections with ESBL-producing *Enterobacteriaceae* (ESBL infections). In the late 1990s, ESBL infections were uncommon causes of HAIs, but now there are nearly 200,000 infections per year in the U.S. and about 50 percent of these are community-associated. Doctors are faced with trying to treat an outpatient UTI infection without admitting a patient for IV antibiotics. Soon, oral carbapenems will also be available for treating outpatient UTIs.

Increased use of carbapenems is a likely consequence of an increasing number of ESBL infections. This is especially worrisome since it will now increase the selective pressure for carbapenem-resistant *Enterobateriaceae* (CRE) infections. CRE emerged in the late 1990s, and today are listed as an urgent threat by CDC.[4] About 40 percent of the CRE in the United States produce a carbapenemase, a plasmid-mediated enzyme that hydrolyzes all beta-lactam drugs including carbapenems.[5] It is easiest to think of these carbapenemases as a broad-spectrum version of ESBLs, and to think of ESBL-producing *Enterobacteriaceae* as pre-CRE.

In fact, many CRE harbor multiple resistance mechanisms including ESBLs. CRE infections in the U.S. occur in healthcare settings. Elsewhere in the world, CRE are an increasingly common cause of community-associated infections. The CDC reported a relatively flat trend for CRE infections. These numbers likely reflect efforts to prevent HAIs. If CRE follow the same trend as ESBLs, we can expect to see more community-associated infections in the U.S. in the future. Preventing community-associated infections is much harder than preventing HAIs.

New drugs for treating CRE infections are scarce. For serious infections, the only drugs recommended for monotherapy are three new beta-lactam/beta-lactamase inhibitor drugs: ceftazidime-avibactam, meropenem-vaborbactam and imipenem-relebactam. However, these drugs work for infections with some types of CRE and not others. For example, the three new drugs are most active for CRE infections with class A carbapenemases but not CRE with class B carbapenemases. Resistance to ceftazidime-avibactam is occurring in class A enzymes, limiting treatment options to two drugs, not three.

Treatment of serious infections caused by CRE with class B carbapenemases requires a combination of ceftazidime-avibactam and aztreonam, essentially

creating the drug aztreonam-avibactam which is still in phase 3 clinical trials.[6] Aztreonam-avibactam and another drug in phase 3 clinical trials, cefepime-taniborbactam, offer some future relief for treating these infections. However, infections with class B carbapenemase CRE are likely to become more common and resistance to new drugs is likely to occur, resulting in hard-to-treat or untreatable *Enterobacteriaceae* infections for the foreseeable future.

CRE are challenging antimicrobial susceptibility testing (AST) systems. Normally, laboratories perform AST for drugs on the panel of their primary AST device first. If an isolate is resistant to these drugs, then off-line testing is performed of additional drugs. To treat a serious CRE infection without delay, initial susceptibility testing of an *Enterobacteriaceae* isolate should include extended-spectrum cephalosporins, carbapenems, ceftazidime-avibactam and either meropenem-vaborbactam or imipenem-relebactam.

Delaying results for additional off-line testing can delay appropriate treatment of a potentially life-threatening infection. In one study, delayed appropriate treatment was associated with a 20 percent increase in the risk of in-hospital mortality/discharge to hospice, regardless of susceptibility status, and a 70 percent increase in length of stay.[7] If a CRE isolate is resistant to all the new beta-lactam/beta-lactamase inhibitor drugs, then it likely carries a class B carbapenemase and needs susceptibility testing to aztreonam-avibactam. Because there are no FDA breakpoints for this drug combination, testing is not available on any commercial AST device. It is only available in regional laboratories of the AR Lab Network.[8] When new drugs like this come to market, it is essential to add these to AST devices as quickly as possible to avoid delays in appropriate therapy.

Testing trends and challenges

Enterobacteriaceae are just an example. The other AR threats present similar challenges to the healthcare community despite differences in epidemiology. Common to all AR threats is the need for robust diagnostic testing and the impact these tests can have on antibiotic stewardship and prevention strategies. The diagnostic needs for antibiotic resistance generally fall into three categories:

1. Tests to determine if an antibiotic is needed. A test that can differentiate bacterial vs. viral vs. non-infectious diseases would fundamentally improve the way antibiotics are used, especially if the test can be used at the bedside and it worked across infectious syndromes. The quest for a biomarker test with these characteristics has been elusive. Advances are occurring in syndrome-specific markers of infection. This includes tests to more accurately diagnose sepsis from other causes of fever, and tests to more quickly identify an infectious agent from a positive blood culture or other clinical specimen.

2. Tests that determine which drug works best. Phenotypic antimicrobial susceptibility testing is still the gold standard diagnostic for therapy decisions. Molecular testing is fast and can provide important epidemiological data, but tests detect resistance and not susceptibility. Doctors need to know which drugs are most likely to be effective. Rapid AST from a positive blood culture is a reality today, but there is a need to make rapid testing more widely applicable to all AST needs. The challenge is to increase speed without sacrificing accuracy. No matter how AST data are generated, epidemiological tools are needed to collect and analyze data for better empiric treatment decisions and to identify new trends in resistance.

3. Tests for infection control decisions. The uptake of colonization testing for AR threats is slow in the U.S. This may reflect the lack of reimbursement for tests used in outbreak response rather than tests for individual patient care. New data showing that colonization in a patient proceeds infection with the same pathogen may help to overcome reimbursement issues. In addition, delays in availability of FDA-cleared colonization tests occur because the cost of test development is very high and the return on investment (ROI) is hard to predict early in an outbreak. The first FDA-cleared test for CRE colonization occurred in 2016, 15 years after the first report of CRE. There is still no colonization test for *Candida auris*, a fungus that is another urgent AR threat. Mitigating these risks will help with new test development.

Antibiotic resistance is a health crisis that will be with us for a long time and continue to evolve. The forecast is that this problem will get worse before it gets better. Diagnostic laboratories need to be prepared.

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Dr. Jean Patel joined Beckman Coulter after nearly 17 years at the Center for Disease Control (CDC) in the Antimicrobial Resistance Reference Laboratory and the Office of Antimicrobial Resistance. Prior to that, she was the Assistant Professor of Pathology and Laboratory Medicine, and the Assistant Director of Clinical Microbiology at the University of Pennsylvania. Dr. Patel is known worldwide for her expertise and publications in antimicrobial susceptibility testing.

Study tests immunotherapy in people with cancer and autoimmune diseases

By National Cancer Institute

Researchers have launched a clinical trial to test an immunotherapy drug in patients who have both cancer and an autoimmune disease, such as rheumatoid arthritis, lupus or multiple sclerosis.

Immunotherapy drugs enhance the ability of the immune system to detect and kill tumor cells. In recent years, these therapies have benefited a growing number of patients, including some patients with advanced cancers.

But doctors have not known whether immunotherapy is safe and effective for people who have both cancer and an autoimmune disease, because such patients have been excluded from clinical trials of immunotherapy drugs.

"Having an overactive immune system is the main reason that many patients with both cancer and autoimmune diseases have not been included in hundreds of clinical trials of immunotherapy drugs," said Hussein Tawbi, M.D., Ph.D., of the University of Texas MD Anderson Cancer Center and one of the lead investigators for the new trial.

For many doctors who treat patients with both diseases, the lack of information on the effects of immunotherapy in such patients has led to a "clinical conundrum," Dr. Tawbi continued.

"As doctors, we have been afraid of using these drugs in patients with autoimmune diseases because we don't have evidence that they are safe for these patients," he added. "There's no guidance on how to handle these cases."

The main concerns, Dr. Tawbi explained, are that "the immune-related side effects may be more severe in patients with both diseases, or that their autoimmune conditions may get much worse because of immunotherapy."

In addition, because these patients have been excluded from clinical trials, doctors don't know "whether they may respond better [than other patients]—or possibly worse because they could be on therapy to suppress the immune system," he added.

The new clinical trial, which is sponsored by NCI, is intended to help researchers understand the potential harms and benefits of using immunotherapy in patients with certain autoimmune diseases.

The trial could also yield insights into the biology of autoimmune diseases, which could help researchers explore new treatments, according to Dr. Tawbi.

"This study is the first of its kind," he said. "What we learn may allow us to extend the promise of immunotherapy in a safe manner to patients who have cancer and an existing autoimmune disease."

Between 10 percent and 30 percent of cancer patients have an autoimmune disease as well, so the results of the trial could have implications for many patients, said Elad Sharon, M.D., M.P.H., of NCI's Cancer Therapy Evaluation Program and another leader of the study.

"Releasing the brakes" on the immune system

Autoimmune diseases occur when the immune system goes awry and starts to attack the body's healthy tissues.

Immunotherapy drugs, such as immune checkpoint inhibitors, "release the brakes" on the immune system, allowing immune cells to detect and attack tumor cells.

In some patients, immunotherapy can cause the immune system to recognize some of the body's healthy tissues as foreign and attack them. This can lead to side effects such as inflammation of the inner lining of the colon, the lungs or heart muscle.

Some doctors have been concerned that stimulating the immune system against tumors might "unleash the wrath of autoimmunity," causing potentially severe and even life-threatening complications, Dr. Tawbi noted.

To address such concerns, the new clinical trial will enroll 260 people who have advanced cancer and an autoimmune disease, including dermatomyositis, systemic sclerosis, rheumatoid arthritis, lupus, inflammatory bowel disease, Crohn's disease, multiple sclerosis and Sjogren's syndrome.

Participants will receive nivolumab (Opdivo), an immune checkpoint inhibitor approved by the Food and Drug Administration to treat a number of cancers, including Hodgkin lymphoma and liver, lung, kidney and bladder cancers.

To determine the safety of the drug in the new trial, the researchers will monitor participants for the sudden emergence of severe autoimmune symptoms, known as flares. The researchers will assess the drug's effectiveness by tracking patients' responses to treatment, how long patients survive without their diseases getting worse, and how long patients survive.

The expanding use of immunotherapy

In recent years, the use of immunotherapy for patients with cancer has been expanding rapidly. Immune checkpoint inhibitors, for example, have been tested in a growing number of cancer types, in combination with other therapies, and in patients with different stages of disease.

These efforts underscore the need to develop scientific evidence to guide decisions about whether to use a rapidly growing class of treatments for patients with autoimmune disease and cancer, according to Dr. Sharon.

"One of the main reasons for doing the trial is that immunotherapy has cured some patients with metastatic cancer," said Dr. Tawbi.

"If we can learn how to use immunotherapy to treat people with both cancer and autoimmune diseases, then we could offer these patients potentially curative therapy," he added.

Anecdotal evidence from treating patients

Although no clinical trial has tested immunotherapy in cancer patients who have an autoimmune disease, some oncologists have shared their experiences using immunotherapy to treat such patients.

For example, a series of case reports in medical journals has suggested that patients with cancer and an autoimmune disease may respond to immunotherapy drugs as well as patients without autoimmune disease.

"When you activate the immune system, patients may experience more immune-related side effects, as one would expect," said Alexandra Drakaki, M.D., Ph.D., of the David Geffen School of Medicine at UCLA. But patients who have these side effects might still respond to immune checkpoint inhibitors, she continued.

"We hope to learn more about this from the new NCI-sponsored clinical trial," she added.

Dr. Drakaki has used immunotherapy drugs to treat some of her patients with advanced cancer and autoimmune disease outside of a clinical trial, and most of the immune-related side effects have been manageable, she said.

In a recent article about treating patients with cancer and an autoimmune disease, Dr. Drakaki and her colleagues wrote that the potential risk of dying from cancer may outweigh the potential harms of worsening autoimmune symptoms, which may be largely reversible.

It may be appropriate to include patients with advanced cancer and autoimmune diseases in clinical trials of checkpoint inhibitors when no other effective options for treating cancer are available, the authors noted.

In her own clinic, some of Dr. Drakaki's patients with advanced cancer and autoimmune disease have been willing to accept the risk of worsening autoimmune symptoms in exchange for a promising cancer treatment. These patients, she noted, were relatively healthy and had autoimmune diseases that were "well controlled."

"They just want to be alive," she said. "They don't care if their autoimmune symptoms are going to get worse temporarily."

Dr. Drakaki, however, stressed the need to develop a multidisciplinary care team that can manage cancer, as well as autoimmune diseases in patients.

"As oncologists using immunotherapy drugs in patients with autoimmune conditions, we need to work closely with our colleagues who have expertise in treating and managing immune-related side effects," she said. "We oncologists could not—and should not—do this alone."

Teams of experts

The idea of bringing together experts on autoimmune diseases and cancer was central to the development of the new trial.

"We have engaged some of the top experts on autoimmune diseases in the country to provide guidance on classifying the severity of these disorders in patients who also have cancer," Dr. Tawbi said.

For each type of autoimmune disease that patients in the trial may have, a team of experts has developed treatment strategies and ways to closely monitor the severity of autoimmune symptoms throughout the study.

By developing standard criteria for classifying the severity of autoimmune symptoms and responses to treatment, the researchers hope to create a base of scientific evidence that could be used in the future to select patients with both cancer and an autoimmune disease who are candidates for immunotherapy.

In addition to collecting clinical data, the researchers will collect blood and tissue samples for further investigations, including tissue from organs that had been affected by both autoimmune disease and cancer.

Ultimately, the researchers hope to better understand the mechanisms that give rise to treatment-related side effects in patients with autoimmune diseases, which could provide insights into the biology of autoimmune diseases, as well as the side effects of immunotherapy.

"We will study the interactions between the antitumor immune response and the autoimmune response," said Dr. Tawbi. "This will give us an opportunity to investigate a range of issues, including the dynamics of a flare."

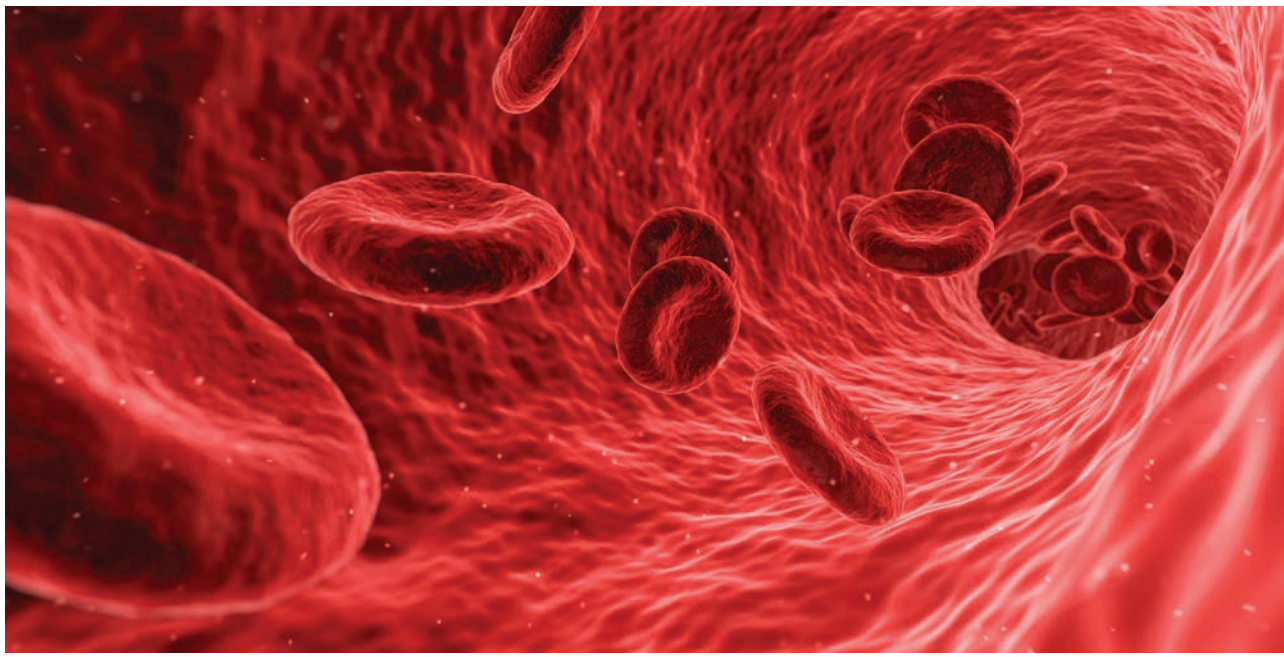
An exciting aspect of developing the study has been the opportunity to work closely with experts on autoimmune diseases from some of the leading academic medical centers across the United States, noted Dr. Sharon, adding that he expects the collaboration will yield a wealth of information.

"We hope to gain a better understanding of how the immune system changes in patients with autoimmune diseases and cancer who receive immune-directed therapies," he said. "What we learn could eventually lead to new therapies for patients with autoimmune conditions as well as patients with cancer."

(This article was reprinted by courtesy of the National Cancer Institute. The original link to the article can be found at https://www.cancer.gov/news-events/cancer-currents-blog/2019/immunotherapy-cancer-autoimmune-diseases-clinical-trial)

Fighting sepsis to improve outcomes and reduce cost

By M. Laura Parnas, PhD, DABCC



Despite its modest public profile, sepsis ranks as the leading cause of death in hospitals today. Approximately 30 to 60 percent of patients diagnosed with the condition die,[1,2] and one in every three patients who die in a hospital in the U.S. has sepsis.[3] Each year, the condition strikes more patients than HIV/AIDS, stroke, and breast and prostate cancer combined.[4]

In addition, 19 percent of hospital patients with sepsis are readmitted within 30 days, contributing to a significant financial burden that makes sepsis the single most expensive condition U.S. hospitals face—costing an estimated $24 billion dollars annually.[5]

Reducing mortality and alleviating the impact that sepsis has on hospital workflow and budgets remains a top healthcare priority, with many institutions establishing a multidisciplinary sepsis management team to design a formal process for identifying and managing the condition. The clinical laboratory provides critical value in this process, as new diagnostic tests can help physicians diagnose this life-threatening complication quickly, saving lives and reducing treatment costs.

The difficulty of accurate diagnosis

Sepsis is the body's extreme immune response to persistent infection, essentially turning the immune system against the body itself. The immune response causes poor blood flow, and the decreased blood flow deprives cells of oxygen and other nutrients, potentially leading to tissue damage, organ failure and, eventually—in a condition known as septic shock—death.

While the most common cause of sepsis is bacterial infection, other types of pathogens can cause it as well. This broad pathogenesis for sepsis and the historical lack of specific diagnostic tests has perhaps led to the overuse of antibiotics and, paradoxically, contributed to its increasing prevalence. The number of patients hospitalized for sepsis in the U.S. doubled between 2000 and 2008,[6] and now exceeds 1.7 million annually.[7] Approximately 270,000 people die from sepsis each year in the U.S.[8]

With appropriate recognition, early diagnosis and optimal treatment, it is estimated that 80 percent of sepsis deaths could be prevented.[9] The CMS SEP-1 core measure,[10] which prescribes the tests and interventions required when sepsis is suspected in an adult, has led to changes in care. However, diagnosing sepsis can be very difficult, especially in light of the unspecific signs and symptoms of the condition. In addition, the progression of sepsis is rapid and the corresponding mortality rate for each stage increases dramatically.

Selecting the right test

Traditionally, clinicians have ordered several different tests to aid in the diagnosis and treatment of sepsis.

Blood cultures are used to identify the infecting pathogen when a systemic infection is suspected. Unfortunately, cultures normally take 24 to 48 hours to show growth, and this delay in obtaining results renders them ineffective as a diagnostic test for sepsis. In addition, they often lack the sensitivity to identify the specific infecting pathogen, and many critically ill patients are already receiving antibiotics, which further decreases culture sensitivity. Only about 30 to 40 percent of patients with a clinical diagnosis of sepsis have positive

blood cultures.[11] The primary role of cultures in sepsis management is to provide information about the identity of the pathogen to help the clinician understand whether the therapy being administered is correct or needs to be modified.

Lactate at increased levels is an indicator of tissue hypoperfusion (oxygen deprivation) and thus, the test can be used to help measure the extent of organ or tissue damage. Many conditions can cause elevated lactate levels--such as strenuous exercise, heart failure or a damaged or diseased liver--and thus, lactate is not a specific biomarker for sepsis. However, lactate helps in sepsis management by improving the identification of patients in need of early and aggressive fluid resuscitation.[12]

C-reactive protein (CRP), an acute phase reactant produced by the liver, is elevated when there is inflammation in the body. However, elevated levels of CRP may be due to a variety of conditions that can cause inflammation, and as such, this biomarker is not specific to sepsis. Rather, it is a general test to check for inflammation rather than to pinpoint the exact location or cause.

Procalcitonin (PCT) has emerged as one of the most clinically important biomarkers for sepsis today. A PCT test does not replace blood cultures, lactate or CRP, as each of these tests gives the clinician different patient risk information. The advantage of PCT is that it is both an early and a specific biomarker for a systemic reaction to a bacterial infection. The early recognition and confirmation of bacterial sepsis is a crucial factor to improve patient outcomes.

PCT in the race against time

When exposed to bacterial toxins, cells release PCT along with inflammatory cytokines,[13] so the biomarker can be used to gauge levels of inflammation and assess the degree of bacterial infection within the body.[14] During viral infections, PCT production is lessened by Interferon gamma (IFN-γ) that is released during the host response to the virus.[15] Thus, PCT concentration will not rise in viral infections as it does in the presence of a bacterial infection.

As a result, determining PCT concentrations can give physicians the confidence to determine whether antibiotic therapy is appropriate and to administer it quickly. This is critical especially for emergency department physicians, who can be the first point of contact with septic patients.

PCT concentrations are also associated with the progression of sepsis to more advanced stages - severe sepsis and septic shock. Measuring PCT concentrations on the first day of patient assessment can help clinicians identify the risk of progression in order to take appropriate anti-infection control measures. In addition, some PCT assays have a risk assessment claim in which changes in the level of PCT from day 1 to day 4 can be used to help assess the 28-day all-cause mortality risk. Thus, clinicians can assess PCT concentrations over time to monitor patient risk and gain confidence that the control measures and antibiotics they have selected are working. Conversely, if results indicate they are not working, appropriate adjustments can be made quickly.

The evolution of PCT assays

The first manual PCT assays[16] were developed and used in Europe in the late 1990s and were approved for use in the U.S. a decade later. Designed for single-point evaluations, the systems could only handle a limited number of tests at one time. A number of manufacturers licensed the original patented assay technology and used it to develop their own platforms.

In 2014, a groundbreaking clinical trial,[17] the MOSES PCT Monitoring Sepsis Study, showed that the odds of patients with sepsis surviving doubled if their measured PCT concentrations decreased by more than 80 percent between the first and fourth day of their treatment. According to Kumar et al., every hour that proper treatment for sepsis was delayed reduced survival chances by 7.6 percent.[18] The significance of these findings was addressed in the indications of use for the first fully automated PCT assay cleared by the FDA in 2016, which enabled PCT tests to be processed in less than 20 minutes. Thus, the combination of automation and faster tests can help expedite diagnosis and contribute to improved outcomes, including decreased mortality.

Multiple studies indicate that healthcare institutions that implement automated PCT testing to evaluate patients who present with suspected infection are seeing significant and quantifiable results. In one retrospective study, investigators found that the use of PCT screening on the first day of ICU admission was linked to significantly shorter (1.2 days) hospital stays, as well as an overall decrease in the cost of care ($2,759 per patient).[19] Another study comparing the effectiveness of antimicrobial treatment before and after PCT testing was introduced to guide antibiotic decision-making found that the length of hospitalization decreased by 47 percent, in-hospital mortality went down by 62 percent, and 30-day readmission levels were cut in half.[20]

In light of the growing prevalence of sepsis and its troubling mortality statistics, the clinical lab can provide significant value to healthcare institutions as they formulate strategies to identify and manage the challenge effectively. By helping clinicians identify and accurately diagnose sepsis quickly, they can help improve hospital workflow, enhance antibiotic stewardship, reduce treatment costs and, ultimately, save lives.

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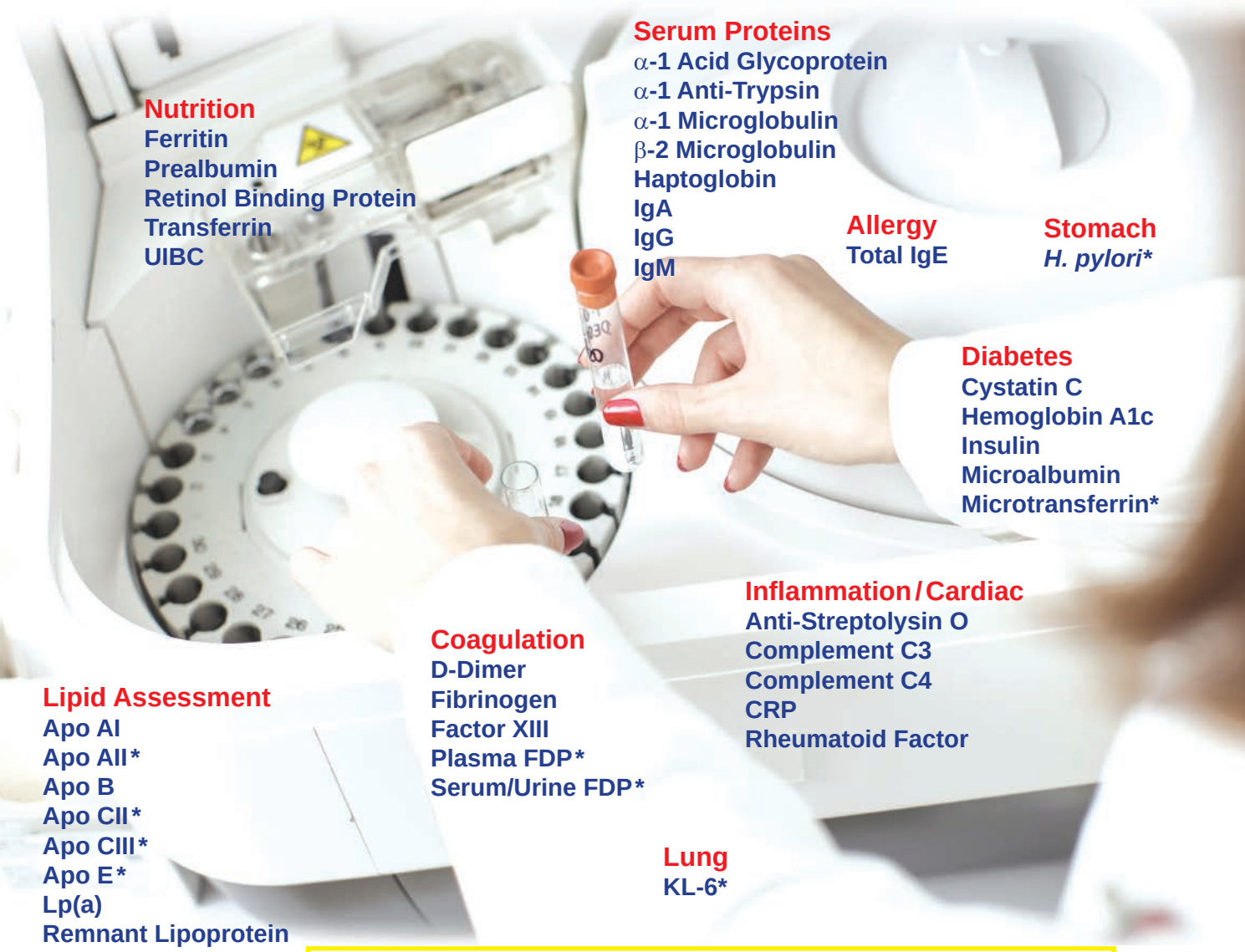

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How modern dried blood spot technology is helping combat HIV

By Dana Welle, DO

The global epidemic and spread of the Human Immunodeficiency Virus (HIV) and the resulting disease called AIDS (acquired immunodeficiency syndrome) has reached a death toll of more than 30 million since the outbreak began in the 1980s.[1,2] Since then, we have made major strides in providing antiretroviral (ART) drugs to more than 24 million people worldwide, but more needs to be done when it comes to fighting the spread of this devastating disease.[2]

In 2018, more than one million new infections were recorded around the world, providing some insight into how we have failed to prevent the spread of HIV, especially when a simple blood test is all that is needed to test patients.[1] This is where Dried Blood Spotting (DBS) Technologies may make a difference in helping us to not only prevent new infections, but to also adequately treat those already on ART drug regimens.

DBS is seeing a revival as companies are creating new iterations for easier use and expanding on the ability to safely ship from any corner of the world.[3] This allows researchers who are studying and treating HIV/AIDS to reach those vulnerable populations living in remote areas or developing countries,[4] and those who might be stigmatized to get testing when available. In the U.S. alone, 79 percent of all new infections occurred in the youth aged 20 to 24.[5] The young in developing countries are the least likely to be tested or know they are infected due to lack of immediate symptoms.[6]

Though it's well understood that early detection is a key component to deterring the virus from spreading, privacy concerns along with access, both logistically and financially, to testing has been an ongoing problem.[7] Circumventing the need for clinic visits with a self-sampling DBS alternative, especially in underdeveloped regions, could increase their likelihood of getting tested and for the monitoring of ART drug regimes.[8]

With the basic infrastructure of a postal service in place, just about anyone can take a blood sample by themselves, without the need for a trained technician, by using DBS collection devices directly inside their home. With only a few drops of dried blood, someone can ship their sample through the mail and get a clinical result within days. These dried blood microsamples are considered nonregulated and non-biohazardous material, which simply requires a basic triple-packaging system for shipping via post.[9]

So why has this method not seen wider adoption? Accuracy issues plague the original devices, and the sensitivity of analyzer technology has not caught up with the processing requirements of micro-samples, effectively keeping this option on the periphery for many years.[10]

The good news here, dried blood micro-sampling technology has been quietly evolving in the background for some time now. As advanced analyte detection methods become ever more sensitive, paired with the automation of sample processing for DBS, the idea of self-sampling for clinical diagnostics is becoming an option. Some contemporary DBS devices are even now capable of separating serum and plasma, which are key blood components to detecting HIV as early as nine days after infection using RNA viral load testing.[11] DBS is quickly being reassessed and viewed as a competent, more cost-effective way for early detection, as well as the monitoring of ART drugs.[12,13] Creating an uncomplicated, remote self-sampling procedure for the public could assist in optimizing methods for early HIV detection and preventing its further spread.

Lastly, point-of-care testing – specifically for HIV – has been available for the past few years in most developed countries. It is forecasted for continued growth, providing not only the ability to be tested remotely, but offering a high degree of autonomy. However, for these point-of-care tests, false-positive results have been cited with off-the-shelf options, such as rapid tests using oral fluid, spotlighting the need for a solution that involves a collection of blood biomarkers. DBS, with its evolution over the last decade and its increased awareness by those who are researching grave illnesses, such as HIV/AIDS, is the future of sample collection and the way patients can access healthcare.

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Clinical lab industry AMPed for future of molecular pathology

By Brenda Silva

A chilly morning in Baltimore brought molecular diagnosticians together to discuss the hot topic on all of their minds – what does the future hold for molecular pathology? The panel discussion was held on the last day of the Association for Molecular Pathology (AMP) conference in November and was clearly one of the most-anticipated sessions of the annual meeting – evidenced by the standing-room-only attendance. During the session, many lab- and healthcare-related topics were brought up for discussion; however, no others received more attention and requests for additional information than the following three topics.

Looking to the future

Session moderator Victoria Pratt, PhD, Professor, Director of Pharmacogenetics and Molecular Genetics Laboratories at Indiana University School of Medicine in Indianapolis, IN, opened the discussion by asking the four-person panel where they see molecular pathology going in the future, encouraging round-table opinions from each of the panelists.

Federico Monzon, MD, Chief Medical Officer at Castle Biosciences in Friendswood, TX, was quick to point out the field of molecular pathology is "so rapidly changing, you can't just focus on one thing for the future. It's diversification, it's looking at transcending sequencing; it's going beyond genomics. Informatics helps us with the ever-increasing complexity in molecular data, but we all need to embrace new technology and products to really take advantage of what's available to us."

In agreement with Monzon's assessment, Timothy Stenzel, MD, PhD, Director of the FDA's Office of In Vitro Diagnostics and Radiological Health in Silver Spring, MD, added, "I think our future has never been brighter than it is today, but our ability to adapt to the changes that are coming is critical. We are going to be moving more into precision medicine, which is so important now, and I believe we are going to see a lot more specialization and sub-specializations as well in the future."

Focusing on the role of molecular pathology (MP) in the future, Gabriel Bien-Willner, MD, PhD, Medical Director of the MolDx program at Palmetto GBA in Texas, said, "The rest of medicine sees molecular pathology and molecular diagnostics as the future of medicine. With the amount of data we have, we really are at the center of the future of medicine. We are in the middle of changing paradigms on how we treat patients, and we're going to be challenging things even more in the future, so we need to be ready for whatever changes come our way."

Reiterating the importance of clinical data, Karen Kaul, MD, PhD, Chair of the Department of Pathology and Laboratory Medicine at Northshore and Clinical Professor of Pathology at the University of Chicago's Pritzker School of Medicine, pointed out that "pathologists generate 75 percent of the data that determines 75 percent of the downstream action in the medical management of patients. The amount and type of data is expanding and changing dramatically with the advent of personalized medicine." Regarding sub-specialization, she said, "Additionally, our community needs to ensure our trainees are prepared to take care of patients more precisely when they finish training, which is a challenge with this rapid evolution we are seeing."

Affects of AI on MDx

As automation becomes a larger part of many clinical labs, the role of artificial intelligence (AI) / machine learning (ML) is expected to impact the field as well, with molecular diagnostic (MDx) demands being met by potentially faster and more accurate technology. Continuing the session discussion, Pratt focused on questions about how AI/ML could affect MDx in the future.

Panelist Dr. Stenzel reported, "Our office has been dealing with AI for a while, and we're seeing a huge increase in people coming in to work in AI, but we're still a long way off from being fully integrated. With AI/ML in the future, how you teach and test will be key. When we initially compared the efficiency and productivity of pathologists with AI/ML, it was always people who came out as winners, but now we're seeing a shift with AI/ML starting to win more."

Acknowledging existing industry apprehension about using AI, Dr. Bien-Willner asserted, "AI is a scary word to some people, but we shouldn't be scared of it because there are a lot of AI-related ways to help pathologists do their job more efficiently. In terms of replacing pathologists at some time in the future, AI never will – because it lacks the human element, and there are certain things pathologists just do better. But when it comes to using AI, we should still embrace it, and find ways to get involved with it, which will help us keep pace with the available technologies."

Looking at AI/ML as a necessity for clinical labs in the future, Dr. Kaul predicted, "AI, for the near future, will be tools that will help us be more accurate and more efficient. With the predicted shortage of pathologists in the future, we may need these AI tools. They could not only make us better, more effective and more efficient, but maybe more cost-effective as well."

Next-generation pathologist success

As panelists looked ahead to the future of the clinical lab, Pratt raised the question of what could be done – in an ideal scenario – to better assist the next generation of molecular pathologists and ensure their academic and professional success, both for themselves as well as their patients.

"Our trainees need greater ability to talk to clinicians in an interactive way, in a consulting role," asserted Dr. Kaul, adding, "They also say they haven't learned enough about lab management, regulatory issues, etc., when they finish residency and fellowship, so our training curricula needs to include these skills, in addition to the factual and diagnostics knowledge needed."

Also noting a disconnect between education and application, Dr. Bien-Willner said, "There is a huge gap outside of the lab with how data results are applied to the patient. Molecular pathologists deal with oncologists who often don't know how to apply the findings we give them. They ask us what to do with the data we provide, so we tell them it's cancer and they cut it out. Future pathologists could help oncologists more by helping them really understand the role everyone plays in patient care, and how we all have to work together for the patient."

Voicing his agreement, Dr. Monzon added, "For a long time, we've only focused on providing detailed lab reports. Now, we find we've done ourselves a disservice by creating a barrier between the lab and the oncologists and their patients. In the future, we have to come out of the lab more to help remove this barrier."

Summarizing a plan for the future, Dr. Stenzel suggested, "Information is power – we have to learn how to communicate with other specialties. There is also a competency issue – learn the basics and keep learning, because the field is going to keep changing in the future."

Takeaways for the future

When Pratt asked for their final thoughts in a word, the panelists used collaboration, communication, involvement and evolution to describe the future of molecular pathology. These four keywords, along with feedback given both throughout the session, as well as during an after-session Q&A period, offer the optimistic viewpoint of an industry that has acknowledged the issues that exist and has accepted the challenges and opportunities that are yet to come.

The Need for Molecular Pathologists

By Karen Kaul, MD, PhD

Clinical medicine is increasingly complex, with a constant evolution in laboratory tests, diagnostic algorithms and consensus guidelines. Practicing clinicians are challenged to keep current with the rapid advances in laboratory medicine, even in the area of their expertise. The 2015 Institute of Medicine report, "Improving Diagnosis in Healthcare," strongly suggests that pathologist input and interaction with clinical colleagues would improve laboratory utilization and clinical outcome, as diagnosis is truly a team effort.[1,2]

Educating and providing consultation is a role that pathologists must embrace,[2] and is particularly needed in genomics and personalized medicine, both rapidly evolving areas in which many clinicians have not fully trained. Molecular tests are often expensive, and may guide the use of expensive treatments, so "getting it right" is key for optimal patient management. Correct ordering and interpretation of lab tests can affect the speed, outcome and cost of clinical management for many patients.

Thus, pathologists need to stand ready to increase their assistance to clinical colleagues in the correct use and understanding of the results of molecular and other tests. Opportunities exist via individual consultation, by participating in review of send-out or expensive tests, seeking representation on hospital committees that approve testing algorithms and build order sets, or in more routine settings such as case reviews and tumor board discussions. Our training programs must prepare our trainees to assume these roles, particularly in molecular pathology due to the complexity and expense of the testing.

We must also seek ways to make ourselves available to our clinical colleagues more easily. A recent study noted that only 6 percent of primary care physicians consulted with laboratory professions in a given week.[3] In this era of expanding, decentralized health systems and extensive use of the electronic health record, it may be more difficult for physicians to access pathology and laboratory medicine staff for consultation and advice.

The patterns of inter-physician communication have also changed dramatically, prompted by electronic messaging texting and so forth. To facilitate timely communication with the lab, we built and implemented an electronic consultation system within our hospital network that allows caregivers to reach the lab with any question via an electronic in-basket message within our EMR system.[4] Queries are triaged and answered by in-basket or phone by laboratory staff, residents or fellows. At our institution, approximately 5 percent of these inquiries dealt with molecular questions, often to clarify appropriate test ordering.

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Dr. Karen Kaul is Chair of the Department of Pathology and Laboratory Medicine at NorthShore University HealthSystem and a Clinical Professor of Pathology at the University of Chicago's Pritzker School of Medicine. Dr. Kaul is boarded in Anatomic and Molecular Genetic Pathology and has been deeply involved in development of the field of molecular pathology, the laboratory basis for individualized medicine. She also has been involved in resident and fellow education, having served as a longstanding program director, as well as a member of the ACGME residency review committee for pathology, and as a Trustee of the American Board of Pathology.

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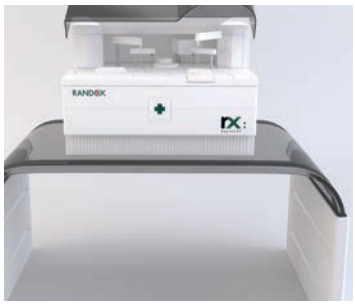

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LABORATORY INNOVATOR

Orchard Software CEO suggests data distribution and analytics could bear the most fruit for labs.

In October 2019, Orchard Software welcomed Billie Whitehurst as its new CEO. Billie has successfully led both large- and medium-sized companies in the private and public market. She brings more than 20 years of leadership and execution experience in healthcare, most recently serving in senior leadership roles at Netsmart, Change Healthcare and McKesson.

Your career began as the Clinical Director at a children's hospital – how did that role transition into a new position and career in the field of IT?

Early in my nursing career, I found there were few tools that supported clinical workflow or really helped to support improved patient safety and quality. In fact, much of what involved health information technology (HIT) was viewed as a burdensome requirement that got in the way of patient care. My view of HIT as a strategic tool changed when I saw positive patient identification systems literally save lives and make a meaningful difference in patient safety. From there, it became clear that there was a lot of room for improvement and in fact, HIT can include powerful tools that effectively support clinicians and patients. With my clinical background and experience, I felt I had a distinct advantage and a responsibility to make a difference here.

Further, we were forcing clinicians to collect and document so much data, but rarely were they able to easily use or share it to improve patience care. The idea of making data reportable and actionable in a proactive way was very appealing. I viewed actionable data as the spark to process improvement and collaborative care across teams, disciplines, and care settings.

With the implementation of more IT solutions in healthcare, what have been some of the biggest changes you've seen over the last 10-20 years?

Positive patient identification has played a role in saving lives and preventing adverse events. HIT standards and discrete data capture have opened the world of analytics and artificial intelligence to healthcare. Interoperability or the ability to share data has improved care coordination, safety and efficiency. It has also been exciting for patients to gain access to their data and begin to become powerful participants in managing their own care.

Are there any IT-related advances on the horizon in the lab that are forecast to become the next important trend or asset to the healthcare industry?

The effective mining and distribution of data could become the most important asset to the laboratory. Whether it's used for AI initiatives, for proactive and real-time use to support workflows and decision-making or to manage the data generated by molecular and genetic testing to support personalized medicine – advanced analytics will be key.

As a leading laboratory information systems (LIS) vendor, are there any product or technology launches planned from Orchard Software that you can share at this time?

Orchard is implementing flexible hosting and SaaS solutions, and advanced tools to facilitate cloud-based technology to meet the needs of end users. Our products integrate everything from POC instruments, core lab instruments and automation lines, as well as tight integration with reference labs. We are also working on product expansion to facilitate complex testing and lab workflows

You have a reputation for "driving innovation, generating rapid growth and improving profitability" according to online comments. How will these same assets serve to drive your goals as the new CEO at Orchard Software?

One of our immediate goals is to accelerate the journey to SaaS and cloud-based solutions. I have deep experience in this area—developing SaaS solutions from scratch and migrating legacy technology into the cloud. I am very excited about the partnerships Orchard has built and feel there is a significant opportunity to continue to collaboratively build on these relationships to improve patient care and promote delivery of new solutions. Regarding efficiency, we are working on tools to expedite our implementations, automate testing, support client-side validation and provide more relevant and well-timed education through e-learning.

What are three items at the top of your to-do list in your role as the new CEO at Orchard Software?

1. Get to know our clients 2. Accelerate the movement to SaaS and hosted solutions 3. Rapid deployment of our advanced new LIS and POCT tools to deliver added value to the healthcare marketplace.

What is the biggest challenge currently faced by labs/LIMS, and does Orchard Software offer any solutions at this time?

One of the greatest challenges across all healthcare IT is achieving interoperable systems that actually store and provide patient data in a way that is beneficial to patient care. Laboratories have worked with an LIS or LIMS for decades, even prior to the advent of the EHR. However, these systems must be able to meet today's connectivity and security requirements and continue to improve laboratory productivity. As mentioned, one of our immediate goals is to transition our products to SaaS and cloud-based solutions, as this architecture proves beneficial to many of today's laboratories. In addition, Orchard stands out as an expert in systems integration with the ability to interface with a multitude of third-party information systems and laboratory analyzers.

With the knowledge that point-of-care testing (POCT) is expected to continue to gain traction in value-based care and the laboratory is expanding its oversight of disseminated laboratory testing sites, we are focusing on development of Orchard Trellis, our POCT connectivity solution. Trellis offers multiple deployment options and utilizes the Orchard Device Engine (ODE) to support cloud connectivity between laboratory instrumentation and the LIS application. The ability to connect within the lab testing spaces to give providers more types of data (not just lab results) to improve patient care is what our cloud-based technologies are all about..

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