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MEDICAL LABORATORY OBSERVER

SEPTEMBER 2019 ▪ Vol 51 ▪ No 9

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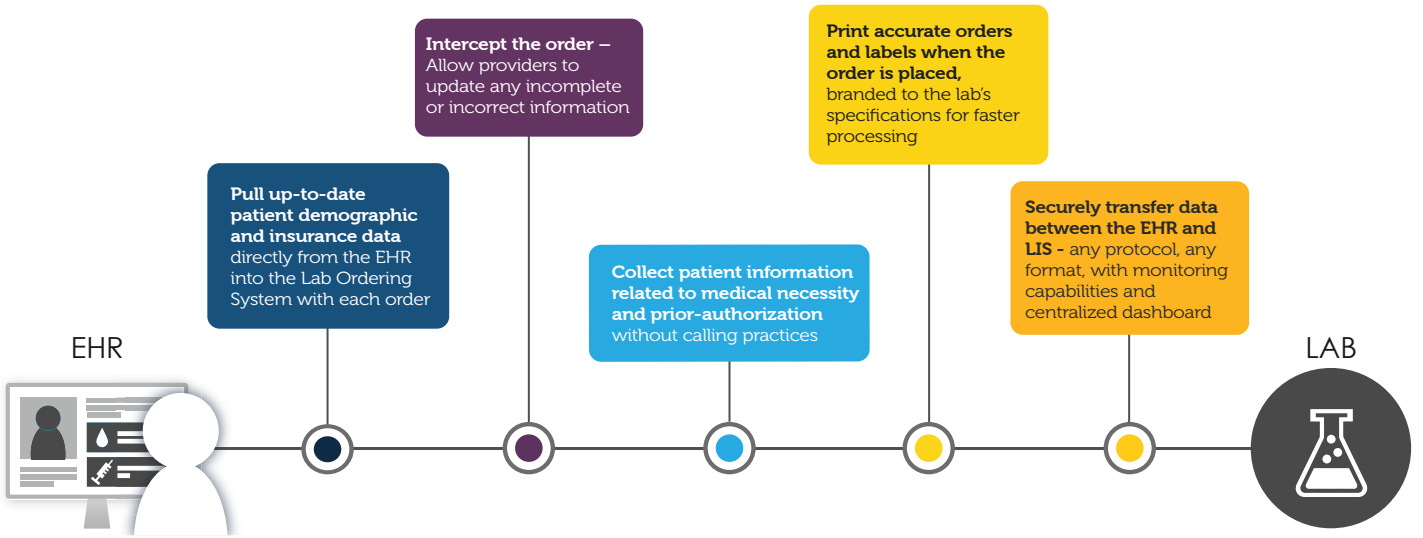

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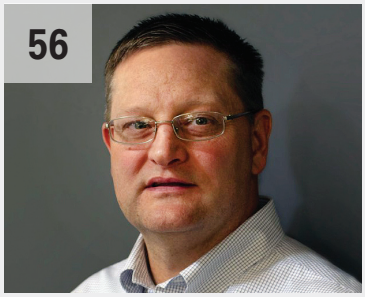

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AACC 2019

By Janette Wider,
Editor

Recently, I returned from attending my first American Association for Clinical Chemistry (AACC) Scientific Meeting and Clinical Lab Expo in Anaheim, CA. Not only was it exhausting, but stimulating, engaging, and promising in terms of laboratory science and those who serve the industry.

I've attended other trade shows and conferences over the years: Healthcare Information and Management System Society (HIMSS), American Health Information Management Association (AHIMA), Healthcare Financial Management Association (HFMA), and American Association of Blood Banking (AABB)—just to name a few. Overall, I enjoyed AACC as much as, or perhaps even more than, the other shows I've had the opportunity to attend.

A particularly interesting press conference I attended was a discussion on industry and government partnerships competing against antimicrobial resistance with representatives from the New York State Department of Health (NYSDOH) and the CDC. The first speaker was from the Wadsworth Center, New York State's public health reference laboratory that responds to urgent public health threats. She explained the NYSDOH is working with ILÚM, a subsidiary of Merck's Healthcare Services and Solutions, developing a research program to detect, track, and manage antimicrobial-resistant infections at healthcare institutions statewide. They are also working with OpGen to develop an infectious disease digital health and precision medicine platform that joins healthcare institutions to NYSDOH and uses genomic microbiology for surveillance and control of antimicrobial resistance.

The goal of this project is to improve patient outcomes and save healthcare dollars by integrating real-time epidemiologic surveillance with real-time delivery of resistance results to care-givers on web-based and mobile platforms. ILÚM is leading the project with the implementation of its technology platform. OpGen is providing its AcuitasAMR Gene Panel for rapid detection of multidrug-resistant bacterial pathogens along with its Acuitas Lighthouse Software for high resolution pathogen tracking.

I also had a great evening at Beckman Coulter's cocktail reception and Mobile Experience Center tour. Beckman Coulter was promoting automation for any size laboratory—small, medium, or large. In the Mobile Experience Center, an air-conditioned unit on wheels, we were able to view automation solutions for the small- and medium-sized lab. The automation experience available for a large-sized lab was done via virtual reality. Due to motion sickness tendencies, I took a pass ... but a few of my collegues dove right in and loved it!

Although I consider all of the meetings I attended at AACC successful, perhaps one of the most fulfilling was my co-editor and I connecting with the very inspiring Technologist Support Specialist, Vanessa Hawrylak MS, MT(ASCP) and her team at Visiun. *MLO* recently collaborated with Vanessa on the article, *Chemistry instrumentation—a critical need in Venezuelan labs* in our June 2019 issue. It discussed the dire need for chemistry analyzers in some of Venezuela's pediatric oncology clinics. We learned about the many positive responses she's received from individuals and companies all over the world who had read the article and expressed interest in donating to her cause. Vanessa happily shared new photos sent to her from a clinic of children getting the care they so desperately need. A follow up article is in the works for 2020—so, stay tuned!

Janette Wider

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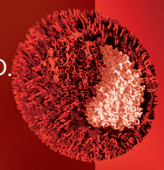

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Prostate cancer

174,650
is the approximate number of new prostate cancer cases in 2019 in the U.S.

31,620
is the approximate number of prostate cancer deaths in 2019 in the U.S.

1 in 9
men will be diagnosed with prostate cancer during his lifetime.

6 in 10
is the number of prostate cancer cases that are diagnosed in men aged 65 or older.

66 years
is the average age of prostate cancer diagnosis.

2nd
is the rank of prostate cancer of cancer-related deaths in American men.

1 in 41
men will die of prostate cancer.

99 percent
of prostate cancer patients are alive five years after diagnosis.

• **Sources:** https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html, https://cancerstatisticscenter.cancer.org/?_ga=2.243855879.387902912.1563899307-318581820.1563463557#!/cancer-site/Prostate

HIV

Persistent HIV in central nervous system linked to cognitive impairment. Many people with HIV on antiretroviral therapy (ART) have viral genetic material in the cells of their cerebrospinal fluid (CSF). These individuals are more likely to experience memory and concentration problems, according to new data published online in the *Journal of Clinical Investigation*.

A study of 69 individuals on long-term ART found that nearly half of the participants had persistent HIV in cells in their CSF, and 30 percent of this subset experienced neurocognitive difficulties. These findings suggest that HIV can persist in the nervous system even when the virus is suppressed in a patient's blood with medication. The study was funded by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Mental Health (NIMH), both parts of the National Institutes of Health (NIH).

Investigators from the University of North Carolina, the University of Pittsburgh, and Yale University studied participants enrolled in the AIDS Clinical Trials Group (ACTG) HIV Reservoirs Cohort Study. This primarily male group—aged 45 to 56—of long-term HIV survivors had infections controlled with ART for on average nine years. Researchers analyzed each participant's CSF for HIV DNA and then compared these data to each participants' results from standard neurocognitive evaluations. About half of participants had viral DNA in cells in the CSF, indicating the presence of latent virus, even though standard HIV RNA 'viral load' tests of the cell-free CSF fluid were positive in only four percent of participants. Investigators also found that 30 percent of individuals with persistent HIV DNA in the CSF experienced clinical neurocognitive impairment compared with 11 percent of individuals whose CSF did not contain viral DNA.

Many researchers hypothesize that HIV-related inflammation causes HIV-associated neurocognitive disorder (HAND). The new findings suggest that the presence of persistent HIV-infected cells in the central nervous system (CNS), despite long-term ART, may play a role in neurocognitive impairment. The authors note that the overall frequency of neurocognitive impairment in this group was relatively low and that the association does not confirm that HIV DNA causes HAND. Overall, the current study found that examining CSF cells revealed a higher-than-expected prevalence of persistent HIV in the CNS, which may be a significant obstacle to efforts to eradicate HIV from the body.

Data management

ELLKAY acquires X-Link. ELLKAY, LLC, a healthcare connectivity and interoperability solutions company, announced its acquisition of the assets of Tampa-based Legal Easy, Inc., including the X-Link medical software interfacing solution.

With the strategic acquisition, ELLKAY expands its healthcare footprint and enables providers with an easier, more cost-effective way to achieve Promoting Interoperability (PI) objectives and quality measures. It also strengthens ELLKAY's core mission of extending solutions that provide true interoperability and access to patient data at the point of care (POC).

Despite regulatory requirements and incentives including PI and the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA), interoperability and data connectivity remain two of the most elusive issues in today's healthcare market. With more than 30 years of experience in integrating disparate systems, Legal Easy, Inc. has collaborated with over 22,000 providers, 350 partners, and 1,700 resellers. The company's core interfacing solution, X-Link, integrates disparate clinical and practice management systems and services, providing integration for more than two thirds of the practice management systems. X-Link's direct-to-physician platform acts in real time and is easy to install, cost-effective to maintain, increases efficiency, and complements ELLKAY's existing enterprise solutions.

Ebola

CDC supports WHO declaration of Public Health Emergency of International Concern for Ebola outbreak in eastern region of DRC. As cases of Ebola continue to increase in the eastern region of The Democratic Republic of the Congo (DRC), and travel-associated cases have been reported in neighboring Uganda, the Centers for Disease Control and Prevention (CDC) fully supports the decision by the International Health Regulations Emergency Committee of the World Health Organization (WHO) to declare the outbreak a "public health emergency of international concern" (PHEIC). A PHEIC is declared if an extraordinary event poses a public health threat to

other nations through the spread of disease and requires a more robust coordinated international response.

The declaration was made by WHO after the International Health Regulations Emergency Committee cited recent developments in the outbreak in making its recommendation, including the first confirmed case in Goma, a city of almost two million people in the DRC on the border with Rwanda and the gateway to the rest of DRC and the world. WHO cautioned against imposing trade or travel restrictions, which would have a negative impact on the response and on the lives and livelihoods of people in the region.

As part of the Administration's whole-of-government effort, CDC experts are working with the United States Agency for International Development (USAID) Disaster Assistance Response Team (DART) on the ground in the DRC and the American Embassy in Kinshasa to support the Congolese and international response. The United States government, including CDC, is working with DRC, Uganda, WHO, and other partners to support the current Ebola outbreak response by providing technical assistance and expertise in disease tracking, case investigation, contact tracing, case management, infection prevention and control, safe burials, community engagement and social mobilization, risk communication and health education, behavioral science, laboratory testing, border health, data management, vaccination campaigns, and logistics.

To rapidly identify cases and prevent further spread of Ebola, CDC is working with the U.S. Embassy in DRC to preposition CDC staff in Goma to rapidly respond to hotspots where the security situation is permissible. As of July 16, 2019, CDC staff have conducted 311 deployments to the DRC, neighboring countries, and WHO headquarters. CDC has 246 permanent staff in the three high-risk countries bordering the outbreak (South Sudan, Rwanda, and Uganda), including 43 in DRC. DRC has more than 150 graduates of CDC's Field Epidemiology and Laboratory Training Program who are playing a central role in this public health response.

The outbreak in DRC is occurring in a region where there is armed conflict, outbreaks of violence, and other problems that complicate public health response activities and increase the risk of disease spread both locally within DRC and to neighboring countries. CDC continues to provide technical assistance to the ministries of health of DRC, Uganda, and other neighboring countries, in collaboration with the USAID DART, the U.S. Embassy in Kinshasa, the Department of State, WHO, and other local and international partners, to ensure the response is robust and well-coordinated and brings the Ebola outbreak to an end.

Genetics

NIH scientists link genetics to risk of high blood pressure among blacks. Variants in the gene ARMC5 may be associated with high blood pressure among blacks, according to a National Institutes of Health (NIH) study led by researchers at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

The study team identified 17 variants in the ARMC5 gene that were associated with high blood pressure by analyzing genetic research databases that include those of African descent. The study is published in the July 3, 2019, issue of the *Journal of the American Heart Association*.

Earlier work by the NICHD group linked some variants of ARMC5 to primary aldosteronism, a hormonal disorder that causes high blood pressure among black patients. In the current study, the researchers analyzed datasets containing genetic information from large numbers of people, including NIH's Minority Health Genomics and Translational Research Bio-Repository Database and the Genomics, Environmental Factors and Social Determinants of Cardiovascular Disease in African-Americans Study, which are based in the United States, as well as the UK Biobank.

The researchers identified 17 variants of ARMC5 that were associated with blood pressure among blacks. One variant, called rs116201073, was "protective" and associated with lower blood pressure. It was more common than the others, and it appeared limited to people of African descent, as it is found only in Africans in the international 1000 Genomes Project.

The researchers also reconstructed the rs116201073 variant in cell lines and found that it was more active than other variants of the ARMC5 gene. However, the exact function of the ARMC5 gene is unclear, and more work is needed to understand what the gene does and how variants may protect or predispose a person to high blood pressure.

Antibacterial drug

New treatment for complicated urinary tract and complicated intra-abdominal infections. According to a recent press release, the U.S. Food and Drug Administration (FDA) has approved Recarbrio (imipenem, cilastatin, and relebactam), an antibacterial drug product to treat adults with complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI).

"The FDA remains focused on facilitating the development of safe and effective new antibacterial drugs to give patients more options to fight serious infections," said Ed Cox, MD, MPH, director for the Office of Antimicrobial Products in FDA's Center for Drug Evaluation and Research. "It is important that the use of Recarbrio be reserved for situations when there are limited or no alternative antibacterial drugs for treating a patient's infection." Recarbrio is a three-drug combination injection containing imipenem-cilastatin, a previously FDA-approved antibiotic, and relebactam, a new beta-lactamase inhibitor.

The determination of efficacy of Recarbrio was supported in part by the findings of the efficacy and safety of imipenem-cilastatin for the treatment of cUTI and cIAI. The contribution of relebactam to Recarbrio was assessed based on data from in vitro studies and animal models of infection. The safety of Recarbrio was studied in two trials, one each for cUTI and cIAI. The cUTI trial included 298 adult patients with 99 treated with the proposed dose of Recarbrio. The cIAI trial included 347 patients with 117 treated with the proposed dose of Recarbrio.

Recarbrio received FDA's Qualified Infectious Disease Product (QIDP) designation. The QIDP designation is given to antibacterial and antifungal drug products intended to treat serious or life-threatening infections under the Generating Antibiotic Incentives Now (GAIN) title of the FDA Safety and Innovation Act. As part of QIDP designation, Recarbrio was granted Priority Review under which the FDA's goal is to take action on an application within an expedited time frame.

A key global challenge the FDA faces as a public health agency is addressing the threat of antimicrobial-resistant infections. Among the FDA's other efforts to address antimicrobial resistance, is the focus on facilitating the development of safe and effective new treatments to give patients more options to fight serious infections.

Procalcitonin testing as an aid to antibiotic stewardship

By H. Roma Levy, MS and Monet Sayegh, MD, MS, BS, MT (ASCP) SH, CLS

Early detection and treatment of serious bacterial infections, sepsis, and septic shock—with appropriate antibiotic and supportive therapy—is critical to patient survival. Delaying antibiotic therapy increases the risk of increasing illness severity and the overall risk of mortality. Because the stakes are so high, the Surviving Sepsis Campaign (SSC) guidelines, organized by the Society of Critical Care Medicine in 2002, strongly recommend intravenous administration of empiric, broad spectrum antibiotics as soon as possible after recognition and collection of blood and site-specific cultures, with a goal of administration within one hour of either sepsis of septic shock.[1]

The challenge, however, lies in the fine act of balancing antibiotic delivery with antibiotic stewardship. Bacterial sepsis symptoms are nonspecific and can be mistaken for many other serious conditions, such as trauma, diabetic ketoacidosis, acute pancreatitis, and myocardial infarction.[2] Additionally, approximately 40 percent of patients have only vague symptoms, such as weakness or pain, and geriatric patients—who have the highest rates of sepsis—frequently have atypical symptoms that can be misconstrued as stroke, dementia, or even simple dehydration.[2,3] Finally, culture results typically may not be available for several days and have a low rate of success: Site cultures are negative in 20 to 47 percent of patients with severe sepsis and only five to 10 percent of blood cultures are positive.[4-6] Consequently, when sepsis or a serious infection such as pneumonia that carries a high risk of progressing to sepsis is suspected but not yet confirmed, antibiotics are typically started out of an abundance of caution or to meet CMS-imposed hospital quality measures.[7] Once antibiotics have been initiated, determining when to modify, de-escalate, or safely stop therapy can be equally challenging and clinicians often assume a "one size fits all" approach based on guidelines dictating standard duration by condition or pathogen.

The importance of antibiotic stewardship

While rapid response to serious infection and sepsis is paramount, antibiotic administration can cause harm to patients and society at large. Antibiotic overuse contributes to selective pressure resulting in multi-antibiotic resistant organisms. In its 2013 report on antibiotic resistance threats, the Centers for Disease Control and Prevention (CDC) noted that antibiotic-resistant infections aff lict over 2 million people and cause approximately 23,000 deaths annually. Adverse effects associated with prolonged and sometimes even short duration antibiotic therapy include severe allergic reactions, end organ and neurological toxicity, localized or systemic candidiasis, and significant disruption of the microbiota throughout the body. The microbiome can take up to a year to recover, during which time intrusion and growth of harmful organisms such as *Clostridioides difficile* (*C. diff*) can occur.[8-10] Tamma et al. found that 20 to 30 percent of antibiotic days received by hospitalized patients are unnecessary and account for 20 percent of all antibiotic adverse events, while Shehab et al. determined that such events were responsible for 19 percent of all emergency department (ED) visits.[8,11]

Procalcitonin can aid therapeutic decision-making that supports antibiotic stewardship

In 2015, CDC released guidance on the core elements of antibiotic stewardship. This guidance emphasizes the importance of developing a hospital-wide program based on a multidisciplinary team approach that includes doctors, nurses, pharmacists, administration, and laboratorians.[12] At the time of its introduction, CDC commented on the evolving role played by diagnostic tests, and noted that procalcitonin (PCT)—an early marker of sepsis and severe bacterial infection—has been successfully incorporated into stewardship programs.

PCT is a prohormone. Under normal conditions, it is produced only by the thyroid C-cells and processed to yield calcitonin and katacalcin. During severe localized or systemic infections, however, endotoxin stimulates PCT release from adherent monocytes, which induce further production by adipocytes in nearly every tissue type (especially the liver). PCT elevates within three to six hours of infection, peaks within approximately 12 to 48 hours, and has a half-life of approximately 20 to 35 hours. PCT kinetics and the impact of antibiotic efficacy

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LEARNING OBJECTIVES

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

1. Discuss campaigns that are aimed to provide guidance on effect antibiotic stewardship programs.
2. Describe the limitations in testing and diagnosis for bacterial sepsis.
3. Recall the utility of PCT testing in diagnosis and therapy in patients with sepsis.
4. Discuss conclusions of various studies of PCT testing in antibiotic stewardship programs and the importance of strict adherence to published algorithms for the best therapy outcomes.

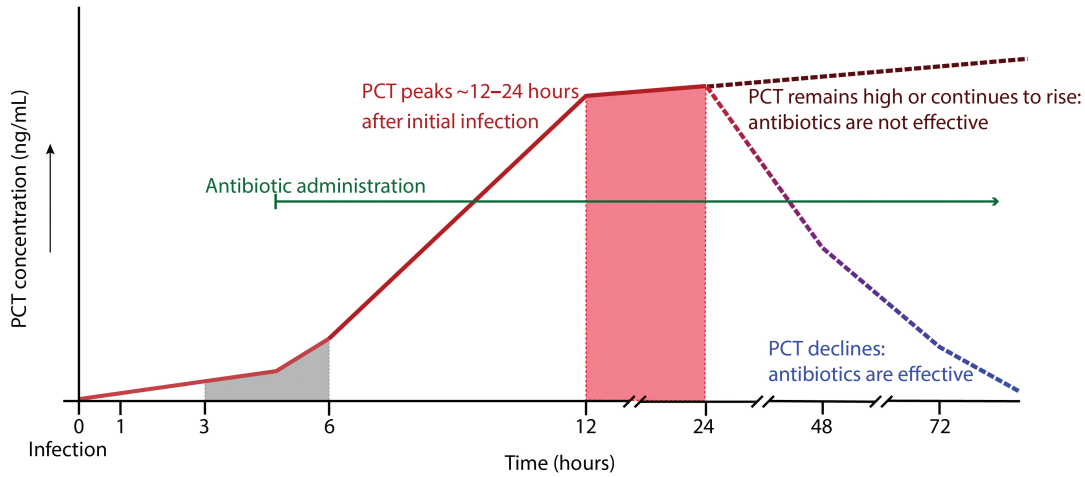

Figure 1. PCT kinetics (adapted from Meisner).[13]

PCT level at admission or suspicion of serious infection/ sepsis (ng/mL)	Antibiotic initiation or continuation recommendation
<0.10	Strongly discouraged
0.1–0.25	Discouraged
0.26–0.50	Encouraged
>0.50	Strongly encouraged

Table 1. Interpreting PCT results for initiating antibiotic therapy. Patient presentation and clinical judgement should always play a significant role in decision-making however, especially since PCT can be elevated under some conditions not associated with infection, therapy should not be administered on the basis of test results in isolation.[14]

Condition	PCT recommendation
Lower respiratory tract infections (LRTI)	PCT ≤0.25 ng/mL OR >80% decrease since the initial test result
Confirmed or suspected sepsis	PCT ≤0.50 ng/mL OR >80% decrease since the initial test result

Table 2. Suggested values for discontinuing antibiotic therapy.

are displayed in **Figure 1**.[13] Decision-making thresholds for initiating and stopping antibiotic therapy are presented in **Tables 1** and **2**.[14]

To date, the majority of studies have focused on two specific uses: Guidance on de-escalating or stopping therapy in patients diagnosed with sepsis, and guidance on starting and de-escalating or stopping antibiotic therapy for patients with lower respiratory tract infections (LRTI).

Patient and financial benefits of PCT guided-therapy for sepsis

Various studies have demonstrated that serial PCT values can safely help guide de-escalation and cessation of antibiotic therapy, resulting in an 18 to 37 percent reduction in antibiotic duration. This variability is most likely related to the cut-off used for stopping antibiotics (one study specified not stopping therapy until PCT reached 0.1 ng/mL) and the degree of clinician adherence to the algorithm (between 44 and 71 percent) **Figure 2**.[15-20] Economic modeling conducted by Mewes et al. projected that PCT guidance could reduce total per patient costs by over $11,300 when considering aggregate costs associated with hospital length of stay, days of mechanical ventilation, laboratory, antibiotics, productivity loss, and development of antibiotic resistance and *C. diff* infections. They also estimated that in the U.S. alone, PCT guidance would result in

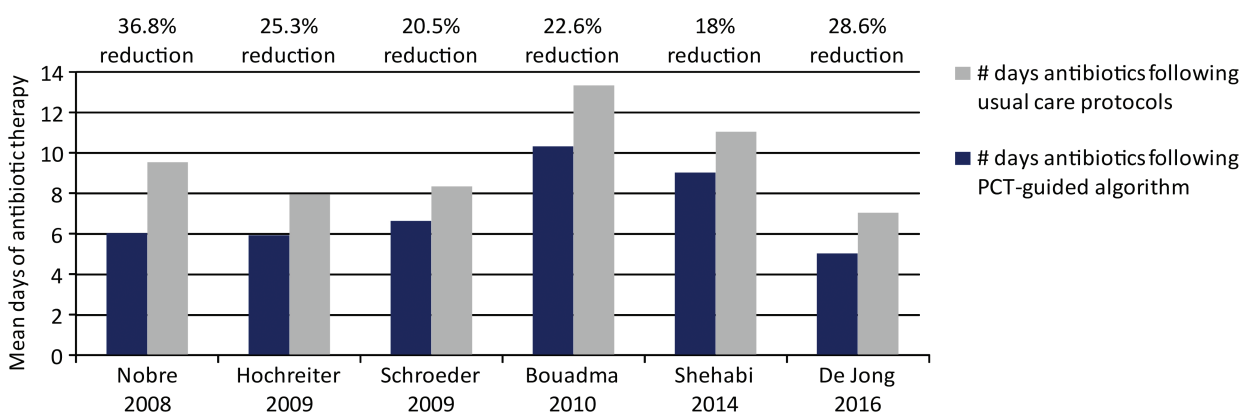

Figure 2. Reduction in days of antibiotic therapy in patients with sepsis using PCT guidance.[15-20]

development of 13,222 fewer cases of antibiotic resistance and 16,103 fewer *C. diff* infections.[21]

PCT guided-therapy in LRTI

As with sepsis, Mewes et al. projected that using PCT guidance in the treatment of LRTI could result in a cost savings of $2,867/patient, development of antibiotic resistance in 64,466 fewer patients, and 31,487 fewer cases of *C. diff*.[21] Several studies have demonstrated safe reduction of mean antibiotic duration for patients with LRTI through a combination of withholding inappropriate antibiotic therapy and reduced therapy days. The ProHOSP (Procalcitonin-guided antibiotic therapy and hospitalization in patients with lower respiratory tract infections) study conducted in six academic and nonacademic Swiss hospitals was one of the earliest and most rigorous trials. The study evaluated the impact of applying the **Table 1** decision cut points and therapy recommendations to the care of 1,361 adults (≥18 years) who presented to EDs with community acquired pneumonia (CAP), bronchitis, acute exacerbation of COPD (aeCOPD), or other suspected LRTI.[22] PCT was tested at presentation and electronically reported within approximately one hour to physicians, along with treatment recommendation. If antibiotics were withheld based on the PCT result, PCT was retested within six to 24 hours. If hospitalization was required, PCT was retested on days three, five, and seven to determine the need for modifying, de-escalating, or stopping antibiotic therapy. Using this algorithm, mean antibiotic exposure decreased from 10.7 days to 7.2 days per patient, representing a 32 to 65 percent reduction, depending on the patient's final diagnosis. Similarly, the rate of total antibiotics prescribed decreased by eight to 27 percent, and the antibiotic adverse event rate decreased from 33 to 23 percent. Most of the reductions in exposure resulted from avoiding inappropriate antibiotic administration for bronchitis and nonbacterial aeCOPD with no increase in adverse outcomes within 30 days (death, ICU admission, complications, or reinfection).

Several other studies conducted using guidance algorithms and protocols that were the same or similar to the ProHOSP study have reported variable results, ranging from 0 to 47 percent reduction in overall antibiotic days of treatment.[22-28] Chief among the negative studies was the recently reported ProACT (Procalcitonin Antibiotic Consensus Trial), which reported no reduction in antibiotic usage.[26,29] A 2015 study by Branche et al. also found no difference in overall antibiotic exposure using PCT guidance, although a trend was noted toward fewer days of prescribed antibiotics, and significantly fewer patients were still receiving antibiotics at discharge.[24]

This has engendered some controversy, however close comparison of several of these studies provides some insight into design and execution differences between trials in which antibiotic usage was successfully reduced and in those where no benefit was found. These observations could help hospitals develop and implement their own successful PCT practices.

1. Algorithm compliance among clinicians was greatest in the studies demonstrating significant reductions in antibiotic days of therapy. Adherence to the ProHOSP study protocol was 90 percent. An evaluation of pre- versus post-PCT implementation on existing stewardship practices at a small rural U.S. hospital with 92 percent adherence to protocol demonstrated a 47 percent reduction in total days of therapy (DOT).[25] Adherence in studies reporting up to 25 percent reduction in antibiotic DOT was 70 to 81 percent, with the exception of one study where adherence was only 59 percent.[23,27,28] In comparison, although adherence was ~74 percent in the ED in the ProACT study, overall adherence over the course of the hospital stay was less than 64 percent in both the ProACT and Branche, et al. studies.[24,26] In addition, whereas most protocols specified explicit algorithm overrule criteria, the ProACT study physicians were allowed complete autonomy over antibiotic usage and chose not to

	ProHOSP[22]	ProREAL[23]	Kristoffersen[27]	Townsend[28]	Broyles[25]	Branche[24]	ProACT[26]
CAP	68a	53.7	46b	74c	54.9	19	20.3d
aeCOPD	17	17.1	27	21	18.8	39	32.2
Bronchitis	11	13.3	3	6	—	—	25
Asthma	—	—	2		—	21	37.3
Viral/Flu	—	1.2	2	—	—	11	—
Non-LRTI	4	13.7	21	—	26.3	6	2.4

Table 3. Patient diagnosis in PCT cohort by percentage of study/population.

a. 71.5% with high pneumonia severity index (PSI) ≥3
b. 37% PSI ≥4 in PCT cohort vs. 29% in control group
c. 70% PSI ≥3
d. 59.8% low severity (PSI <3)

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enroll patients who had conditions for which clinicians are unlikely to withhold antibiotics for any reason. In their analysis, Albrich et al. determined hospitals with higher adherence saw the greatest reductions in directly observed therapy (DOT).[23]

2. Reduction in antibiotic use can be affected by the study population and whether or not results are actionable. The majority of patients enrolled in studies supporting PCT-guided antibiotic reductions were diagnosed with community-acquired pneumonia (CAP) and were generally sicker overall than in either the Branche or ProACT studies (**Table 3**). This has lead Townsend et al. and others to suggest that one of the reasons no difference was observed between cohorts was because these studies were heavily weighted toward low acuity patients who are less likely to be prescribed antibiotics or are typically prescribed antibiotics for shorter duration.[28] Furthermore, as pointed out by UC San Diego's Dr. G. Seymann in a recent industry-sponsored webinar, PCT results are most useful when the results are actionable. Measuring PCT might not be useful in every situation. For example, if symptoms clearly indicate CAP, a single PCT value may not provide additional benefit at the time of diagnosis. However, serial measurements can help the clinician determine if antibiotics are effective before culture results are available and when it is safe to stop treatment. Likewise, if bacterial etiology is uncertain, PCT can help determine if antibiotics are called for, but if LRTI is clearly viral (e.g., positive influenza PCR), PCT might not provide additional useful information.

3. Antibiotic decision-making is best supported by timely and efficient availability of results. Results were available within one hour in the ProHOSP and Broyle's studies. In ProHosp, results were provided directly to care providers via the study website along with treatment recommendations. In the Broyle's study, the PCT order was made via prechecked field on the admission order set if infection was suspected: Results were built into the laboratory report electronically and could be accessed by mousing over the test. In contrast, mean turnaround time (TAT) was 1.5 to 1.6 days in studies reporting only 20 to 25 percent reduction. The authors of these studies commented that DOT reductions likely would have been greater had TAT been much shorter. Both of these studies conducted PCT testing in batch once a day during the week, and one study did not provide PCT testing on weekends. This highlights the benefit of running PCT on analyzers capable of handling random access and stat orders. While some facilities have found one manufacturer's point-of-care PCT test useful for achieving rapid results, it should be emphasized that this test is not sensitive enough to be used for stopping antibiotics when conducting serial testing. Only tests based on the B.R.A.H.M.S. PCT assay currently offer this level of sensitivity.

4. Staff training and continuing education at all levels can contribute to successful program implementation. Studies describing reduced DOT incorporated several elements of formal, in-person training on the rationale behind PCT guidance and how to use the algorithm effectively. Training was provided in the form of seminars and in-service education to all staff across multiple departments who would be in a position to prescribe antibiotics, including residents, nurse practitioners, and physician's assistants. Training was also provided to the lab and pharmacy personnel in some cases. In one study, both online and in-person training was made available. Training and support was ongoing in some cases, and additional supporting materials were made available in the form of posters, pocket cards, handouts on trial and algorithm details, and embedded in laboratory results. Studies with the highest participation in training noted the highest adherence to protocol and the greatest reduction in DOT.

5. Having a dedicated coordinator or PCT champion contributes to program success. The Broyles study illustrates the value of having one department oversee and champion PCT guidance, which in this case was the pharmacy. This decision makes credible sense as the pharmacists and staff were already responsible for oversight of their antibiotic stewardship program. Consequently, pharmacists created opportunities to mentor staff, conduct continuing education, and even override physician decisions to not order PCT testing or contravene algorithm guidance when infection or sepsis was suspected. As a result, this institution realized a 47 percent decrease in antibiotic DOT above and beyond reductions already achieved through their existing stewardship program. Other sites have successfully cultivated infectious disease specialists, nurses, and multidisciplinary teams made up of clinicians, pathologists, and laboratorians to fill these roles.

PCT limitations

Although PCT is highly specific for bacterial infection, there are some situations in which PCT can give a false-positive result if not used with discretion. PCT clearance appears to be affected by renal disease and can be elevated in late-stage chronic kidney disease patients regardless of dialysis requirement in the absence of infection.[30] PCT can also elevate in the case of severe inflammation, as might occur with significant surgery, polytrauma, severe pancreatitis or liver damage, severe burns, medullary thyroid cancer, small cell lung carcinoma, prolonged cardiogenic shock, and in response to some cytokine-stimulating medications.[13,31] PCT can also elevate with some fungal and malarial infections, however, Miglietta et al. note that PCT can distinguish between bacterial sepsis and systemic candidiasis.[31]

Conclusion

PCT can be a useful addition to the clinician's armamentarium. When used according to practices exemplified by several studies, PCT can support antibiotic decision-making essential for reducing unnecessary antimicrobial therapy contributing to the development of antibiotic-resistant organisms and short- and long-term adverse events.

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https://www.youtube.com/watch?time_continue=6&v=6gNh-w_ktTc

The Role of Procalcitonin in Bacterial Infection and Patient Management: A Pharmacy Perspective.
https://www.youtube.com/watch?v=gjAYeJIv4A0

Procalcitonin: Once is Not Enough. The Critical Role of Serial Testing.
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The Importance of Procalcitonin for Antimicrobial Stewardship in Patients with Lower Respiratory Tract Infections in the Emergency Department.
https://www.labroots.com/ms/webinar/importance-procalcitonin-antimicrobial-stewardship-patients-lower-respiratory-tract-infections-emerg

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TEST QUESTIONS

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1. **Which campaign has strong recommendations in the management of patients with bacterial infections and/or sepsis?**
   - a. Sepsis Action Coalition Campaign
   - b. Antibiotic Stewardship Governmental Campaign
   - c. Antibiotic Management Campaign
   - d. Surviving Sepsis Campaign

2. **A goal of the campaign recommends for antibiotic administration to begin within _____ of either sepsis or septic shock.**
   - a. 10 minutes
   - b. 45 minutes
   - c. one hour
   - d. two hours

3. **Bacterial symptoms are easy to identify by physicians and typically present with a unique set of symptoms that do not mimic other conditions.**
   - a. True
   - b. False

4. **Cultures of patients with sepsis have shown a**
   - a. low rate of diagnostic success.
   - b. high rate of diagnostic success.
   - c. moderate rate of diagnostic success.
   - d. none of the above

5. **The following adverse effects have resulted in many patients receiving antibiotic administration:**
   - a. Heart disease, allergic reactions, immune deficiency.
   - b. Allergic reactions, autoimmune disease, candidiasis, organ toxicity.
   - c. Allergic reactions, organ/neurological toxicity, candidiasis, significant disruption of the microbiota.
   - d. none of the above

6. **After antibiotic administration, it can take up to _____ for the microbiome to recover and the patient has an increased risk of developing _____.**
   - a. six months; *C. diff*
   - b. five years; *E. coli*
   - c. one year; *C. diff*
   - d. one year; *E. coli*

7. **The introduction of procalcitonin (PCT) as an early marker of sepsis was originally recommended by**
   - a. JCAHO.
   - b. CDC.
   - c. WHO.
   - d. American Red Cross.

8. **During infection PCT is released into the blood stream by**
   - a. monocytes.
   - b. thyroid C-cells.
   - c. lymphocytes.
   - d. neutrophils.

9. **What time interval does PCT start to rise after the onset of a bacterial infection?**
   - a. one to two hours
   - b. three to six hours
   - c. four to eight hours
   - d. 10 to 12 hours

10. **With effective antibiotic treatment, the PCT should decline about**
    - a. five percent.
    - b. 15 percent.
    - c. 25 percent.
    - d. 50 percent.

11. **Most of the studies that have been conducted have focused on guidance therapy in patients with sepsis and in patients with lower respiratory tract infections.**
    - a. True
    - b. False

12. **Which long-term study concluded that the use of a standard algorithm resulted in significant reductions of antibiotic exposure, the rate of adverse events, and no increase in adverse outcomes within 30 days?**
    - a. ProANTI
    - b. ProACT
    - c. ProHOSP
    - d. none of the above

13. **Which recent study using the same protocols and algorithms as other studies concluded no reduction in antibiotic usage?**
    - a. ProANTI
    - b. ProACT
    - c. ProHOSP
    - d. none of the above

14. **The following observations have been noted in why differing study conclusions have been made except**
    - a. hospitals with the most timely and efficient availability of PCT results lead to the best antibiotic decision making.
    - b. studies with the highest participation in training noted the greatest reduction in days of therapy.
    - c. studies with the state-of-the-art PCT and PCR testing analyzers yielded the most accurate results.
    - d. hospitals with higher adherence to algorithms saw the greatest reductions in days of therapy.

15. **In some instances the pharmacy has been noted to override physician decisions to not order PCT testing and to contravene on algorithm guidance in order to keep antibiotic therapy to standard practices.**
    - a. True
    - b. False

16. **What types of medications affect PCT levels?**
    - a. Cytokine-stimulating medications
    - b. Statin drugs
    - c. Hormone regulating medications
    - d. none of the above

17. **What types of infections can elevate PCT levels?**
    - a. Malarial and viral
    - b. Viral and fungal
    - c. Malarial and viral
    - d. Fungal and malarial

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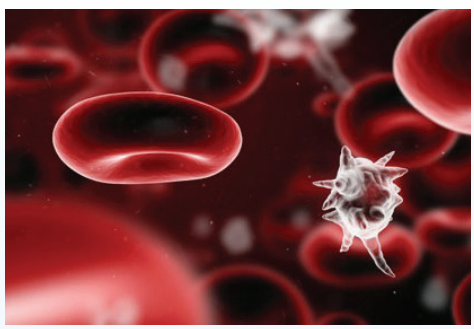

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How testing and teamwork are helping diagnose sepsis faster

By Rachel Burnside, PhD, MBA

The challenges arising from the sepsis crisis remain a primary concern throughout the global healthcare community. The economic and human tolls amassed by this frequently deadly, often-enigmatic condition are high and affect everyone—patients and their loved ones, clinicians, laboratorians, medical administrators, and organizational leaders. The multifaceted and complex nature of sepsis requires a wide-reaching, multi-level, comprehensive solution. It also requires collaboration. And, while no single tool can alone solve the problems presented by sepsis, there is a singular focus emerging among those seeking a solution: To identify sepsis as quickly and accurately as possible to enable timely intervention for more positive patient outcomes.

Understanding the global impact of sepsis

Sepsis, a dysregulated response by the body to an infection, is a life-threatening medical emergency.[1] It is a condition that, as stated by Machiavelli, "at its inception is difficult to recognize but easy to treat; left unattended it becomes easy to recognize and difficult to treat."

Currently, sepsis affects 30 million people worldwide[2] and claims 258,000 U.S. lives, annually.[3] Each year, an estimated 1.6 million people are diagnosed with sepsis in the U.S. and it is the leading cause of hospitalizations. To that end, sepsis places an overwhelming strain on U.S. hospital resources, costing more than $24 billion annually,[4] a figure that is rising 19 percent per year.[5]

Because two-thirds of patients with sepsis enter the healthcare system through the emergency department (ED),[6] it is critical that those making first contact with the patient—clinicians and nurses—are equipped with tools to identify sepsis earlier so that treatment can be more effective, and thus economic burden reduced.

Driving action at the first interaction

Although new innovations and initiatives addressing sepsis are introduced into the healthcare landscape on an ongoing basis, the most critical efforts center around early diagnosis and treatment. Early identification of sepsis leads to faster treatments, including antibiotic administration, which has been proven to reduce the likelihood of death by 7.6 percent for every hour saved.[7]

Testing—a novel biomarker for early sepsis detection

There has never been a single diagnostic test for sepsis.[8] Traditional testing, such as white blood cell count (WBC), blood cultures, and biomarkers are often nonspecific and have limitations. For example, blood cultures require up to three days to obtain results and are positive in only 20 to 30 percent of sepsis patients.[8] Recent evidence of a novel hematology-based biomarker, however, has shown promise in helping ED clinicians detect sepsis sooner, when used with the current standard of care. The biomarker measures morphological changes in monocytes—cells of the innate immune system that serve as first responders in the fight against infection. In a single-center feasibility study, Crouser et al. demonstrated that measuring the monocyte distribution width (MDW)—the increase in distribution of sizes of these cells—improved detection of sepsis over neutrophil morphological measurements and over WBC count alone.[9] Moreover, using both MDW and WBC count was more effective than using either parameter individually.

In a subsequent multicenter study, Crouser et al. again examined the diagnostic accuracy of MDW alone, and in combination with WBC count, in identifying sepsis in the ED.[10] With an established cutoff of >20.0, MDW distinguished sepsis from all other conditions based on either Sepsis-2 or Sepsis-3 criteria. The negative predictive values for MDW ≤20 were 93 percent for Sepsis-2 and 94 percent for Sepsis-3. Combining MDW with WBC count was predicted to inform clinical decision making for clinicians managing septic or potentially septic patients in the ED.

To determine the predicted economic impact of MDW clinical utilization on hospital resources, Paoli et al. conducted a counterfactual analysis.[11] Sixty-seven percent of 349 sepsis patients were predicted to benefit from the MDW results, potentially decreasing the time to antibiotic administration from an average of 3.98 hours based on the standard of care alone, to 2.07 hours when MDW

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was added, assuming a 30-minute turnaround time for the CBC. Potentially, this could reduce mortality by 14.2 percent, hospital length of stay by a mean of 1.48 days, and cost per hospitalization by $3,460. Considering a national mean of 206 sepsis hospitalizations each year per hospital, the modeled predicted annual savings for each hospital totaled $712,783. Note that additional study is required to validate this model.

Confirmatory testing—leveraging sepsis biomarkers

While nonspecific for sepsis, several currently used biomarkers play a supportive but significant role in sepsis care.

Procalcitonin (PCT) is a prohormone that is normally produced in the thyroid, but with bacterial infections is produced by monocyte-lineage cells in the liver. In healthy individuals, PCT levels in the blood are below 0.5 ng/mL. In response to infection, PCT levels rise quickly, becoming elevated between two and six hours after exposure and peaking within six to 24 hours.[12] However, PCT may also be elevated for other reasons, such as after surgery, or from autoimmune conditions. And, while PCT is primarily used to examine a patient's response to antibiotics, some hospitals in the U.S. may use it to differentiate between bacterial and non-bacterial sepsis.

Lactate is used as an indication of sepsis progression and severity. Lactate values >2 mmol/L (>18 mg/dL) are included in the Sepsis-3 definition for septic shock.[13] Monitoring lactate levels is recommended as part of the Surviving Sepsis Campaign 1- and 3-hour bundles, as persistence of elevated lactate has been associated with increased mortality.[14]

Two additional biomarkers, **Interleukin-6** (IL-6) and **C-reactive protein** (CRP), are related to inflammation, and, thus, are also widely used to confirm infection in patients presenting to the ED, although they are less commonly used in the U.S. than in other countries.

Teamwork—a multi-level, collaborative approach

It is clear that lab testing is critical in both diagnosing and managing sepsis. Clinical insight offered by laboratory testing can now be augmented using new evidence-based resources for ED clinicians, highlighting the importance of collaboration between clinicians and laboratorians in the acute-care setting.

Managing sepsis requires an expanded approach beyond the ED. Multidisciplinary sepsis committees are leading the charge at the hospital level, developing processes and introducing new technologies to help elevate sepsis care within their organizations.

Additionally, in the U.S., the Sepsis Alliance is "working in all 50 states to save lives and reduce suffering from sepsis."[15] Sepsis protocols are often state led but sharing information across state lines could prove beneficial.

On a global level, much has been done to drive commonality in language and protocols and to advance conversations surrounding sepsis care. The general nature of the language surrounding sepsis is often vague and can be challenging for hospitals. Initiatives put forth by the Global Sepsis Alliance—World Sepsis Day held on September 13th and the World Sepsis Congress—have drawn attention to the sepsis crises for clinicians and patients. World Sepsis Day has created awareness in the general population of the dangers of sepsis, and the World Sepsis Congress has created opportunities for the exchange of information among industry thought leaders to advance awareness.[16]

In conclusion

Through both technological advancements in testing and continued collaboration among people on all sides of the sepsis crisis, great strides have been made in understanding and managing sepsis in recent years. As this work continues, there is hope that one day we will all realize what the Sepsis Alliance envisions: "A world in which no one is harmed by sepsis."[18]

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Best practices in onboarding open channel reagents and suppliers

By Ronald Jamison

Although manufacturers of branded clinical chemistry analyzers provide robust test menus, they cannot meet every clinical laboratorian's needs and budget. Open channel reagent suppliers fill the gaps in test menus, providing labs with an alternative means of securing controls and reagents that aren't available from their instrument provider.

This enables laboratories to bring new diagnostic tests in-house to improve patient care—by reducing the time to test results, thus yielding faster diagnoses and treatment plan decisions. It can also generate additional revenue streams.

As such, open channel providers offer labs an important service. It's imperative to carefully evaluate these suppliers for the quality of their assays, as well as the services and support they provide to ensure successful use on another manufacturer's equipment.

This article explores the reasons for choosing an open channel assay, obstacles, and considerations when making a switch, and what to look for in a supplier of alternative reagents.

Why switch?

The most obvious circumstance for introducing an open channel reagent is because the instrument manufacturer doesn't offer an assay that's needed. This can be true for many specialty assays, but general chemistry assays as well.

Another reason to switch is performance. Sometimes the manufacturer's branded assay simply doesn't deliver the expected performance, and trying another reagent yields better results.

Finally, cost can lead labs to explore alternative reagents. It may be more economical to source an open channel assay after a lab has reached its purchase volume agreement with its instrument provider. There are some high-revenue assays that can be relatively expensive and using open channel capabilities may help cut costs after contractual obligations with the instrument vendor are met. Also, generics, as in pharmaceuticals, are typically more economically advantageous for the customer, and are available as open channel.

Obstacles to open channel

The makers of chemistry analyzers, reasonably, make their money from the sales of consumables used on the instrument. For that reason, they contract by test volume to ensure a steady, consistent use of their reagents with their instruments. They can also lock open channel reagents out of the instrument, forcing users to request—and sometimes pay for—permission to use alternative assays, or to purchase packaging components such as user-defined wedges that are compatible with their specific analyzer. This allows the open channel reagent to be poured into a component that is suitable for the analyzer.

While instrument manufacturers have safeguards in place that alert them to attempts to use open channel reagents, many have worked collaboratively with open channel reagent providers as a way to ensure customer satisfaction. Often, manufacturers without a specific assay will work with a third-party provider to get their customer the assays they need.

Considerations

As organizations consider open channel reagents, there are many things to evaluate. Among the first considerations is whether the chemistry analyzer has locked parameters or requires a special packaging component to add a third-party assay. If the instrument is provided with fully open channel capabilities, some manufacturers do not require labs to contact them for open channel use. For others, you may have to pay for this privilege or purchase the component.

You should also inquire if the open channel reagent requires an independent calibrator or control that must be purchased, or can you continue to use your current control for the assay being brought in?

For these additional expenses, what is the return on investment (ROI) of bringing the assay in-house? Does the testing volume warrant doing so? Is it being ordered consistently and frequently enough? For example, in a hospital offering chemotherapy treatment, the glucose-6 phosphate dehydrogenase (G6PD) prescreening testing method aids in determining the risk of possible adverse side effects (such as a hemolytic crises) of chemotherapy drugs on patients with a deficiency in G6PD. If there are enough chemotherapy patients, bringing the G6PD assay in-house may be beneficial for better, faster patient care decisions and for the

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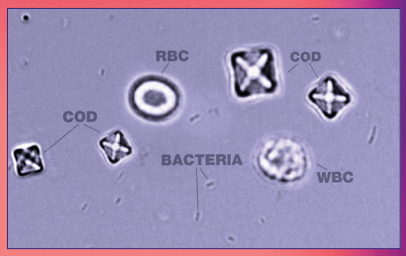

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hospital's bottom line. Assessing the testing volume can help them decide if it's in the hospital's best interests to run the assay in-house.

Selecting an open channel supplier

Once clinical lab directors have decided that an open channel assay makes sense, finding the right supplier of that assay is key to overall success. There are several attributes to look for when selecting a supplier.

First and foremost, the supplier must offer the assay that's needed. Among those with that assay, look for suppliers with a history in the industry of offering user-defined reagents, as well as one with a growing portfolio of assays to ensure you have increased choice as the relationship grows.

A record of quality and lot consistency is critical, as is a supplier who provides data analytics services. Compliance with current good manufacturing practices (cGMP) and International Organization for Standardization (ISO) certifications are also essential, as are reagents that carry the CE mark for sale into 31 European countries.

Regardless of your lab's size, it can be important to work with a supplier that is capable of supporting small- to medium-sized hospitals and laboratories all the way up to and including ultra-high-volume commercial labs and core hospital test environments. Such scale ensures the supplier has support and processes in place for installation and validation, whether open on-board channeling and/or full line reagent conversions.

Finally, look for flexibility in their supplier program. Some suppliers will provide free samples or reagents for validation, while others will want upfront payment but offer discounts on subsequent purchases. In general, you want a supplier who will make a commitment to meet your needs, as you make a commitment to them.

Conclusion

Open channel reagents offer clinical laboratories an alternative choice for meeting complete diagnostic testing needs. Customers appreciate the ability to incorporate open channel reagents into their testing streams; it's an absolute necessity when the maker of their chemistry analyzer doesn't offer the assay, and it's a difference-maker when performance and cost affect the lab's overall productivity and commitment to patients.

Ronald Jamison serves as Vice President, Director of Technical Operations, **MedTest Dx**. He has over 30 years of experience as a Medical Technologist and Executive in the laboratory and IVD manufacturing industry. Jamison currently oversees technical operations to support technical design, development, direction, service, support, production, and performance quality of the company's Pointe Scientific-branded reagents, controls, calibrators, and standards.

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Utilization of lab supplies

By Lisa Moynihan and Janette Wider

The *MLO* editors enthusiastically visited Sarasota Memorial Hospital (SMH) for the second time this year to highlight our local clinical laboratory's utilization of supplies. We knew prior to our arrival that the SMH lab did not utilize an electronic inventory system. Seeing as they had just implemented a very sophisticated automation system (see our article entitled, *SMH lab techs talk automation* in *MLO's* March 2019 issue), the fact that they were manually controlling their inventory piqued our interest even more. Questions like, how do they manage? (just fine, as you will read below); why not electronic? (not possible without a capital request); and who was responsible? The latter question was quickly answered as we were greeted with a platter full of chocolate chip cookies and a conference room filled with seven key staff members—many of who are very seasoned, and all of who are responsible for the lab's inventory.

Now let's get down to business.

One of SMH's clinical laboratory supply rooms

Who is responsible for ordering lab supplies?

Each one of the seven employees we interviewed indicated they were responsible for ordering lab supplies for their department through their hospital-wide software program. SMH is large, measuring 21,500 square feet in their central laboratory. (This does not include Histology whose services are performed by their Pathology Group as an external contract service.) They employ 130 FTE's, which equates to about 150 individuals (as not all staff are full time).

How do you ensure the ordered supplies are being utilized correctly?

It appeared communication was the most effective way to find out if supplies are being utilized correctly.

A bold employee responded, "I ask! I don't give out supplies unless the blood is coming back to us. A lot of (local) doctor's offices use us at their primary lab. I don't want to provide tubes that are going to Quest or LabCorp, so I tell them that upfront. Everyone is receptive of this and it goes well, for the most part."

What's an example of supply misuse that you've encountered?

A senior MT quickly chimed, "Wasting something! Let's just say … that the wash solution in the urinalysis department is getting low. The analyzers will tell you when it is getting low and when to change it. But there's some folks in the world who don't want to wait for that, and they'll change it early. The problem is that the analyzer knows when it needs to be changed, it's all gauged on sensors. If you're changing it too often, there's where your waste comes in and it can make my numbers fluctuate. However, when I took over the role of inventory for supplies in the urinalysis department, it was clear that we should let the analyzer tell us when to change it and now new employees have this incorporated into their training process. I have very little waste."

Expired product was also an example of wasted supplies. To avoid this, another MT stated, "Supplies are dated when they come in. The new ones go to the back, so you have no choice but to use what's going to expire first."

In regard to expiration we were told controls and very unique tests tended to be the supplies that expired before use. However, we were assured expired products were always disposed of properly. The same dynamic exists with their blood tubes. Once the tubes leave the facility, a dedicated person tracks the expiration dates, so the lab isn't receiving expired tubes to do testing on.

What's the biggest challenge/hardest part of your job regarding inventory control?

One MT said, "Probably communication—that people are really letting you know when things are getting low. I really try to stay on top of it, so I don't have a problem with that, but I see it happen in other areas."

"I don't seem to have any problems! I click the (computer) mouse; it takes me two seconds," said another MT. A simple task, she confessed, for when she can't get off the bench.

Another MT said, "My biggest thing is probably when I give a doctor's office a tray of tubes and they let them expire. I get a little upset about that. There's nothing we can do so I adjust by not giving them a full tray the next time and letting them know."

"Same problem with some nursing floors; somebody will stock their cart and the other half (of the supplies) will be found six months later in a cabinet," summed up another.

Needless to say, lack of communication between your peers can be a challenge—regardless of what industry you're in!

How do you improve communication?

Similar to many other industries, our group of interviewees agreed meetings were not the best way to communicate. Instead, face-to-face conversations and/or emails were the preferred choice for improving communication.

"Rounding with nurse educators, MSTs, and PCTs—the people that collect the specimens—let them know to keep an eye on them and ensure they get used in a timely manner, said one MT.

As per another, "When we get the new batches of reagents, we have different lot numbers which require calibration. We communicate by email and for the new supplies that are not calibrated yet, we put a big note with red stickers on the lab supplies that signifies they haven't been calibrated and are part of a new lot."

Retrieving the wrong product is an obvious concern.

Another MT responded, "When you're in a hurry, like in a STAT situation, and you run out of something, people grab things unknowingly. Analyzers know something doesn't belong because it's been bar coded. However, urine strips don't work like that."

Another stated, "I'm always adjusting to ensure that things are foolproof."

"I can't remember the last time we ran out of something," said another.

What happens when you do run out of things?

Having a good relationship both internally and externally is important, which was confirmed by Dana Rickard, SMH's Laboratory Operations Manager. "We can borrow from other facilities. Or have it shipped overnight; however, that can affect budget. We have a good rapport with local hospitals to borrow."

How much pressure do you feel from corporate to keep the budget down?

As per Dana, "We're busy, so we're not getting a lot of pushback. Obviously if we have patients, we need supplies. When we're buying stuff, we aren't buying it for it to sit around, we're buying it because we need it for patient care. If we're getting new supplies, we're always looking at vendors who can give it to us at the best price."

Who is responsible for looking at different suppliers and/or vendors?

According to Dana, "We have several different ways. We have contracts with outside companies through a buying group. We also look at all the major vendors and evaluate based on what our needs are. We make sure we're getting what is best for our patients, not the cheapest. This is a major component of my job and our laboratorians who work on the floor's job. Group buy-in is important!"

Dana raised her arm for all to see, "I'm actually evaluating a unique arm band right now for patients that receive blood, since our contract is up with our (current) vendor. Seeing how long they last on your arm, whether they are waterproof, evaluating them, etc." She reiterated that just because the group likes a product doesn't guarantee they'll purchase it. In the end they select what's best for the patient.

One of SMH's walk-in refrigerators

Can you tell us about your inventory/storage?

We learned SMH lab has a huge off-site supply warehouse (think Walmart) where stock supplies (both refrigerated and non-) can be ordered and received the next day. The warehouse supplies SMH, Lee Memorial Hospital in Fort Myers and a few other hospitals that are part of the conglomerate.

We also learned the lab's purchasing group has a supply room downstairs that has a bar coding system so inventory can be tracked. However, based on the fact that the lab orders the majority of their own supplies and regularly receives standing orders, it's mostly used when they need to supplement.

Keeping their pulse on their coworkers' vacation and holiday schedules was also a tactic used for monitoring

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FDA Clearance of Aptima® Vaginitis Molecular Assays Ushers in a New Era of Comprehensive and Objective Diagnostic Testing for Vaginitis

The FDA granted clearance for two new molecular assays from Hologic's Aptima BV and Aptima CT/TV assay, which provide an accurate and objective method for diagnosing vaginitis, a very common and complex health issue affecting millions of women each year.

About 90% of vaginitis is caused by bacterial vaginosis (BV), vulvovaginal candidiasis (*Candida vaginitis*, CV, also commonly known as yeast infections), or *Trichomonas vaginalis* (TV) infections, either individually or in combination.[1,2] In fact, BV is the most common vaginal infection in the United States, affecting an estimated 21 million women between the ages of 14 to 49.[3] Diagnosis can be especially complicated due to the prevalence of co-infections, as approximately 20% to 30% of women with BV are co-infected with *Candida* species.[1] Mixed infections may require different treatment pathways and the Aptima assays provide comprehensive and clear answers for addressing these infections.

Traditional methods for diagnosing vaginitis (including microscopy, pH determination and Nugent scoring) are highly subjective, often leading to misdiagnosis and ineffective treatment.[1,2] When diagnosed using traditional methods and treated based on those subjective results, more than 50% of women with vaginitis experience recurring symptoms.[1]

"Vaginitis is one of the most common reasons women visit a healthcare provider and Hologic's new molecular assays have the potential to transform how these infections are diagnosed in that very first appointment," said Dr. Edward Evantash, an OB-GYN who serves as Medical Director and Vice President of Medical Affairs at Hologic. "The improved sensitivity and specificity of Hologic's molecular assays over traditional methods in determining the underlying cause of vaginitis not only means identifying the right infection, but enabling the right treatment and, in turn, reducing the potential for recurrent or persistent infections."

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For more information on Aptima assays and the Panther system, visit www.hologic.com.

Aptima® BV Assay

Aptima® CV/TV Assay

References: 1. Aptima BV assay [package insert] AW-18811 Rev. 001. San Diego, CA; Hologic, Inc.; 2019. **2.** Aptima CV/TV assay [package insert] AW-18812 Rev. 001. San Diego, CA; Hologic, Inc.; 2019. **3.** Koumans EH, et al. The prevalence of bacterial vaginosis in the United States, 2001-2004; associations with symptoms, sexual behaviors, and reproductive health. Sex Transm Dis. 2007;34(11):864-9.

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Supply chain deliveries taking place in the SMH lab

supplies. Also, to be watched? Mother Nature! Ordering ahead of time eliminates last minute stress due to weather emergencies.

Speaking of weather, tell us about emergency prep; specifically, Hurricane Irma.

Dana stated, "We ordered supplies when we knew the hurricane was coming but all the major carriers wouldn't bring their trucks into Florida. We had supplies that we couldn't get to because they were stuck in FedEx warehouses in Tampa and Orlando; they weren't coming down into the state any farther."

Hurricane Irma triggered the largest mass evacuation in U.S. history. More than 7 million people in Florida, Georgia, and South Carolina were issued a mix of mandatory and voluntary evacuation orders as the Category 5 storm barreled toward Florida. Sarasota County, including SMH, was affected.

"We managed through! We were worried about the reagents; like, would they stay refrigerated? It was stressful because we didn't know how much damage there would be," shared another.

How much time is spent reconciling usage?

"All the time! We are always looking at it. We are growing right now so we're constantly reevaluating our inventory; if we see a downtick in things it shifts our orders; our standing order will be reduced a little bit; and we've had to do that with the coagulation supplies over the years. Things change; we quit doing this test as much as that test, etc.," said Dana.

"Based on the numbers this year, we will likely all bump up our standing orders," assured another.

Why is controlling inventory important to the laboratory's success?

An enthusiastic response came almost immediately: "It's good patient care! We have to! We have a big outreach department. I have to have urinalysis supplies. It's the number one ordered test in the lab," said the urinalysis MT. Another chimed in, "No reagents, no tests!"

Besides communication, what other suggestions/tips do you have for your peers/ MLO readers?

As per Dana, "We have a system! It's been ingrained in all of us. If you're at home and down to the last bit of milk, you're going to make sure you're going to get more. Don't wait until you are down to the last kit! And rotation! Stay on top of things!"

Linda said, "It took me a while to set it up in the computer and sit and work with the numbers and go by the percentages annually but once I did, I actually really do enjoy it. I look at it regularly to make sure we're not out of things. It's challenging for me but also an enjoyment! And if I go on vacation, I rely on my colleague; we try to do the same for each other."

Felix commented, "I'm very happy to share the responsibility; but it's part of the job description for EVERYBODY!"

The entire group concurred.

We know you don't have an electronic inventory system—but is there one in the pipeline?

Dana replied, "We looked at one; we wanted to piggyback off of the one downstairs in the supply chain; but we had to have wands and things we weren't ready for yet … it wasn't going to be cost effective at the time. We haven't revisited it yet; patient care comes first. We manage pretty well. We have some awesome peeps!"

Many thanks to the stellar SMH laboratory team who participated in our on-site interview:

- **Dana Rickard: Laboratory Operations Manager**
- **Felix Machuca: MT, Hematology and Coagulation**
- **Sandy Erickson: MT, Chemistry**
- **Linda Bowen: MT, Urinalysis**
- **Mark Durfee: PreAnalytical Lab Supervisor, 1st shift, Phlebotomy**
- **Dawn Wilson: Customer Service Representative**
- **Jaime Kennedy: Administrative Assistant**

The case for a COQ project

By Jennifer Dawson and Andy Quintenz

Cost of Quality (COQ) programs are widely used across virtually all industries, having been first introduced in the 1950s by Joseph M. Juran (1904–2008), a Romanian-born American engineer and management consultant. He was a highly regarded pioneer in quality and quality management. COQ formally appeared on the modern medical laboratory scene in 2014 with CLSI's Report, *Understanding the Cost of Quality in the Laboratory*.[1] In recent years, there have been many COQ articles and seminars available to medical laboratories.

There are both good and poor quality costs. Good quality costs consist of prevention costs and appraisal costs. Poor quality costs consist of internal failure costs and external failure costs. A lab that spends more up front on appropriate prevention and appraisal costs can significantly drive down internal and external failure costs.

In an article titled, *Exploring cost of quality in the lab,*[2] published in the December 2018 issue of *MLO,* core COQ concepts were reviewed along with ideas for how to get started.

In this article we'll explore ways for laboratory staff to get started with a specific COQ project that may help demonstrate the return on investment (ROI) to administration.

Identifying a project

Once a laboratory decides to start tracking COQ, it is recommended to start with a pilot project. A lab will often have some sort of trigger that prompts the desire to track costs associated with failures. A pilot project will help the lab get its feet wet before implementing a full-fledged COQ program.

When selecting the focus of the COQ project, consider what types of non-conforming events (NCEs) the laboratory experiences that likely have the most impact on the lab's budget and/or patient safety. Perhaps the lab experienced a few serious mislabeling errors or turnaround time issues for STAT specimens. Or perhaps the lab frequently experiences lower severity issues such as Quantity Not Sufficient (QNS) specimens, demographic data entry errors, or quality control (QC) failures. Whatever the case may be, try to zero in on the issues that it is fair to assume cumulatively cause your laboratory the most problems. Select one or maybe two issues for your pilot project.

Outline data collection plan and data capture

It will first be necessary to determine what tool will be used for the COQ initiative. There are laboratory focused templates[1,3] that can be used as a starting point. Start with one of these templates (or devise your own) and consider if all types of failure costs that the laboratory may experience are reflected. Hospital laboratories that perform collection and deliver results to doctors within the organization receiving results will have a broader workflow to consider than a reference laboratory will.

It is also prudent at this stage to introduce the project to key management so they can provide input before data is collected. This will make it more likely that they will understand and value the results of your project. It will also be necessary to determine the duration of the project, how data will be stored, and responsibilities for capturing data.

Before the project is started, ensure that all responsible staffers are appropriately trained on what NCEs to include in the project, use of the tool, and COQ calculation (as applicable). See **Figure 1** for a simple checklist for developing a COQ project within your laboratory.

Checklist for developing a COQ project

- ☐ Select and define the NCE(s) to be tracked
- ☐ Determine the duration of the project
- ☐ Develop the tool to capture COQ data
- ☐ Determine how data will be stored
- ☐ Define responsibilities for capturing data
- ☐ Introduce the project to management and solicit feedback
- ☐ Train responsible individuals to report NCEs
- ☐ Train responsible individuals to perform COQ calculations
- ☐ Kick off the COQ project
- ☐ Aggregate and analyze the data
- ☐ Prepare charts and graphs
- ☐ Calculate projected ROI and create a case for investment in improvement initiative
- ☐ Determine the appropriate forum and audience for presentation
- ☐ Present the data and findings

Figure 1. COQ project checklist

Aggregate and analyze the data

Once data has been captured for the defined period of time or at an interval that makes sense (such as monthly or quarterly), aggregate and analyze the collected COQ data. A simple spreadsheet can be very helpful in facilitating aggregation and the generation of charts and graphs. It is helpful to demonstrate the failure costs associated with the NCE(s) over time, as well as average and median failure cost values. (**Figure 2**)

Charts and graphs can also help to visualize the aggregated data. (**Figure 3**) It is worth noting that denominators should be included where possible to ensure that

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	Jan	Feb	Mar
NCE frequency	13	17	16
Avg. COPQ	$170.74	$165.66	$180.21
Median COPQ	$123.98	$114.93	$101.08
COPQ	$2,220	$2,816	$4,212
Department FTEs	30	31	33
COPQ adj. by FTE	$73.99	$90.85	$127.64
Test volume	1500	1623	1580
COPQ adj. by test volume	$1.48	$1.74	$2.67

Figure 2. Aggregation and analysis of COPQ data

Figure 4. *Please note that ROI is typically expressed as a percentage, so "x100" is provided for ease of use.

Annualized COPQ	$31,677
Proposed fix apx. cost	$3,500
ROI	805%

Figure 5. ROI calculation example

the organizational context is properly understood over time. It may be that the organization grew from 10 to 100 employees or perhaps volume decreased 30 percent over the time period being tracked. Adjusting NCE frequencies and COQ values with appropriate denominators such as full-time employee count, revenue, and test volume can help to ensure that fluctuations, such as growth and attrition, are accounted for. (**Figure 2**)

Be prepared, as the data collected may be surprising! Many times, the true financial implications for a particular NCE are not fully appreciated until this exercise is carried out.

Create a case for investment in quality improvement

Once the aggregated data is analyzed and confirms that there is an opportunity for improvement—both from a quality perspective as well as financial—determine the root cause of the NCE in question. Determine what types of costs of good quality (COGQ) will be necessary to eliminate it.

Perhaps revising a standard operating procedure (SOP), implementing a new internal audit, or training staff will be necessary. It is possible a more significant investment will be necessary such as automation or a newly created position. Be conservative yet thorough in the selection of the proposed corrective action that will eliminate the root cause of the NCE.

Next, calculate how much this corrective action will cost the organization. Be as accurate and concise as possible. Annualize the failure costs that you calculated earlier in the project and consider this the amount that will be gained over the next year should the proposed corrective action prove successful. Calculate an ROI for your proposed corrective action. (**Figures 4 and 5**)

Present the data

Now that the cost of poor quality (COPQ) data and justification for investment in COGQ has been calculated, it is time to present the information.

First, determine the appropriate audience and forum. It may be that the lab has a monthly quality improvement meeting or perhaps it will be necessary to schedule a meeting for this purpose. Consider the audience the information will be presented to and their differing viewpoints. Review the presentation and ensure that it effectively makes the case intended. Before you present, understand the difference between hard and soft costs, as well as cost savings, and cost avoidance. (**Figure 6**)

It is helpful to have more granular calculation COPQ and ROI calculation data handy while presenting information in the event that any of the numbers are called into question or if any of the attendees have specific questions.

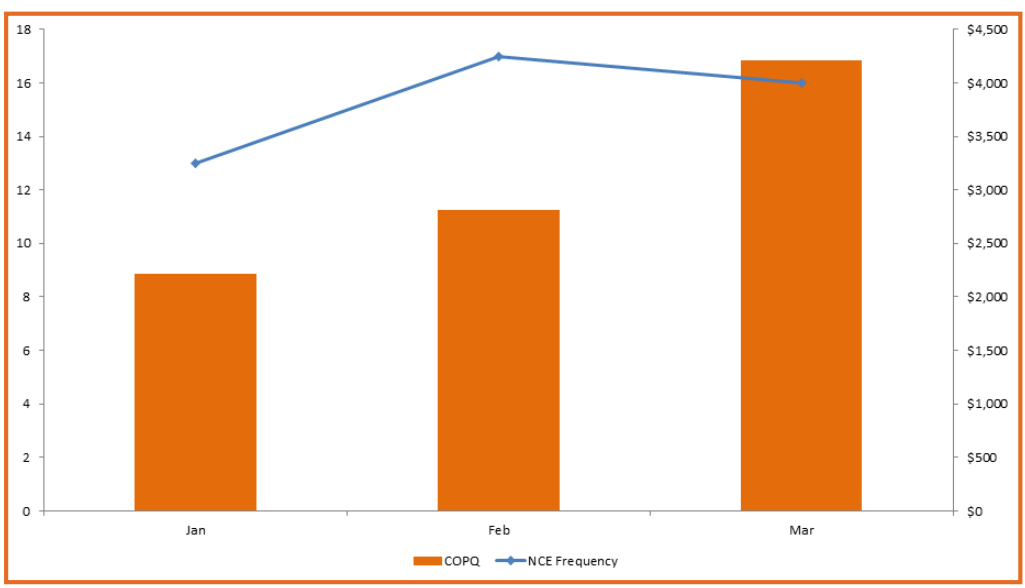

Figure 3. Non-conforming frequency and associated COPQ

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Hard Costs vs. Soft Costs

- Hard costs are direct costs which tend to be more easily calculated. Hard costs include items such as salaries, instruments and reagents, proficiency testing programs, or accreditation fees.
- Soft costs are indirect costs and are more difficult to calculate. They may include loss of potential revenue when an instrument is down, low patient satisfaction scores, or loss of reputation due to incorrect diagnosis.

Cost Savings vs. Cost Avoidance

- Cost savings result from action taken that lowers current spending. Training program for nurses performing blood draws that results in reduced redraws which saves labor and materials.
- Cost avoidance measures result in preventing future costs. For example, preventing a price increase or obtaining value added services as part of an agreement.

Figure 6. Costs

Conclusion

Developing a pilot COQ project is a cost-effective and educational way of moving your laboratory to longer-term and ongoing COQ programs that will benefit your organization as a whole. It is also the most efficient way to demonstrate the value of COQ principles to your laboratory's financial decision-makers. A successful project will help you demonstrate to administration the ROI COQ can achieve and ultimately achieve buy-in for larger-scale programs at all levels of your organization.

Please visit mlo-online.com for references.

Jennifer Dawson serves as a Lab Quality Consultant with Pinnacle Lab Quality. She specializes in development, deployment, and redesign of best practice Quality Management Systems and cultivation of a culture of quality.

Andy Quintenz serves as Scientific and Professional Affairs Manager for **Bio-Rad Laboratories Quality Systems Division**. He works to promote an understanding of laboratory regulations and best practices, as they pertain to QC and EQA/PT programs.

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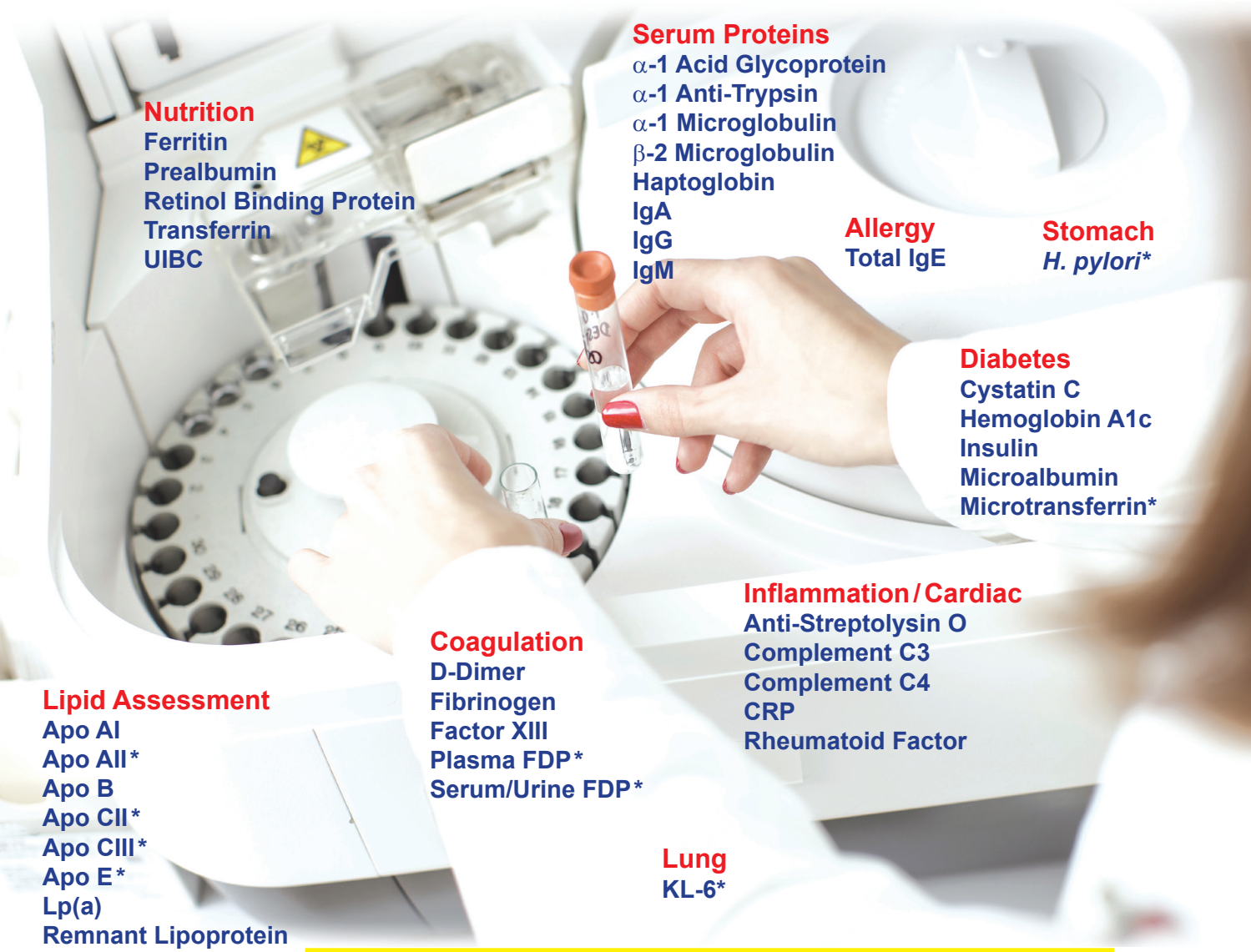

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New HA and HB therapies offer innovation for patients and expanded testing opportunities for laboratories

By Paul Riley, PhD, MBA

In Plato's dialogue *Phaedrus,* the titular protagonist states, "Things are not always what they seem; the first appearance deceives many; the intelligence of a few perceives what has been carefully hidden."

Accordingly, how frustrated do you feel when you receive the wrong dish at a restaurant, or the wrong product after ordering online? More relatable to our everyday life in the lab—what happens if you expect one result after carefully running a lab test, but you observe a different result instead? Most would find it very frustrating and would want to understand the root cause.

New hemophilia therapies

Presented here is valuable information around new therapies for patients with the rare, serious inherited bleeding disorders hemophilia A (HA) and hemophilia B (HB). Factor VIII (FVIII) and factor IX (FIX) are the coagulation factors missing in patients with HA and HB, respectively. Regular infusions are required to maintain balance in the coagulation system to ensure bleeding stops in response to injury (**Figure 1**). Though males are mostly affected, due to the X chromosome location of the genes encoding FVIII and FIX, women are also affected if they carry two mutated copies of the gene, or if they carry one copy but also have other risk factors for bleeding. Some of the currently available and new HA and HB therapies require intimate knowledge of the different patient therapy options, or patient care could suffer due to the unexpected effects of some therapies on commonly used coagulation assays.

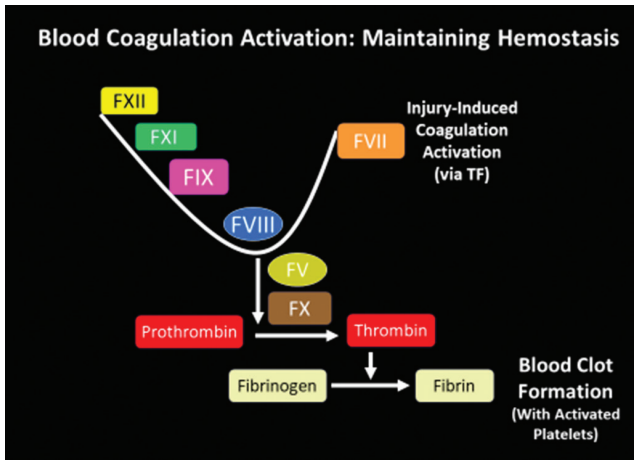

Figure 1. Blood coagulation cascade, in response to injury via tissue factor (TF) / factor VII (FVII) activation. Hemophilia A (HA) is caused by deficiency in factor VIII (FVIII, shown as blue circle above). Hemophilia B (HB) is caused by deficiency in factor IX (FIX, shown as pink square above). Other abbreviations: factor XII (FXII), factor XI (FXI), factor X (FX), and factor V (FV).

The new therapies present tricky problems faced daily by medical technologists, especially those in reference labs, university hospitals, children's hospitals, and other centers associated with hemophilia treatment centers (HTCs). Traditional clotting assays used in the lab, especially activated partial thromboplastin (aPTT) assays used for screening, along with a PTT-based one-stage clotting assays (OSAs) may show unexpectedly low or high results with certain current therapies.

The most common FVIII and FIX assays used in clinical laboratories are based on the OSA method. Chromogenic substrate assays (CSA) are also available, but may require extensive validation, as dictated by local practices. Though CSAs are generally less vulnerable to interference, CSAs are not a one-size fits all solution and may also experience interference from some therapies.

Changing landscape

The HA and HB therapy landscape is rapidly changing. The introduction of new therapies results in lab staff needing to understand each therapy and the effect on coagulation assays. If the lab is not kept abreast of new patient therapies in use, unexpected results may arise, causing confusion or potential patient care risks.

In the past, the only option for HA and HB patient treatment was plasma replacements, followed by introduction of more effective plasma-derived FVIII or FIX. Recombinant FVIII and FIX therapies were introduced to improve patient safety, but recent years have seen an explosion of new options for HA and HB patients designed to decrease the dosing frequency.

The newer generation extended half-life (EHL) therapies take several forms, including B-domain deleted (BDD) FVIII, or factor fusions to the Fc domain of human IgG_1, albumin, or polyethylene glycol (PEG). Each modification strategy allows for reduction in the rate of clearance of the therapy from the body while reducing incidence of autoantibody, or inhibitor development. Thus, all of the aforementioned strategies allow for significant reductions in dose frequency and more effective treatment, allowing greatly improved quality of life.

Recent breakthroughs

A more recent breakthrough in HA therapy was the introduction of emicizumab (HEMLIBRA), a bispecific antibody recognizing both human activated factor IX (FIXa) and factor X (FX), bypassing the need for FVIII. Most importantly, emicizumab can be given subcutaneously, allowing patients to self-dose with greater ease compared to other therapies.

Further innovations are currently in progress for HA and HB patients, including antibodies targeting tissue factor pathway inhibitor (TFPI), silencing RNA (siRNA) targeting antithrombin (AT), and genetic therapies containing replacement FVIII and FIX. New therapies in development offer potentially more benefits for HA and HB patients, including subcutaneous dosing, reduced dosing frequencies, utilization of the same therapy for both HA and HB patients, and potentially curative outcomes for at least some patients.

For the lab, some of the existing EHL therapies have produced confounding results. For example, PEGylated FVIII and FIX interfere with some OSA activators, due to the interactions of the PEG molecule with the aPTT activator surface (**Table 1**). Other factor modifications described here may also show different effects from FVIII and FIX molecules with no modifications. Due to interference issues, labs may choose to use a chromogenic substrate assay (CSA) for monitoring patients on selected EHL therapies, but if the clinicians do not communicate with the lab regarding the specific patient therapy in use, the lab will not know whether to choose the OSA or CSA. In addition, some of the therapies, including BDD FVIII require the OSA result to be multiplied by two, regardless of the OSA activator, and it is unclear whether the lab would need to validate the multiplication factor, or the clinician simply interprets the OSA result for the selected patients.

With the introduction of emicizumab, which does not require routine drug or FVIII level monitoring, the lab may still need to monitor FVIII levels in patients experiencing breakthrough bleeding receiving regular FVIII infusions. If FVIII levels are needed, no OSA can accurately monitor FVIII levels unless an emicizumab calibrator and control are used. Alternatively, a CSA may be used for the emicizumab patients receiving FVIII infusions, but if the patient has a FVIII auto-antibody, or FVIII inhibitor, then only a CSA with bovine-sourced reagents can be used. On the other hand, if the patient does not have a FVIII inhibitor, and clinicians want to measure emicizumab drug levels, then only a CSA with human-sourced reagents can be used, or an emicizumab-calibrated OSA. Thus, care of emicizumab patients requires clinicians and labs to closely work together on patient monitoring practices.

Use of a CSA may be justified by labs for more than just EHL therapy monitoring. CSA approaches are useful for patients with lupus anticoagulants affecting the OSA, and also for patients with certain FVIII and FIX gene mutations associated with non-severe HA and HB.[10] In the case of the latter two situations, CSA will best allow for correct diagnosis and treatment monitoring.

Factor modification or therapy classification	Example therapies (and factor targeted)	Effect on OSA	Recommended Assay
PEGylation	ADYNOVATE (FVIII)	All OSA underestimate; need to multiply result by factor of 2; CSA unaffected	OSA, but multiply result by 2, or CSA[1]
	ESPEROCT (FVIII)	Silica-based OSA underestimates by 60%, others by 20%	Validated OSA or CSA[2]
	REBINYN (FIX)	Most OSA underestimate, except polyphenol-activated-based OSA	Polyphenol-activated OSA or CSA[3]
FVIII single-chain	AFSTYLA (FVIII)	All OSA underestimate; need to multiply result by factor of 2; CSA unaffected	OSA, but multiply result by 2, or CSA[4]
FVIII with vWF	HUMATE (FVIII)	OSA unaffected, but need to also run vWF:RCo	OSA and vWF:RCo[5]
Fc fusion	ELOCTATE (FVIII)	OSA unaffected, but CSA may overestimate	OSA[6]
	ALPROLIX (FIX)	Silica-based and kaolin-based OSA underestimates, but other OSA unaffected	Ellagic acid-based OSA or CSA[7]
B-domain deleted (BDD)	REFACTO (FVIII)	All OSA underestimate; need to multiply result by factor of 2; CSA unaffected	OSA, but multiply result by 2, or CSA[8]
BDD / PEGylation	JIVI (FVIII)	Silica-based OSA underestimates, kaolin-based OSA overestimates, but CSA unaffected	Ellagic acid-based OSA or CSA[9]
Albumin	IDELVION (FIX)	Kaolin-based OSA underestimate by 50%,but silica-based OSA shows acceptable recovery; CSA unaffected	Silica-based OSA or CSA[1]
Bispecific antibody	Emicizumab/ HEMLIBRA (bypasses FVIII)	All OSA overestimate FVIII levels in patients on emicizumab, CSA with bovine-sourced reagents unaffected	To measure levels, emicizumab calibrated OSA, but to measure FVIII levels in patients on emicizumab, use CSA with bovine-sourced ingredients[10]

Table 1. List of factor VIII (FVIII) and factor (FIX) modification strategies, effect on aPTT-based OSA, recommendations for laboratory assay to use OSA or CSA, and literature or drug package insert; not an exhaustive list of all HA and HB therapies currently available in the North American market. Other abbreviations: polyethylene glycol (PEG), von Willebrand Factor (vWF), ristocetin cofactor (RCo).

Conclusion

In conclusion, specialized clinical labs, especially those associated with HTCs will have patients on many different HA and HB treatments, both standard and EHL, potentially requiring them to utilize OSA with different activators, along with CSAs. Generally, it will not be possible to only use one OSA or one CSA method for all patients requiring FVIII and FIX testing. As laboratorians following the words of Plato, we must always be prepared to investigate what lies behind the facade. Armed with the correct information, we are in the best position to find the reasons for unexpected results and ensure the best possible patient care is provided safely.

Please visit mlo-online.com for references.

Paul Riley, PhD, MBA, serves as Scientific Business Development Manager at **Diagnostica Stago, Inc**. Paul earned a PhD in biochemistry from Temple University in 2006, with the subject of the dissertation regarding the function of coagulation factor XI. He also did postdoctoral training in a related area before becoming a product manager and scientific affairs specialist in 2009. During his time at Stago, Paul also completed an MBA degree program at Cornell University in 2014. He has spoken to dozens of medical technologist, clinical laboratory scientist, pharmacist, and clinician audiences about various topics within hemostasis and coagulation.

Developing a flu readiness plan

Factors your healthcare system should consider to manage increased testing demand

By Jamie E. Phillips, PhD

Influenza viruses cause annual epidemics, and in some cases pandemics. The Centers for Disease Control and Prevention (CDC) estimates that influenza illnesses affected up to 42.9 million people in the United States during the 2018-19 flu season, resulting in as many as 20.1 million medical visits, 647,000 hospitalizations, and 61,200 deaths.[1] Despite the well-known societal burden of influenza, the ability to predict the prominent strains that circulate annually and match vaccines to those strains can be a challenge. Even when vaccines are well matched to circulating strains, CDC studies indicate that they only reduce the risk of contracting flu illness by about 40 to 60 percent.[2]

The difficulty of predicting seasonal flu outbreak severity and associated testing demand can present a formidable challenge for clinical laboratories. But the lack of an effective plan to manage heavy flu testing demand can have significant ramifications for entire healthcare systems. They may include increased staff workloads and elevated stress levels, strained resources, overcrowding in patient care settings, and delays in time to diagnosis—which can cause associated delays in appropriate patient isolation measures and, potentially, inappropriate or delayed therapeutic interventions. Laboratorians who want to reevaluate their current flu testing protocols now have access to new predictive tools and a broader range of CLIA-waived testing options that can improve diagnostic accuracy at the point of care (POC).

Forecasting and nowcasting

Together with traditional influenza forecasting, the use of real-time data and machine learning—or "nowcasting"—has become a valuable tool to assist labs in preparing for flu season and making ongoing modifications to testing protocols throughout the season based on emerging trends.

The CDC collects data from both public health and clinical labs regarding the total number of respiratory specimens tested for influenza and the number of specimens that test positive for influenza by virus type. This data is used to produce a weekly surveillance report known as FluView,[3] which informs labs about the presence and spread of influenza viruses in their geographic areas and helps them anticipate demand for testing. However, there is a slight lag between the weekly reports and actual influenza activity.

To address this issue, research teams have devised methods to estimate influenza-like illness in near-real time. The new methods take advantage of the large volume of diagnostic and syndromic data being reported from healthcare and public health settings to aid with infectious disease control efforts and decisions through the use of models. The methods incorporate a variety of techniques, from statistical modeling and machine learning to mechanistic and epidemiological models. Many utilize web-based data sources such as Internet search frequencies and electronic health records (EHRs),[4] and they generate outputs such as influenza epidemic detection, peak timing prediction, and peak intensity prediction.[5]

Optimizing testing protocols

Developing an optimal flu readiness plan involves more than allocating staff and stocking a sufficient number of tests to meet anticipated demand. There are several factors lab and healthcare networks should consider in order to develop a flu readiness plan that is cost-effective and matches up well with the institution's workflow capabilities and testing protocols.

Test sensitivity and specificity. For an illness with a 48-hour effective therapeutic window, like influenza, the ability to accurately detect and identify the pathogen is clearly of critical importance in diagnostic testing. In the categories of sensitivity and specificity, viral culture and nucleic acid amplification testing (NAAT) provide the best performance.[6] While antigen-based Rapid Influenza Diagnostic Tests (RIDTs) have been widely used, their relatively low sensitivity (about 50 percent in some studies) compelled the FDA in 2017 to reclassify them from Class I to Class II devices with special controls.[7] The agency put the special controls in place for RIDT manufacturers to increase sensitivity and undergo annual strain testing.[8] The higher sensitivity and specificity of NAAT, which is now available in

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CLIA-waived settings for flu testing, can also eliminate the need for laboratory confirmation of negative results. In addition, recently updated clinical practice guidelines from the Infectious Diseases Society of America (IDSA) recommend the use of rapid molecular assays over RIDTs or antigen-based tests in outpatient settings to improve detection of influenza virus infection.[9]

Turnaround time. Because of their high sensitivity, viral culture and lab-based polymerase chain reaction (PCR) testing are often used in tandem to determine circulating influenza strains and define subtypes. However, normal turnaround time (TAT) for these lab-based tests is 48 hours or more. Because antiviral therapies must typically be initiated within 48 hours of onset of clinical symptoms for the patient to receive optimal benefit, labs need to deliver a faster time to result. One way to achieve this without sacrificing sensitivity and specificity is to deploy CLIA-waived molecular testing (NAAT) at the POC. Several studies demonstrate that timely influenza diagnosis may decrease unnecessary laboratory testing for other etiologies, support antiviral and antibiotic stewardship, and improve the effectiveness of infection prevention and control measures.[10,11]

Workflow and staffing. Testing methods and sites (e.g., central lab vs. POC) can vary considerably in their impact on workflow and what staff resources are required. For example, with the implementation or expansion of point-of-care testing (POCT), labs may need to consider location-specific staffing needs and hands-on time required to meet the demands of increased patient traffic during periods of high influenza activity. The hands-on time is an especially important factor to consider if a test itself has a fast TAT but running the test requires a lengthy set-up process or is labor-intensive for the operator. The workflow time allowance can be significantly greater if a method is used that requires confirmation testing for negative results, such as RIDTs.

Multiplex testing. Some test methods incorporate multiplex assays, or combination tests, which detect multiple pathogens in a single test. For example, there is an overlap in the clinical symptoms and seasonality of influenza and respiratory syncytial virus (RSV). The use of a multiplex molecular test that simultaneously detects influenza types A and B and RSV simplifies the test protocol, reduces diagnostic uncertainty, and helps guide treatment decisions. Also, the prompt, accurate detection of influenza and RSV infections can help quickly identify local outbreaks of disease.[12]

Cost. While both RIDTs and some NAATs are CLIA-waived for use in POC settings, the molecular tests are typically more expensive on a cost-per-test basis. However, the cost differential can be much smaller or even reversed when the overall clinical impact is included in the analysis. One study, for example, indicated significant cost savings for an institution's flu testing program through NAAT implementation in the

Creating a flu test checklist

Each testing method and approach has advantages and limitations. The following questions will help apply some standardized criteria to assist in determining which test is most suitable for your facility, particularly if you are considering a decentralized testing model:

- What level of sensitivity and specificity is needed for the test(s)?
- What is the hands-on time to run the test(s)?
- What is the time to result for the test(s)?
- Will confirmation testing need to be run for negative results?
- Will a dedicated operator be needed to run the test(s)?
- Will monitoring operator proficiency be needed?
- Will a multiplex test be needed?
- Who will oversee a decentralized testing program?
- Will contamination safeguards need to be put in place?

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emergency department setting.[13] To be accurate, cost analyses should take into account the potential clinical and workflow impact of the implementation of a test method in a decentralized setting across an entire institution.

Contamination concerns. Despite the advantages associated with establishing CLIA-waived molecular testing in a decentralized model, it's important to note that any NAAT platform deployed at the POC should have a safeguard in place, such as a closed system design, to offer protection from possible environmental nucleic acid contamination. One study purposefully contaminated a CLIA-waived NAAT system and still found that, despite contamination, all negative results were reported negative. However, with any molecular testing, reducing the risk of contamination is an important consideration.[14]

Conclusion

Staying aware of real-time influenza trends as they emerge, and evaluating your current testing protocols through a new lens can help you prepare an optimal flu readiness plan for your health system and help your lab navigate the challenges of the upcoming flu season.

Image courtesy of Roche Diagnostics

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Getting to the end: Telomeres in clinical settings

By John Brunstein, PhD

We'll start this month's foray into topics molecular with a reminder of some basic DNA polymerase biology. That is, they work to create one nascent strand at a time, 5′ to 3′ with respect to the growing strand and therefore 3′ to 5′ as seen along the template strand. This replication of the template strand—known as the leading strand—leaves the other template strand single stranded. Once this single stranded region is long enough, a specialized enzyme (DNA primase) lays down a short RNA primer (facing back toward the replication fork where the template strands part), and the rest of the DNA replication machinery initiates off of this and makes a new daughter strand until it bumps into, and get ligated to, the previously replicated section. This side of the fork is known as the "lagging strand," because it's replication lags that of the full-speed-ahead leading strand.

DNA polymerases and the terminus problem

If your chromosome is a circle, this works fine. Both strands eventually make it all the way around and close off. Many unicellular organisms, organelles likely derived from unicellular organisms (that is, mitochondria and chloroplasts), and many viruses have taken advantage of this, but large multicellular organisms like humans have linear chromosomes. (An interesting aside is why; one immediate observation is that linear chromosomes are amenable to recombination which along with sexual reproduction is a critical means of generating novel population diversity to drive adaptability. Recombination between circular chromosomes would seem to generate concatemers or other undesirable structural alterations.) Regardless of the biological reason, we've got linear nuclear chromosomes and we're stuck with it. Worse, for the lagging strand at each end of a linear chromosome, this is a death sentence. Some terminal portion of that strand just won't get replicated, and thus the intact double stranded length of the chromosome gets a little bit shorter from each end (on opposite strands) with every DNA replication cycle. While losses of 30-200 base pairs out of millions of bases pairs doesn't sound like a lot, over biological time scales and numbers of cell divisions, it all adds up—or perhaps one should say, subtracts down—to linear chromosomes shrinking away to nothing over time, losing genes from their outer tips one by one until you'd got an inviable organism and it dies off.

Telomeres and telomerase complex

That we're walking around proves there's some way to rescue this problem. Actually, there's a number of ways from polymerase priming proteins to palindromic terminal self-priming "hairpin" structures, but the one used by humans and most higher organisms is an RNA/protein complex called the telomerase holoenzyme. Its RNA component acts as a template and the proteins do various accessory functions to allow telomerase to grab onto the ends of linear chromosomes and add on multiple concatemer copies of a short DNA sequence (TTAGGG), in effect padding the ends of chromosomes with non-informational bumpers—telomeres—which can be partly lost each replication cycle without harm.

As organisms (or more properly, cell lineages within an organism, more about that later) age, telomerase tends to lose activity and so over time the length of these telomeres gets shorter and shorter. This is a normal part of cellular aging, and when telomeres (or more correctly, any one out of the 92 telomeres per cell) gets "too short," programmed cell death (apoptosis) is triggered so the cell can be cleared away and replaced with younger, more vigorous tissue. Normally this occurs after something on the order of 50 to 70 replication cycles post fertilization for each cell lineage. (High levels of telomerase activity in gamete formation essentially "reset the clock" on egg and sperm, meaning each zygote starts this cellular timing device afresh.) Not surprisingly, this process is a topic of ongoing study as one key aspect of how organisms age as a whole.

Measuring telomeres

This discussion of long versus short telomeres suggests there must be lab methods to determine these lengths. There are a couple of methods, one based on restriction fragment sizing (which provides actual numeric length values, but is generally limited to use in research settings) and another based on quantitative PCR (qPCR; more approachable to clinical labs, but it provides a relative size against a reference in a preparation-dependent manner which is not readily amenable to comparison of results between labs). A flow cytometric approach is also possible for some cell types, as described below. In any case, measurement methods exist, and we know that in newborns telomeres are around 8 kb in length, dropping to 3 kb in adults and 1.5 kb or less in elderly people and/or rapidly dividing cell lineages. It's noted however, that there's quite a wide range of sizes both by age

and by tissue type. Because of this wide 'normal' range and variance across tissues, measurement of telomere lengths in a sample is not for instance valid as a means to identify age of a forensic DNA sample source. If one were to attempt this, an additional complexity would be that data suggests an impact of genetic ethnicity on telomere length. It may however be a marker for things such as chronic inflammatory conditions, in which continuous division of immune cell populations leads to their telomeres shortening relative to less rapidly dividing tissue types in the same individual (such as skeletal muscle; heart muscle would be an even better control but is more of a challenge to obtain).

Clinical syndromes

As with any critical biochemical pathway, there are known examples of genetic diseases rooted in the telomerase system with characteristic presentations. Most serious among these is probably dyskeratosis congenita (DC), first recognized over 100 years ago and which presents as some mixture of nail dysplasia, abnormal skin pigmentation, oral leukoplakia, bone marrow failure, stenosis of various ducts (lachrymal, urethral, esophagus), liver disfunction, and a host of other problems including high incidence of several types of cancers. As of a recent review,[1] underlying causes in approximately 25 percent of cases are due to mutations in the dyskerin protein (*DKC1* gene, found on the X chromosome) but in the remaining cases can be traced to mutations in 13 other genes with known action in telomere maintenance. Genes on this list include *TERT* (the catalytic component of holoenzyme), *TERC* (the RNA template component), *CTC1* and *STN1* (along with *TEN1*, a trimeric modulator of telomerase activity), and *RTEL1* (regulator of a required helicase activity). Because so many genes and possible mutations are involved, telomerase disorders can be observed with multiple inheritance patterns including X-linked recessive, autosomal dominant, and autosomal recessive. From a diagnostic molecular testing perspective, it is convenient that a single test—direct observation of telomere lengths (usually by fluorescent *in-situ* hybridization (FISH) on lymphocytes from the patient), with results scoring below one percent of population average for the patient age—is considered a reliable and specific test for this condition regardless of which underlying mutation is causal. A more detailed diagnostic follow-up would most likely be best amenable to an NGS panel approach targeted to the 14 genes referred to above.

Other named conditions closely linked to telomerase abnormalities include Hoyeraal Hreidarsson syndrome, Coats plus, and Revesz syndrome. Other conditions may be associated with telomere abnormalities but can arise from a range of other etiologies, making it unclear whether the observed telomere abnormalities are somehow causal or merely associated. Some examples of this include Myelodysplastic syndrome, fibrosis of the liver or lungs, and aplastic anemia.

Telomeres and cancer

Finally, there's an obvious interaction between telomeres and cancer, since cancerous cells by definition among their many attributes escape senescence and become immortalized. Not surprisingly then, part of the cellular transformation process often includes reactivating or upregulating telomerase activity such that observed telomere lengths in cancer cells and cultured immortal cell lines are at the extreme upper end of what's normally seen (around 99th percentile). There is however evidence that these telomeres may not always be normally structured and may have attributes such as significant single stranded regions which tend to lead to "sticky" chromosome ends and subsequent chromosome fusions. Such fusions and resulting breakage products are not uncommonly seen in cancerous cells. Paradoxically, while telomerase disorders result in abnormally short telomeres, cohorts of patients with one of these classical conditions show striking elevated risks to develop cancers with incidence rates as much as several hundred times that of controls.

The common activation of telomerase activity in cancer cells has led to studies on whether measurement of telomerase activity in biopsy samples can be used as a biomarker for malignancy. While this can be complicated by the fact that some normally proliferating tissue may also transiently express enough telomerase activity to be detected, some studies have shown promise in this regard although telomerase activity, in and of itself, is probably insufficient for determination of malignancy. Similarly, while it has been suggested that perhaps targeted inhibition of telomerase activity could be employed as an antineoplastic strategy, the knowledge that other non-cancerous tissues can and do express telomerase in situations such as wound healing, suggests this approach would lack specificity in targeting and likely have significant and deleterious off target effects.

In the end (no pun intended), telomeres turn out to be far more than just the aglets of our chromosomes and alterations in them can have significant clinical impacts. By nature, these are most directly ascertainable by molecular methods and thus while not the stuff of everyday diagnostics (DC has an estimated incidence rate of one to nine per 1 million births), they are a subject for analysis in at least specialty molecular lab settings and likely of interest to all.

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HPV: A major etiologic agent of head and neck cancer

By Keisha Burnett, EdD, SCT (ASCP)CM and Linda L. Williford Pifer, PhD, SM (ASCP), GS (ABB)

When American actor and producer Michael Douglas publicly announced in 2010 that his "throat" cancer was "probably" the result of having engaged in oral sex, his family and fans reeled with shock.[1] However, Douglas is to be lauded for giving the world a desperately needed wake-up call to the unpleasant fact that high-risk human papillomaviruses (HPVs) are not at all fastidious about which mucous membranes they can and will invade. In fact, the prevalence of oropharyngeal cancer among men has steadily risen more than 300 percent in the past 40 years.[2] Although tobacco and alcohol are contributory causes, controlled studies reveal that the primary blame rests upon HPV.

Careful investigation has further revealed that head and neck cancer is more prevalent in men and that they have a lower survival rate from these malignancies. It is also documented that men practice oral sex slightly more often than women, and that due to anatomical differences, men are exposed to HPV-infected mucous membrane tissue more than women.

Furthermore, the same study concluded that younger males (aged 35 to 45) were practicing oral sex more than their 60 year old cohorts, as more of the younger males tested positive for HPV 16 (the most prominent viral strain causing head and neck cancer).[3] Thus, changes in sexual behaviors may very well be fueling the previously mentioned 300 percent increase in oropharyngeal cancer over the past four decades.

How common is HPV and how is it contracted?

HPVs consist of more than 200 related DNA-containing strains that are the etiologic agents of everything from non-cancer-causing warts, to dangerous high-risk varieties such as strains 16, 18, and many more. HPVs are the most commonly sexually transmitted infection (STI) in the United States, today. High-risk HPVs are readily transmitted by vaginal, oral, and anal sex. Although barrier protection ameliorates the risk, it does not eliminate it entirely.[4]

Unlike hepatitis B, C, human immunodeficiency virus (HIV), and other retroviruses, papillomaviruses are decidedly not blood and body fluid-transmitted, although measurable viremia does occur during HPV infection. These viruses can be transmitted directly by skin-to-skin contact, thus any skin infected with HPV is directly "contagious."[5] Fortunately, this is not the case with HIV/AIDS.

HPV vaccine is recommended by the FDA for everyone from age nine to 45 with young boys and girls beginning vaccination at around age 11. Women are advised to remember their important prophylactic yearly cancer screening visit.

HPV infection is extremely common, and the Centers for Disease Control and Prevention (CDC) estimates that around 79 million Americans are now infected with the virus. About 14 million more are added to this number each year. Of these, 19,400 women and 12,100 men are projected to develop cancer. In fact, it is estimated that the majority of sexually active Americans will at some time during their lives contract HPV if they do not receive the vaccine at the recommended ages.[6] Of the vast number of HPV types, only 14 are known to be linked to a high prevalence of neoplasia and these are types 16 and 18. Most of the HPVs which do not cause malignancy are kept under control by the immune system.

Anatomic sites

HPV lesions and cancers can occur in the mouth, throat, at the base of the tongue, vulva, vagina, penis, and anus. The HPV virus is altogether different from herpes, which is also a virus, and which can likewise be transmitted by vaginal, oral, and anal intercourse.

Papilloma lesions are usually painless, flat, and wart-like. Advanced lesions are frequently described as dry and cauliflower-like, dissimilar from the blistered, crusty, and sometimes painful sores caused by herpes virus.

Where does HPV-derived head/neck cancer occur?

Head and neck cancers can arise in the following regions: Oral cavity including the tongue, salivary glands, and the larynx. They may be found in the nasal cavity including the paranasal sinuses. Malignant lesions can also arise in the pharynx including the nasopharynx, oropharynx, and hypopharynx.[7] HPV infects the squamous cells that line these organs and also those of the genital tract. Oropharyngeal cancer has become the most common HPV-related cancer in the U.S. and the number of cases being diagnosed each successive year is increasing.[8]

Symptoms

HPV-related cancer symptoms can include hoarseness or a change in voice quality, problems with swallowing, a lump in the neck or a sore in the mouth, a sore throat or earache that does not resolve with time, or a bleeding nose, mouth, or throat that occurs intermittently.[7] Vocal cord or glottis cancer has been very much on the rise in patients under 40 who have never smoked. In these patients, hoarseness was one of their most prominent symptoms. High-risk HPV was found in 100 percent of patients fitting this clinical profile in one study.[9]

Sub-cellular mechanisms of malignancy?

According to the CDC, HPV causes 70 percent of oropharyngeal cancers, which are those that arise at the base of the tongue, tonsils, and soft palate.[7] Malignant transformation probability due to infection with HPV 16 is proportional to the appearance of viral oncogene-coded gene products E6 and E7. These gene products inhibit p53 and retinoblastoma tumor suppressor actions. *In situ* hybridization techniques for integrated HPV 16 are highly specific but have low sensitivity,[8] nevertheless, the technology has been highly useful in proving the point that HPV is indeed

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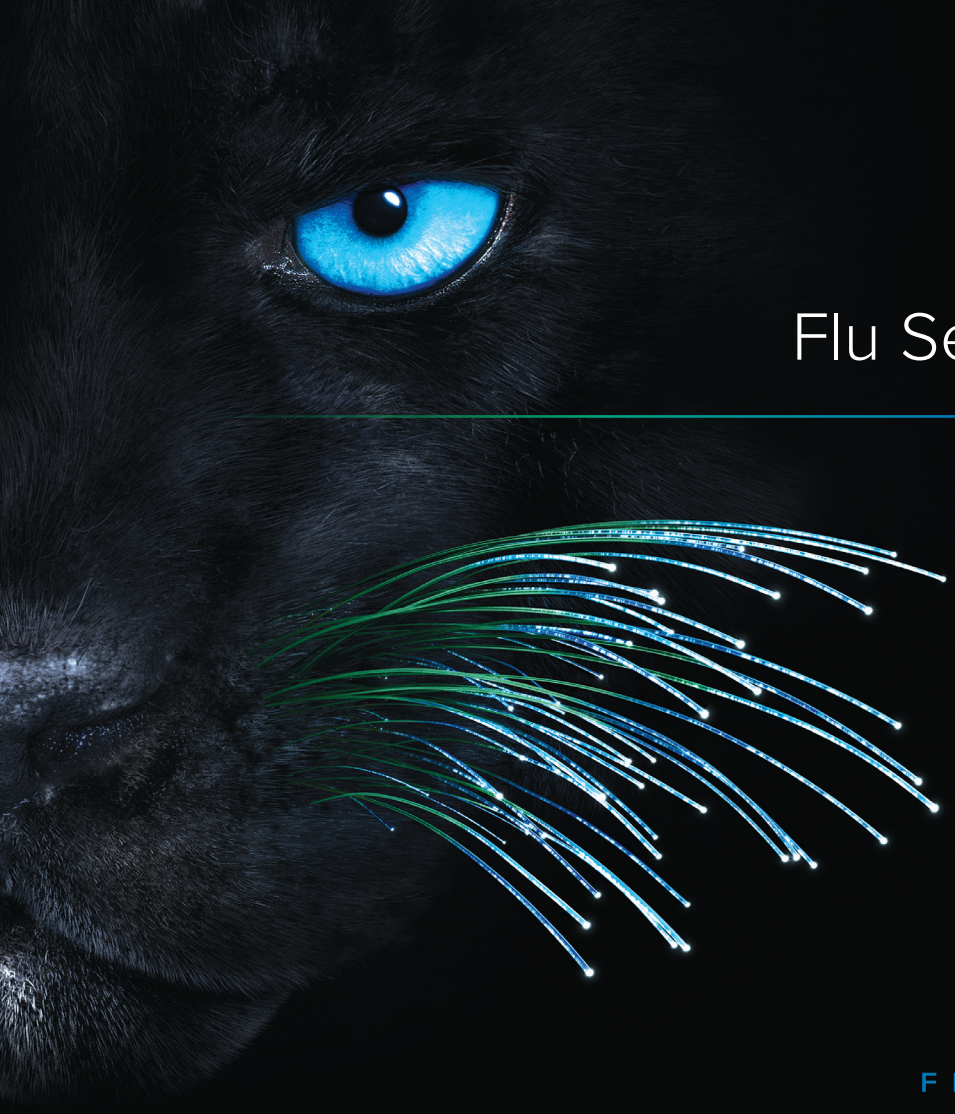

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the "smoking gun." Husain and Ney have stated that high risk HPV 16 is responsible for 90 percent of oropharyngeal squamous cell carcinomas (OSCC).[8]

Viral oncogene products E6 and E7 are produced when the viral genome integrates with the host DNA. This increases the probability that the effects of p53 (tumor suppressor) and retinoblastoma tumor suppressor functions will be proportionately brought into play.

In high-risk HPV strains, E6 and E7 influence many cellular proteins which have an impact upon the outcome,[9] thus driving the neoplastic process. Protein p53 and E6 interact and push the cell's degradation while retinoblastoma (Rb) is inactivated by E7 upon linking with it.

Both p53 and Rb are tumor suppressors and are intimately involved in the repair of DNA and cell demise.[8] In brief, E6 and E7 are oncoproteins that are essential to the malignant process.[9,10] When E6 is bound to p53, the latter is destroyed and cannot control the all-important cell cycle. It is highly noteworthy that p53 is non-functional in at least 50 percent of all human cancers.[11]

The E6 HPV protein is also very important because it induces the expression of telomerase—the "immortality" enzyme—which continuously repairs the tips of chromosomes, and which is not normally present in adult somatic cells. This enzyme prevents the degradation of chromosomes and enables malignant cells to divide endlessly. Ultimately, HPV viral proteins E6 and E7 work together to essentially take over cell division and propel cell dynamics in the direction of malignancy.[11]

Diagnosis news

Some experts in the field hoped that they might be able to determine the efficacy of the HPV vaccine by conveniently scanning for the presence or absence of HPV 16 in saliva specimens at intervals post-immunization and then correlating that with the presence of tumors. However, in a study by Ramirez and Zelvallos, detection of HPV 16 in tumor specimens and saliva from the same patient was discordant in more than one quarter of patients tested.[12] It became clear that it would not be possible to base anti-HPV vaccine efficacy upon anything other than tumor sampling in conjunction with highly analytical examination of tumor tissue for this purpose to obtain reliable data. In its present state of technology, HPV derived from saliva would provide an interesting corollary. The same would apply for diagnostic situations.[13]

Liquid biopsies tracking HPV-DNA originating in OSCC in one prospective study had 100 percent accuracy in ruling out recurrence of malignance.[14] However, its positive predictive value for recurrence was only a disappointing 42 percent. Conclusions were formed that the test had promise, but it was far too expensive and provided potentially too many risky false negatives to be brought into use at this time.[14] There is work continually being done to perfect it.

NGS and HPV

We have recognized for several decades that the fundamental causation of cancer is somatically acquired mutations. Cancer is a disease of DNA and the result of a malfunctioning genome. However, we now have new technology, next generation sequencing (NGS), that enables us to localize the HPV DNA within the human genome that is causing the malignancy.

NGS permits the sequencing of an entire human genome within a reasonably short period of time. It is currently being used to personalize treatment in pilot pediatric cancer genome projects and in other studies around the world.[15] Individualized shot-gun metagenomic sequencing would offer enormous insight into the nature of HPV-induced cancers of the head and neck variety as well as other malignancies caused by this and certainly other viruses.[16] Much as we have learned to thwart HIV by designing integrase inhibitors that prevent the pro-viral DNA from integrating into the host cell DNA, learning where in the human genome various types of HPV are prone to insert might offer clues for treatment strategies.

In a noteworthy study reported by Morris, Chandramohan, and West et al, the "molecular landscape" of recurrent and metastatic head and neck cancers were examined and insights from a precision oncology sequencing platform were gained revealing the highly promising future of this unfolding technology.[17] They noted that to advance precision head and neck oncology, it was first necessary to produce a thorough catalog of molecular alterations in rare and incurable cancers. These are virtually always dramatically distinct from the primary tumors from which they arose. It will be critical to provide NGS profiles of all of these tumors and matched normal controls as well in order to develop rational therapies.[18]

In a far simpler format, NGS has already been employed to search for alpha, beta, and gamma sub-species of HPV 16 in saliva in a prospective study of over 95,000 cancer-free subjects. At a 3.9-year follow-up, 132 subjects were found to have head and neck squamous cell carcinoma (HNSCC) associated with type 16 HPV in saliva (males = 103; females = 29). Their average age was 66.5. Data was controlled for tobacco and alcohol use.[19]

Conclusion

In conclusion, we have made vast progress with HPV and stripped bare many of its ugly and very deadly secrets. We have become open to discussing HPV, removing it as a "taboo" topic, cloaked in ignorance. We're now armed with a powerful weapon capable of bringing it under control. It must be wielded aggressively for the protection of young people before they are ever exposed to the virus. We must educate parents, young people, and all who might derive benefit from immunity to the most dangerous strains of HPV. We have nothing to lose but a very deadly form of cancer itself, and many years of healthy life to gain.

Please visit mlo-online.com for references.

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Updating proficiency testing regulations

A look at the proposed rule.

By Robin E. Stombler

After years of data gathering and deliberation, the Centers for Medicare and Medicaid Services (CMS) issued a proposed rule updating proficiency testing regulations related to analytes and acceptable performance. It is the first major change proposed for clinical proficiency testing performance since 2003, when alterations to grading challenges were finalized.

The public comment period on the proposed rule closed in June 2019. While it may take time for the agency to dissect and consider the 107 comments received into a final regulation, there are several trends that clinical laboratories may want to note.

Defining proficiency testing needs for microbiology

To help microbiology laboratories determine the type of proficiency testing needed, the proposed rule would divide testing into categories within each microbiology subspecialty: Bacteriology, mycobacteriology, mycology, parasitology, and virology. This change would remove the current listing of types of services for microbiology subspecialties. The intent of this change, should it be finalized, is to reflect better current microbiology practices and allow for new technologies to be incorporated more readily.

Bacteriology categories for which proficiency testing would be required, include:

- Gram stain including bacterial morphology; direct bacterial antigen detection;
- bacterial toxin detection;
- antimicrobial susceptibility or resistance testing on select bacteria;
- detection and identification of bacteria (including detection of growth or no growth in culture media or identification of bacteria to the highest level that the laboratory reports results on patient specimens).

Mycobacteriology categories for which proficiency testing would be required, include:

- Acid-fast stain;
- detection and identification of mycobacteria (including one of the following: Detection of growth or no growth in culture media or identification of mycobacteria; and antimycobacterial susceptibility or resistance testing).

Mycology categories for which proficiency testing would be required, include:

- Direct fungal antigen detection;
- detection and identification of fungi and aerobic actinomycetes (including one of the following: Detection of growth or no growth in culture media or identification of fungi and aerobic actinomycetes; and antifungal susceptibility or resistance testing).

Parasitology categories for which proficiency testing would be required, include:

- Direct parasite antigen detection;
- detection and identification of parasites (including one of the following: Detection of the presence or absence of parasites or identification of parasites).

Virology categories for which proficiency testing would be required, include:

- Viral antigen detection;
- detection and identification of viruses;
- antiviral susceptibility or resistance testing.

Among the public comments, some suggested that the proposed use of "detection of growth or no growth in culture media" needed clarification. Two examples of how the definition of "growth/no growth" could be misconstrued included urine colony count and a PCR assay reporting bacterial vaginitis from yeast infections. Instead, some recommended that "presence or absence of bacteria without identification" is a more universal descriptor. Others requested clarification on the acceptable use of molecular methods in identification.

Types of organisms included in proficiency testing

Current regulations list specific organisms for proficiency testing. The proposed rule suggests outlining more general types of organisms appropriate for each microbiology subspecialty. This is intended to allow flexibility in determining which samples laboratories might receive for proficiency testing.

Under **bacteriology**, sample sources would include, as appropriate, gram-negative bacilli, gram-positive bacilli, gram-negative cocci, gram-positive cocci. Also, the current general listing of types of organisms would continue.

Under **mycobacteriology**, annual proficiency program content would include *Mycobacterium tuberculosis* complex and *Mycobacterium* other than tuberculosis, if appropriate for the sample source.

Under **mycology**, the required content would include yeast or yeast-like organisms, molds that include dematiaceous fungi, dermatophytes, dimorphic fungi, hyaline hyphomycetes, mucormycetes, and aerobic actinomycetes.

Under **parasitology**, annual content would include intestinal parasites, blood and tissue parasites, as appropriate.

Under **virology**, the annual proficiency content would require respiratory viruses, herpes viruses, enterovirus, and intestinal viruses, as appropriate.

Public comments on the proposed rule suggested that this grouping of microbiology needs to provide further details to labs. Better understanding the required coverage for organism sample types, specimen type, and test methods would assist labs in enrolling in annual proficiency testing programs. There were also questions as to if it is sufficient for labs to report identifications at the species level or if it is necessary to include more specific detail.

Unintended cost consequences

The proposed rule suggests that ten laboratory participants, at a minimum, be required before a program may offer a proficiency testing analyte. Public commenters expressed concern that this recommendation may limit the ability of laboratories to obtain difficult-to-find samples and comparison data. Some suggested this action would ultimately increase the price of proficiency testing by limiting the number of proficiency testing providers able to comply. Another proposal would limit the online submission of proficiency

testing data to one submission, or else require a mechanism for tracking changes to electronically reported results. Several public comments explained that this proposal would complicate unduly the submission process. Concerns noted that this requirement would increase costs as proficiency testing providers would need to reconfigure programs and adopt new audit systems. These costs would likely be passed to laboratory customers.

Unintentional operational consequences

According to the Clinical Laboratory Improvement Amendments of 1988, proficiency testing programs must be offered by either a private nonprofit organization or a state government. The proposed rule suggests a change that would require "all functions and activities related to administering the PT program must be performed by a private nonprofit organization or state." Given that the U.S. Department of Health and Human Services already has authority to "resolve technical, administrative, and scientific problems" that may arise with proficiency testing program operations, the proposed rule appears to overreach.

As noted in several public comments, "all functions and activities" is a broad reach that may require a wide range of services to convert to nonprofit status. This may include shipping, legal, source samples, information technology services, among others. This has the potential to impact the operations of all proficiency testing providers and their ability to provide services.

Hemoglobin A1c

The proposed rule recommends a ten percent acceptance limit for hemoglobin A1c test results. Even though acceptance limits are not intended for use by individual laboratories, a number of public comments expressed concern that this limit is too wide. Some believe it would permit the treatment of patients based on inaccurate test results. One commenter noted that the performance criteria of target value +/- ten percent is acceptable for non-commutable material coupled with a +/- six percent acceptable rate for commutable whole blood material.

Conclusion

CMS and the Centers for Disease Control and Prevention have been analyzing analytes and acceptable performance measures well in advance of issuing this proposed rule. While modernization of proficiency testing rules is overdue, the next iteration should reflect current practice and permit enough flexibility to accommodate future clinical laboratory testing innovation. It is not yet known when a final rule will be issued.

Robin E. Stombler, is President of Auburn Health Strategies, LLC, a strategic and business development firm representing health and science organizations.

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Influenza A & B 2 assay

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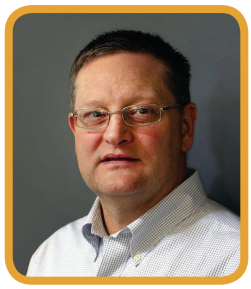

An interview with Dr. Brian DuChateau, VP of Scientific Affairs, Binding Site

What's your educational background? I received my Bachelor of Science degree with a double major in Medical Microbiology and Immunology at the University of Wisconsin-Madison. From there, I continued my education at the University of Wisconsin, graduating with a PhD from the Department of Bacteriology with an emphasis in Medical Microbiology and Immunology. I completed a post-doctoral residency in Clinical Immunology at the Chicago Medical School and later received board certification from the American Board of Medical Laboratory Immunologists (ABMLI).

What is your career background? I started my career on the clinical service side of immunology directing clinical diagnostic laboratories. I directed a large, multi-site clinical diagnostic reference laboratory representing over 300 employees in nine different labs conducting over 2.5 million tests per year. Subsequently, three partners and I established a laboratory with a mission to integrate clinical and anatomic pathology using innovative testing methodologies (like molecular diagnostics and flow cytometry) and informatics. In 2009, I made the transition from clinical service to the IVD industry. Currently, I'm the VP of Scientific Affairs at Binding Site, where I have the opportunity to lead market development initiatives while also providing scientific support.

What is the most rewarding aspect of your job? I am an entrepreneur at heart, but I'm also a technically driven guy. So, I really like the technical aspects of my job along with the commercial responsibilities. It is very rewarding to know that what I do helps medical professionals help patients.

What projects are you currently working on? I am very excited to be involved in one of the largest R&D initiatives ever embarked upon at Binding Site. As experts in protein diagnostics, we are leveraging our expertise to develop a quantitative immuno-precipitation technique that uses MALDI-TOF MS to detect protein targets.

This technology could be applied to a wide variety of different targets, but our first application will be for the detection and quantitation of para-proteins associated with monoclonal gammopathies. This technology has the potential to significantly improve the way we diagnose and monitor patients with monoclonal gammopathies. The system is intended to overcome many limitations associated with conventional serum protein electrophoresis and immunofixation. Our goal is to develop a system that will demonstrate increased sensitivity, unambiguous result interpretation, results that are not confounded by the presence of therapeutic mAbs, along with automation and improved workflow. Our plan is to launch a CE-IVD version of this system in Europe in 2021, followed by a launch in the United States upon FDA clearance in 2022.

What's the biggest challenge the clinical lab is facing today? Any ideas on how to solve this challenge? The clinical laboratory is constantly being asked to do more with less. Despite decreases in reimbursement and institutional budgets, labs continue to face expanding menus of complex testing methodologies and our aging population in the U.S. is driving increased testing volumes. This challenging situation is exacerbated by a continued shortage of skilled laboratory personnel.

Solutions to help with these challenges include the utilization of more automated instrumentation and advanced diagnostic technologies. New analyzers in areas such as mass spectrometry provide greater capacity and throughput while significantly reducing hands-on labor time. This could provide lab personnel more time to focus on result interpretation, quality requirements, and taking leadership roles in multi-disciplinary initiatives such as guideline-compliant testing for high-impact disease states.

What do you hope will be accomplished in the clinical laboratory in the next five to 10 years? I hope for several things: That we will see the advent of new diagnostic methodologies utilized for Minimal Residual Disease (MRD) detection; that we will more comprehensively understand the clinical significance of genotypes identified using molecular techniques; that there will be an even greater emphasis on the development of companion diagnostics; and that Current Procedural Terminology (CPT) coding and reimbursement rates will keep better pace with the development of new innovative diagnostic methodologies.

What advice do you have to those looking to enter the clinical laboratory field—whether it be as a laboratorian or an executive such as yourself? Currently in the United States about 10,000 people turn 65 each day. From a clinical lab perspective, that creates opportunity on at least two different fronts: (1) An aging population increases diagnostic testing volumes; and (2) as individuals retire from an industry already stricken by labor shortages, more job opportunities are created. So, my advice would be that the time is right to start a career in the clinical laboratory field.

In your opinion, what is the most interesting thing going on in the clinical laboratory today? I think cell-free DNA, circulating tumor cells (CTCs), and single-cell analysis all hold true promise. Laboratory technologies that could become routine and significantly improve upon the manner in which we diagnose and monitor disease in the clinical lab is always top of mind.

What do you like to do off the clock? I have three sons who are involved in youth wrestling, which takes up a lot of my time.

I also very much enjoy trout fishing, especially the rivers in northern Michigan. When I retire, I would like to become a full-time fisherman.

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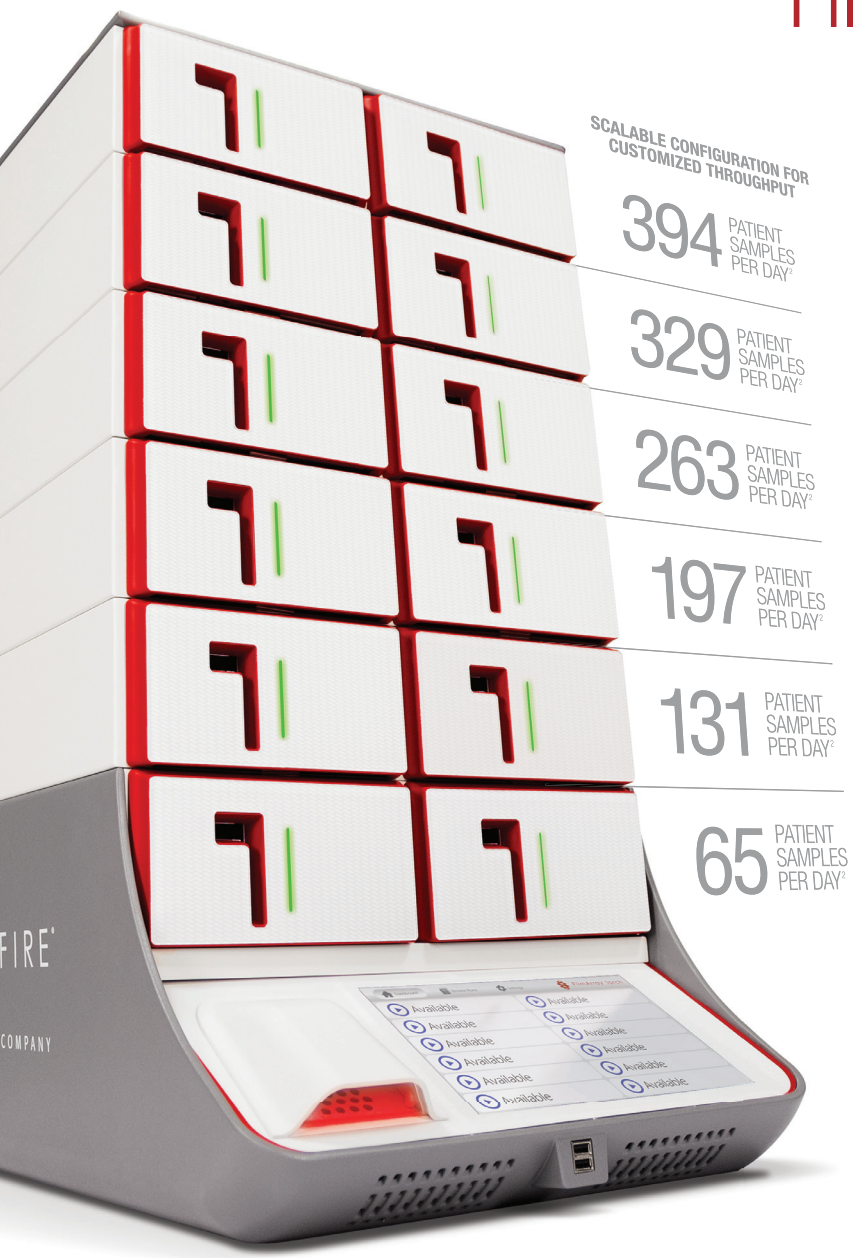

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