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New ways of approaching sepsis will improve patient outcomes
By Joseph Chiweshe, MD, MPH, and Suzanne Ekelund, MSc

Direct-from-whole-blood testing will speed sepsis diagnosis
By Thomas J. Lowery, PhD

CE Test
Tests can be taken online or by mail. See page 20 for testing and payment details.

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Breaking the dragon

This morning I came across a disturbing headline while drafting Labline, MLO’s daily e-newsletter: “Increasingly popular practice of inhaling heroin linked to severe brain damage.” I grimaced at the thought. What kind of skills and resources do laboratorians need to deal with this somber problem? Flashback to 1994. Myself, along with everyone else in the movie theater, simultaneously gasped in horror as Uma Thurman’s character in Pulp Fiction discovers a baggie filled with what she thinks is cocaine, and continues to snort mass amounts, only to realize that something is very wrong—she has inhaled morphine—and falls into a violent coma. Mass confusion ensues and the audience is paralyzed in fear. Of course, in Hollywood, the pretty wife of a renowned mobster miraculously recovers with an emergency shot of adrenaline directly to the heart and she lives, with, we assume, no brain damage. In reality, not so much.

Morphine and heroin are both well-known narcotic drugs. They are similar substances, with enough overlap in molecular structure, mechanism of action, and range of effects to blur the distinction between the two. Both are opioids, which reduce pain perception in the brain.

Inhaled heroin use now represents a global phenomenon and is approaching epidemic levels east of the Mississippi River as well as among urban youth. Chasing the dragon (CTD), as it is called, is the process of heating heroin and inhaling its fumes. This method of heroin use has greater availability, greater ease of administration, and an impressive high comparable to sniffing or snorting. Although it has a safer infectious profile compared to heroin injection, it often has catastrophic brain complications.

Three out of four heroin users start off abusing prescription opioids. Today’s typical heroin addict starts using around age 23, is more likely to live in affluent suburbs, and was likely unwittingly led to heroin through painkillers prescribed by his or her doctor. According to the CDC, the number of overdose deaths related to heroin increased by 533% between 2002 and 2016, from an estimated 2,089 in 2002 to 13,219 in 2016. In terms of regulation and funding, the 21st Century Cures Act, passed in 2016, allocated $1 billion over two years in opioid crisis grants to states, providing funding for expanded treatment and prevention programs. In April 2017, Health and Human Services announced the distribution of the first round of $485 million in grants to all 50 states and U.S. territories. In August 2017, the launch of an Opioid Fraud and Abuse Detection Unit within the Department of Justice was opened. State legislators are introducing measures to regulate pain clinics and limit the quantity of opioids that doctors can dispense. As recently as last month, the White House announced a new multimillion dollar public awareness advertising campaign to combat opioid addiction. The first four ads of the campaign are all based on true stories illustrating the extreme lengths young adults have gone to get a hold of the powerful drugs.

The government appears to be trying, and the long-term horizon sounds somewhat promising, but what can be done now? What, if any, things can medical laboratorians do to assist in the dire issue of chemical addiction and its disabling, and often deadly, effect on the human race?

Aply, this year’s AACC president’s session at the 70th AACC Annual Scientific Meeting & Clinical Lab Expo in Chicago will explore the role of clinical labs in solving the opioid epidemic in the United States, and what strategies are underway to combat the misuse of these drugs.

I, for one, will be in attendance. I’ll save you a seat.
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**Fast Facts**

**Sepsis**

1. Sepsis is the number-one leading cause of hospital deaths in the United States.

80 percent

of sepsis deaths could be prevented with rapid diagnosis and treatment.

8 percent

is the increase in mortality for every hour that sepsis treatment is delayed.

62 percent

of people hospitalized with sepsis are re-hospitalized within 30 days.

26 million

is the number of people affected by sepsis worldwide every year.

5 million

is the number of children who die of sepsis each year.

More than 1.6 million

is the number of people diagnosed with sepsis in the U.S. each year.

258,000

people die from sepsis in the U.S. each year.

75,000

is the number of maternal deaths from sepsis worldwide each year.

$18,400

is the average hospitalization cost of a sepsis patient in the U.S., which is double the average cost per stay of all other conditions.

**Zika virus**

Undetected Zika infections may be triggering miscarriages and stillbirths. A collaborative study among six of the National Primate Research Centers shows pregnancy loss due to Zika A infections that don’t cause women any symptoms may be a common but unrecognized cause of miscarriages and stillbirths.

Collecting data from several species of nonhuman primates (rhesus macaques, pigtail macaques, and marmosets), scientists found that 26 percent of female nonhuman primates inoculated with Asian/ American Zika virus (ZIKV) in the early stages of pregnancy experienced miscarriage or stillbirth later, despite the fact that the animals showed few clinical signs of infection.

During the pregnancies of the Zika-infected monkeys, scientists monitored their progress through ultrasounds, amniocentesis, and blood draws.

“The primary conclusion from this multi-center study with important implications for pregnant women infected with ZIKV is that stillbirth and miscarriage occur more frequently in infected nonhuman primates than animals not exposed to the virus,” explains lead author Dawn Dudley, PhD, with the Wisconsin National Primate Research Center.

The study is published in the journal *Nature Medicine*. The authors conclude that “the high rates of fetal loss among ZIKV-infected nonhuman primates (NHP) pregnancies raise concern that Zika-associated pregnancy loss in humans may be more frequent than currently thought.”

The results parallel human reports of more significant adverse outcomes in babies exposed to ZIKV during the first trimester. No treatments or vaccines for Zika exist, although scientists are experimenting to find ways to cope with this emerging mosquito-borne infectious disease.

**HPV**

No link between HPV vaccination and risk of autoimmune disorders. A new study in the *Canadian Medical Association Journal* (CMAJ) found no increased risk of autoimmune disorders in girls who received quadrivalent human papillomavirus (HPV4) vaccination, adding to the body of evidence for the safety of the vaccine.

Human papillomavirus (HPV) is the most common sexually transmitted disease (STD) worldwide, affecting 50 percent to 75 percent of sexually active people. The HPV4 vaccine is effective at protecting against 90 percent of the strains that cause cervical and anal cancer. Despite studies showing the safety of the vaccine, there have been concerns about a possible link to autoimmune disorders.

For the study, researchers used a repository of 24-hour urine samples collected prior to surgery and annually thereafter in 26 patients, 16 who developed osteolysis and 10 who did not.

The levels of certain markers helped the investigators identify patients at risk for osteolysis long before the emergence of signs through imaging tests—in some cases, six years before a diagnosis was made. Although single markers showed moderate accuracy, the combination of α-CTX, a bone resorption marker, and IL-6, an inflammatory marker, led to high accuracy in the differentiation of patients who eventually developed osteolysis from those with no signs of osteolysis.

“We are hopeful that early biomarkers for implant loosening will alert surgeons to be especially vigilant in their follow-up of at-risk patients and may eventually lead to treatments delaying or avoiding the need for revision surgery,” says senior author Dr. D. Rick Sumner, of Rush University Medical Center, in Chicago.

“Perhaps even more intriguing is that the two biomarkers we identified also differed before surgery among patients who eventually developed peri-implant osteolysis and those who did not, supporting the concept that other researchers have proposed of genetic risk factors for loosening.”

**Chemistry**

Urinary markers predict bone problems after hip replacement. In a study published in the *Journal of Orthopaedic Research*, investigators have identified urinary markers that differentiate total hip replacement patients who eventually develop bone tissue destruction, or osteolysis, from patients who do not.

To determine whether the HPV4 vaccination triggered autoimmune conditions such as lupus, rheumatoid arthritis, type 1 diabetes, and multiple sclerosis, researchers looked at data on 290,939 girls aged 12 to 17 years.
in Ontario who were eligible for vaccination between 2007 and 2013. Of the total 180,819 girls who received the HPV4 (Gardasil and Merck) vaccination in school-based clinics, there were 681 diagnosed cases of autoimmune disorders between one week and two months after vaccination. This rate is consistent with the general rate of diagnosed cases in this age group.

**Hematology**

**Scientists create blood with potential for future treatments.** Researchers at Stanley Manne Children’s Research Institute at Ann & Robert H. Lurie Children’s Hospital of Chicago have discovered a way to increase the efficiency of mature blood production in a dish. They first converted human skin cells to pluripotent stem cells, which are stem cells that have the potential to develop into many different kinds of cells. Then they coaxed these stem cells into becoming a variety of blood cells, including immune cells called “natural killer” cells that are part of the body’s natural defense against cancer and infection. Results of their study, which hold promise for future treatments, were published in *Experimental Hematology*.

While studying the earliest steps of how blood cells develop from pluripotent stem cells, which mimic embryonic stem cells, researchers observed that *in vitro* what is called “definitive” or mature blood forms independently from “primitive” blood, which normally appears early in the development of an embryo. Previously it was not clear whether primitive blood was a precursor to definitive blood or they developed separately.

“In our study we found that developmental pathways toward definitive and primitive blood diverge early in the process, confirming that *in vitro* definitive blood does not develop from primitive blood,” says first author Yekaterina Galat, BS, Research Associate at Manne Research Institute at Lurie Children’s. “We showed that by inhibiting the development of primitive blood we can increase the amount of definitive blood and expand the number of definitive cell types, including red blood cells and immune cells like macrophages and natural killer cells. Our ability to differentiate large quantities of blood cells from induced human pluripotent stem cells could be important for drug testing, pharmaceutical research, and disease modeling, as well as developing therapies for cancer, blood disorders, and immune deficiencies,” says senior author Vasil Galat, PhD.

**Alzheimer’s disease**

**Viruses may play a role in Alzheimer’s disease.** Analysis of large data sets from post-mortem brain samples of people with and without Alzheimer’s disease has revealed new evidence that viral species, particularly herpesviruses, may have a role in Alzheimer’s disease biology.

Researchers funded by the National Institute on Aging, part of the National Institutes of Health, made the discovery by harnessing data from brain banks and cohort studies participating in the Accelerating Medicines Partnership-Alzheimer’s Disease consortium.

Reporting in the journal *Neuron*, the authors emphasize that their findings do not prove that the viruses cause the onset or progression of Alzheimer’s. Rather, the findings show viral DNA sequences and activation of biological networks—the interconnected systems of DNA, RNA, proteins and metabolites—may interact with molecular, genetic, and clinical aspects of Alzheimer’s.

The research group, which included experts from Icahn School of Medicine at Mount Sinai, New York City, and Arizona State University, Phoenix, originally set out to find whether drugs used to treat other diseases can be repurposed for treating Alzheimer’s. They designed their study to map and compare biological networks underlying Alzheimer’s disease.

What they found is that Alzheimer’s biology is likely impacted by a complex constellation of viral and host genetic factors. They also identified specific testable pathways and biological networks.

The researchers used multiple layers of genomic and proteomic data from several NIA-supported brain banks and cohort studies. They began their direct investigation of viral sequences using data from the Mount Sinai Brain Bank and were able to verify their initial observations using datasets from the Religious Orders Study, the Memory and Aging Project, and the Mayo Clinic Brain Bank.

They were then able to incorporate additional data from the Emory Alzheimer’s Disease Research Center to understand viral impacts on protein abundance.

Through the application of sophisticated computational model modeling the researchers made several key findings, including:

• Human herpesvirus 6A and 7 were more abundant in Alzheimer’s disease samples than non-Alzheimer’s.
• There are multiple points of overlap between virus-host interactions and genes associated with Alzheimer’s disease risk.
• Multiple viruses impact the biology of Alzheimer’s disease across domains such as DNA, RNA and proteins.

**Cancer**

**New study shows higher vitamin D levels could lower risk for breast cancer.** Results from a new study published in *PLOS ONE* shows women who have higher vitamin D blood levels have a significantly lower risk for breast cancer.

Analyses were done combining data from two randomized trials conducted at Creighton University with data from a cohort from GrassrootsHealth. The combined data included more than 5,000 women, aged 55 and older, who had a broad range of vitamin D blood levels.

The study found that those women with a blood level of >60 ng/mL had an 80 percent lower risk for breast cancer than those with levels of 20 ng/mL or less. There was a dose response relationship between blood levels of vitamin D and cancer incidence, i.e., between 20 and 60 ng/mL. The higher the blood vitamin D level, the lower the risk of breast cancer.

Joan M. Lappe, PhD, RN, was the principal investigator of the two NIH-funded randomized trials conducted at Creighton University that were included in the study. Her 2007 study on bone health and vitamin D blood levels found, in a secondary analysis, that women who took vitamin D and calcium supplementation for four years had a 60 percent lower risk of all-type cancer than women who took placebos. In her 2017 study of cancer and vitamin D, she and her team found that women with a vitamin D blood level of 55 ng/mL had a 35 percent significantly lower risk for all-type cancer than those with levels of 30 ng/mL. Lappe says the study provides strong support that vitamin D plays an important role in breast cancer prevention and demonstrates that blood levels of vitamin D for breast cancer prevention need to be higher than currently recommended.
New ways of approaching sepsis will improve patient outcomes

By Joseph Chiweshe, MD, MPH, and Suzanne Ekelund, MSc

Sepsis stems from the dysregulation of a host’s inflammatory response to an infection. It is estimated that approximately 1.5 million cases are documented within the United States annually. The associated physiologic and biochemical changes often lead to multiple organ dysfunction, with death as a frequent outcome. The syndrome carries a high mortality rate, claiming the lives of approximately 258,000 people per year. A look at the rates of 27 U.S. hospitals from 2005 to 2014 showed an incremental case increase from 15 to 18.6 per 1,000 hospital admissions, with a corresponding mortality rate of 51 percent.

From an economic standpoint, sepsis places a severe burden on the U.S. healthcare system. It is the most expensive inpatient condition to treat, with annual costs of approximately $24 billion (in 2013). That year, that amount accounted for 6.2 percent of all hospital-related costs; the average patient hospitalization cost over $18,000. The overall observed increase in cases has been attributed to individuals living into older age, with approximately 60 percent to 85 percent of sepsis cases occurring in patients older than 65 years. Globally, a concerted effort has been made to raise sepsis awareness, as projections indicate that the incidence and associated costs of sepsis will continue to increase in the future.

The changing definition of sepsis

The definition of sepsis has evolved over time. Beginning with Sepsis-1 at a 1991 consensus conference, it was developed around the Systemic Inflammatory Response Syndrome (SIRS) criteria. Sepsis-1 was defined as infection or suspected infection leading to SIRS. These criteria included a heart rate greater than 90 beats per minute, a breathing rate greater than 20 breaths per minute, a body temperature greater than 38 degrees or less than 36 degrees Celsius, and a white blood cell count greater than 1200/mm or bandemia greater than 10 percent. Sepsis-2 expanded on Sepsis-1 criteria, but maintained the need for at least two of the SIRS criteria in addition to a suspected or confirmed infection. The most recent Sepsis-3 definition, as of 2016, consists simply of life threatening organ dysfunction caused by a dysregulated host response to infection.

Role of the host immune response

The host immune response plays a crucial role in the progression of sepsis and thus has been an area of increasing study. A patient’s immune system is the first line of defense against offending pathogens and is composed of an innate as well as an adaptive system. The innate system is triggered by foreign pathogens but does not exhibit any memory to antigens, whereas the adaptive system does exhibit memory to prior pathogen stimuli.

The innate system functions through pattern recognition receptors located on the surface of cells that in turn have the capability to initiate signaling cascades responsible for the generation and release of inflammatory cytokines. It is composed of natural killer cells, mast cells, eosinophils, basophils, macrophages, neutrophils, and dendritic cells. These coordinate within the immune system to identify and eliminate potentially infectious pathogens.

In comparison, there are two types of adaptive responses: humoral immunity, via antibody production by B-lymphocytes, and cell-mediated immunity, by T-lymphocytes. Activated monocytes have been associated with adaptive immunity and antigen presentation. In addition to their role in the immune response against infection, they have been implicated in the pathogenesis of several inflammatory disorders, including sepsis.

Limits of microbial detection

As the diagnosis of sepsis is often difficult due to patients having varied presentations, diagnosis generally calls for a combination of clinical, laboratory, and imaging-based modalities. Clinical history provides insight, as there are a number of comorbidities that increase a patient’s risk for sepsis. These include obesity, chronic diseases such as diabetes and HIV, and other disease states such as cancer. Of all the comorbidities, the most significant risk factor appears to be hematologic cancers.

Microbial culture has long been the standard for the detection of bacteria in support of making a clear diagnosis. However, traditional culture tends to be a
time-consuming process that is marred by a high rate of false negatives, particularly in the case of slow-growing organisms or in patients with ongoing antimicrobial regimens. Estimates as low as 30 percent have been quoted for conventional techniques’ ability to detect offending microbes in patients with known infectious sources. Upwards of 25 percent of patients are found to be culture negative. In cases where detection does occur, it has been estimated that gram positive organisms account for 46.8 percent of infections, with gram negatives at 62.2 percent, fungi at 19.4 percent, anaerobes at 4.5 percent, and parasites at 0.7 percent. Patients may carry more than one infectious organism. The most common inciting sites of infection are respiratory, bacteremia (site unspecified), genitourinary, abdominal, and wound/soft tissue, in that order.\(^7\)

In recognition of the limits of microbial detection, there is growing interest in potential alternatives. Among alternatives being investigated are technologies including PCR, microarray analysis, bacteriophage, and microfluidics, including flow cytometry and immunoassays. Another area of interest has been implantable devices such as central venous catheters that are embedded with diagnostic capability. These “smart venous catheters” use the electrical impedance characteristics of bacterial biofilm formation to detect microbial growth.\(^8\)

**Clinical use of biomarkers**

To date, approximately 200 biomarkers have been studied in the evaluation of sepsis. The most frequently used biomarkers are C-reactive protein (CRP), procalcitonin (PCT), and lactate. CRP is synthesized by the liver in response to signaling factors released by macrophages. It can increase 1000-fold in the blood in response to inflammation and infection. The normal test result should be less than 10 milligrams per liter (mg/L).\(^9\) PCT is a precursor to calcitonin, a hormone associated with calcium levels. Its concentration is elevated in circulation in response to inflammation, and in this situation it is not cleaved to calcitonin. Although higher PCT concentrations tend to suggest a systemic bacterial or fungal infection, these levels do not correlate with the severity of sepsis or with mortality.\(^10\) PCT has been increasingly used to trend response to therapy within clinical settings.

Serum lactate is another tool that is being used as a more sensitive marker for potentially impending septic shock. Lactate is formed from the reduction of pyruvate, which is generated largely by anaerobic glycolysis. In tissue hypoxia, lactate is overproduced via increased anaerobic glycolysis and worsens if liver dysfunction and acute kidney injury occur due to a decreased ability to clear lactate from the body.\(^11\)

**Viral and fungal detection**

The majority of sepsis cases are bacterial, and the discernment of bacterial from fungal, or in rare cases viral, sepsis is of importance for appropriate therapy selection and antimicrobial stewardship. Although rare, viruses, particularly influenza viruses, are increasingly a cause of severe sepsis, either directly or as a result of post-viral secondary bacterial infections.\(^12\)

To this end, biomarkers such as IFI27, MxA, 1-3-β-D glucan, and ASPAG are being investigated for their clinical utility. For the IFI27 biomarker, an increased IFI27 gene expression in peripheral blood indicates an immune response to particular respiratory viruses.\(^13\) As for the myxoma resistance protein 1 (MxA), it is
induced during viral infections as well, so MxA testing could be helpful in differentiating between viral and bacterial infections. MxA has also been investigated as a potential viral infection marker in children, at least with RSV and rotavirus. Invasive aspergillosis (IA) is a fungal infection that particularly affects immunocompromised hosts. Several studies have indicated a high incidence of IA in ICU patients. Additionally, prospective surveillance studies among transplant recipients have shown IA to be the most common type of fungal infection among stem cell transplant recipients and the second most common type of fungal infection among solid organ transplant recipients. The U.S. Food and Drug Administration (FDA) approved the detection of galactomannan, a molecule found in the cell wall of Aspergillus species. Serum monitoring of galactomannan can potentially allow initiation of antifungal therapy before life-threatening infection occurs. 1-3-β-D-glucan (BDG) offers another potential target, because it is found as a cell wall component in most fungi, with the exception of the cryptococci, the zygomycetes, and Blastomyces dermatitidis. Cytokines and cell surface receptors Inflammatory marker investigations have been difficult because these markers are shared across a variety of inflammatory conditions and disease states. Cytokine levels for TNF Alpha, IL-6, IL-8, and IL-1B have been shown to elevate as part of the septic response. The most studied of these is IL-6, a pro-inflammatory cytokine produced by lymphocytes, fibroblasts, and monocytes. It has been suggested that IL-6 concentration in sepsis is the best marker of the severity and outcome for sepsis, because it serves as an important mediator during the acute phase response to inflammation in sepsis. In regard to cell surface receptors, one leading candidate is neutrophil CD64 expression, which has so far shown good performance as a potential diagnostic marker in the evaluation of infection and sepsis. Other promising biomarkers Inflammatory response cells like monocytes and neutrophils are also showing promise as aids to diagnosis. Monocytes are large leukocytes that circulate in the peripheral blood and are recruited into tissues at sites of inflammation, where they differentiate into large phagocytic cells called macrophages. Crouser et al’s feasibility study showed that monocyte distribution width (MDW), compared with other potential early sepsis parameters, best distinguished sepsis from SIRS and severe sepsis from noninfected ED patients, with a sensitivity of 77 percent, specificity of 73 percent, negative predictive value of 98 percent, and positive predictive value of 21 percent. Human neutrophil lipocalin (HNL), originating from the neutrophils, has been shown to be useful in sepsis, but, so far, the number of relevant studies is limited. HNL is the same as neutrophil gelatinase-associated lipocalin (NGAL), which is a potential biomarker for predicting acute kidney injury (AKI). However, NGAL used for AKI originates from the kidneys. The way to distinguish the origin continued on page 14
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of NGAL is to look at the form of the molecule. If there is a predominant amount of monomeric and/or heterodimeric NGAL as compared with monomeric NGAL, that indicates NGAL originating from the kidney; an equal or predominant amount of homodimeric NGAL, as compared with monomeric or heterodimeric NGAL, indicates NGAL originating in the neutrophils. (The heteromorphic form is NGAL linked to matrix metalloproteinase-9.) It is common practice to call the marker HNL when used in sepsis and NGAL when used in AKI.

Another approach involves the combination of biomarkers. The diagnostic role of PCT and MR-proADM, both in sepsis and in localized infections, together with their contribution to effective antibiotic therapy, has been evaluated. The combined use of PCT and MR-proADM increased the post-test probability of the diagnosis of bacterial infections compared to PCT alone. In addition, several studies have investigated the prognostic value of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) in patients with infection. Elevated sTREM-1 concentrations had a moderate prognostic significance in assessing the mortality of infection in adult patients. However, sTREM-1 alone is insufficient to predict mortality as a biomarker.

In summary, the continued efforts both to raise sepsis awareness and to improve upon our current diagnostic approaches are of vital importance. As the Sepsis-3 definition points to life-threatening organ dysfunction caused by a dysregulated host response to infection, the medical community now, more than ever, needs to be vigilant to those cases that present with early and often difficult-to-navigate constellations of signs and symptoms. There must be a paradigm shift in how the individual sepsis patient is viewed, as there are many subgroups that will remain challenging to distinguish based on clinical observation alone. This calls for refinement of diagnostic tools and biomarkers that can aid clinical decision support as well as better optimize therapeutic intervention for better patient outcomes.

Additionally, making it easier for providers to access the latest in guidelines and research via mobile technologies such as the clinical sepsis guide app will hopefully aid those on the front lines of the battle for better sepsis care and outcomes. If we are to move the needle on sepsis, it will call for multidisciplinary and team-based approaches, working in concert with all stakeholders in the sepsis ecosystem.

REFERENCES
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mid the many complexities involved in the management of patients with sepsis, the key question is simple: how soon can the correct treatment be initiated? Sepsis is a race against time, because survival rates deteriorate by eight percent for every hour of inappropriate treatment.1 If targeted therapy is provided within a few hours of patient presentation, the progression of a bloodstream infection to sepsis can be prevented, reducing the likelihood of health consequences that are always significant and often fatal.

Lee Health’s experience
Laboratorians at Lee Health System in southwest Florida are leading the way by slashing the time to the detection of sepsis-causing pathogens with blood culture-independent, direct-from-whole-blood testing. The new approach and technology enable clinical health professionals to begin appropriate targeted therapy much sooner than they could with traditional blood culture-dependent assays. In a recent study published in the Journal of Antimicrobial Chemotherapy, investigators at Lee Health found that patients with potentially deadly infections received targeted therapy 28 hours faster with direct-from-whole-blood tests.2

Using the FDA-cleared direct-from-whole-blood fungal panel, the lab also contributed to the hospital’s cost stewardship initiatives and drove savings for the hospital, because faster negative results reduced unnecessary antimicrobial therapy by an average of four days and an estimated cost saving of $280 per patient. Further, Lee Health’s clinical investigators presented research on a new bacteria assay at the May 2018 “Making a Difference in Infectious Disease” (MAD-ID) annual meeting. Lee Health reported that “final results were realized within four hours from direct-from-whole-blood testing” and that a positive result was received 20 hours sooner than a positive blood culture result and a negative result was received 122 hours sooner than a negative blood culture result, a statistical significance of p<0.001.3 The authors identified 37 opportunities for antibiotic de-escalation due to the direct-from-whole-blood testing, further bolstering their stewardship program.

Blood culture: uses and limits
Targeted therapy requires knowing which specific pathogen is at work, and the experience at Lee Health represents a departure from the conventional way of identifying sepsis-causing pathogens in the bloodstream. There have been many important advances over the years to improve the blood culturing process and speed up the post-blood culture tests for identification and antimicrobial susceptibility testing. However, these tests remain limited by the necessarily long time to positivity for a blood culture result, which can be more than 24 hours because blood culture requires growing pathogen cells. In addition, blood culture often misses 35 percent to 50 percent of the organisms for the first blood draw.4,5 The number of cells present after a blood culture positive are typically in the 10,000 to 1,000,000 CFU/mL range, which is a more than 1,000-fold increase in clinically relevant levels of sepsis-causing pathogens in the blood (1-15 CFU/ml). The wait for blood culture positivity, if the cells adequately grow at all, and the time needed for subsequent species identification force clinicians to delay targeted therapy during a critical window of time when a patient is suspected of sepsis.

Direct-from-whole-blood testing will speed sepsis diagnosis
By Thomas J. Lowery, PhD

Figure 1. Comparison of sepsis pathogen identification methods.
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It will likely be only a matter of time before whole-blood diagnostics become part of the standard of care for patients suspected of sepsis and bloodstream infections. The opportunities for both improved patient care and cost savings are just too great to be ignored. A major milestone for this advance will be the addition of such diagnostics into sepsis protocols—running these tests at the same time as cultures and lactates are run. Indeed, this is already happening in some hospitals.

Cost pressures for labs are ever-increasing, so the economic justification for any new test must be rigorous. In the field of sepsis-related infections, however, the potential to reduce hospital and intensive care unit (ICU) length of stay, while reducing the use of drugs, is compelling. Importantly, there are also potential CPT reimbursement codes for direct-from-whole-blood tests in the outpatient setting.

The value of the new tests will be measured by the impact they will have on the amount of money that hospitals spend for sepsis, which is now the most expensive inpatient cost in the United States.

The complete measure of the new assays, however, will be their impact on the sepsis public health crisis as a whole. The implementation of rapid results and treatment is uniquely positioned to strike a huge blow to sepsis and the hundreds of thousands of lives it takes each year. A shift to more accurate and faster testing can potentially result in thousands of patients going home to their families instead of the tragic and avoidable, alternative.

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Looking ahead

Looking ahead

A new breakthrough in management for patients suspected of sepsis and bloodstream infections must be driven by the lab through rapid identification of infection-causing species without the wait for blood cultures. The lab is a pivotal member of any critical care team, and it can take patient care to a new level: rapid results from the lab can improve the patient treatment pathway by augmenting existing algorithms to enable treating physicians to make a targeted attack on infections. There are numerous targeted potential pharmaceutical options, but they require specific information from the lab on the infection to provide full value.

In 2014, the FDA cleared the first direct-from-whole-blood test, which provides fungal species identification results in three to five hours. In clinical use, rapid identification has enabled targeted therapy on Day 0 and delivered cost savings to the pharmacy budget, as reported in peer-reviewed studies published over the last year. A bacteria panel, cleared by the FDA in May 2018, identifies five of the most common and deadly sepsis-causing species of bacteria: Enterococcus faecium, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Staphylococcus aureus. In a prospective pivotal trial that included 11 centers and more than 1,400 subjects, test results were achieved 2.5 days faster than with blood culture with excellent accuracy, including overall average sensitivity of 90 percent and overall average specificity of 98 percent. In addition, 69 patient infections were detected by the new test that were missed by a blood culture that was run at the same time. The technology enabling this advance combines magnetic resonance with advances in nanotechnology to measure how water molecules react in the presence of magnetic fields. In addition to the manufacturer of the cleared bacterial and fungal tests, a number of diagnostics companies, both large and small, have recognized the clinical value of the approach and are working to enter the emerging direct-from-whole-blood market.
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TEST QUESTIONS

1. How many cases of sepsis are documented in the United States each year?
   - a. 0.5 million
   - b. 1.5 million
   - c. 2.5 million
   - d. 3 million

2. What is the main pathology associated with sepsis?
   - a. kidney failure
   - b. respiratory failure
   - c. multiple organ failure
   - d. none of the above

3. The syndrome of sepsis carries a high mortality rate and is the most expensive inpatient medical condition to treat.
   - a. True
   - b. False

4. Sepsis most commonly occurs in
   - a. neonates.
   - b. infants.
   - c. young adults.
   - d. the elderly.

5. Which is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection?
   - a. Sepsis-1
   - b. Sepsis-2
   - c. Sepsis-3
   - d. Sepsis-4

6. The innate immune response helps to eliminate infectious pathogens through
   - a. signaling cascades on cell surface receptors that generate and release inflammatory cytokines.
   - b. the activation of monocytes and antigen presentation.
   - c. antibody production of B-lymphocytes.
   - d. none of the above

7. The innate immune response has been implicated in the pathogenesis of many inflammatory disorders, including sepsis.
   - a. True
   - b. False

8. What type of cell has been associated with adaptive immunity antigen presentation and plays a role in immunity against sepsis infections?
   - a. neutrophil
   - b. basophil
   - c. B-lymphocyte
   - d. monocyte

9. Which modality/modalities should a sepsis diagnosis include?
   - a. laboratory
   - b. clinical
   - c. imaging
   - d. all of the above

10. Which risk factor appears to be the most significant in the development of sepsis?
    - a. diabetes
    - b. obesity
    - c. hematologic cancers
    - d. HIV

11. What factors contribute to concerns about microbial culture being the standard for detection of infection?
    - a. It is time-consuming and requires specialized training.
    - b. It requires specialized training and has a high cost.
    - c. It is time-consuming and has a high rate of false negatives.
    - d. It requires specialized training and has a high rate of false negatives.

12. The five most common sites of sepsis infection, from first through fifth, are:
    - a. abdominal, wound/soft tissue, respiratory, bacteremia (site unspecified), genitourinary
    - b. respiratory, bacteremia (site unspecified), genitourinary, abdominal, wound/soft tissue
    - c. bacteremia (site unspecified), genitourinary, respiratory, wound/soft tissue, abdominal
    - d. none of the above

13. Central venous catheters with embedded diagnostic capability are being explored as an alternative to microbial detection for the diagnosis of sepsis.
    - a. True
    - b. False

14. Which biomarker is synthesized by the liver in response to factors released by macrophages and can be measured to detect inflammation and infection?
    - a. TSH
    - b. CRP
    - c. PCT
    - d. lactate

15. Which biomarker is used to document response to therapy within clinical settings?
    - a. PCT
    - b. CRP
    - c. lactate
    - d. LDH

16. Which biomarker is used as a sensitive marker for the potential development of septic shock?
    - a. LDH
    - b. PCT
    - c. lactate
    - d. CRP

17. Which virus is an increasing cause of sepsis, and which biomarkers are being studied for their clinical utility?
    - a. influenza; IFI27, MXA, 1,3-β-glucan, ASPAG
    - b. norovirus; IFI27, MXA, β-D-glucan, ASPAG
    - c. rhinovirus; IFI27, MXA, 1,3-β-glucan, ASPAG
    - d. RSV; IFI27, MXA, 1,3-β-glucan, ASPAG

18. Which molecule is found in most fungi and could potentially be used for fungal infection detection?
    - a. β-D-glucan
    - b. 1,3-β-glucan
    - c. 1,3-D-glucan
    - d. IFI27

19. Studies suggest that the best cytokine marker to be used in the investigation of the severity and outcome for sepsis is
    - a. TNF Alpha.
    - b. IL-3.
    - c. IL-8.
    - d. IL-6.

20. Biomarkers are being studied for sepsis detection and diagnosis, including those from blood cells, and it is believed that a combo of biomarkers might provide the best outcome.
    - a. True
    - b. False

P = Poor; E = Excellent

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   - P 1 2 3 4 5 E

2. To what extent was the article well-organized and readable?
   - P 1 2 3 4 5 E

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Digital influenza surveillance enters the laboratory

John Tamerius, PhD, and Sushruth K. Reddy, BS

Influenza viruses cause a substantial burden of illness each year in the United States, estimated at 9.2 to 35.6 million cases of infection, 4.3 to 16.7 million clinic visits, 140,000 to 710,000 hospitalizations, and 12,000 to 56,000 deaths annually. We are coming off a particularly aggressive influenza season, with peak percentage of outpatient visits for influenza-like illness (ILI) at the third-highest recorded since 1997-98. Mortality attributed to pneumonia and influenza peaked at 10.8 percent, the highest percentage reported since the 2014-15 season, and included the most reported pediatric deaths (171) since the 2012-13 season. The hospitalization rate for laboratory-confirmed influenza for all ages combined was the highest documented in twelve years. The overall costs will likely range from $50 to 87 billion when economic analyses for the past influenza season are completed.

Influenza surveillance and the CDC

Given the magnitude of this challenge, influenza surveillance plays a vital role across the healthcare landscape, including hospitals, clinics, urgent care centers, and laboratories, where its benefits include:

• Aiding healthcare and laboratory administrators to predict surge demand
• Promoting timely vaccination campaigns
• Facilitating hospital and laboratory human resource planning
• Enabling alerts and educational notices for the healthcare community, patients, and public
• Stimulating pharmacy resource planning and allocations.

The U.S. Centers for Disease Control and Surveillance (CDC) developed its first surveillance program nearly 70 years ago, and today it has expanded to cover many infectious diseases. Confronted with influenza epidemics annually, the agency must monitor these constantly changing viruses throughout the year, and in collaboration with public health partners and diagnostic laboratories, the CDC collects and analyzes data from multiple surveillance systems to determine when, where, and what viruses are circulating. These efforts track currently circulating influenza viruses, identify novel influenza viruses of public health importance, monitor antiviral drug susceptibility, and characterize circulating seasonal viruses for guiding influenza vaccine virus selection and production. The CDC communicates this and a wealth of additional information to nationwide public health officials, clinical laboratory management, physicians, hospital administrators, pharmacy chains, antiviral manufacturers, and the public each year. Timely and effective communication is key, and it is always a challenge. The current CDC program has five principle categories for influenza surveillance.

CDC’s ILINet surveillance category

The U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet) arm compiles weekly reports from more than 2,800 healthcare providers on the total number of physician visits and number of these visits associated with an ILI, defined as fever and cough and/or sore throat without an identified cause (other than influenza). During the 2017-18 influenza season alone, ILINet compiled data for more than 1.1 million patients with ILI among nearly 34 million patients evaluated in outpatient clinics across the U.S. This (and the CDC’s other surveillance arms) has provided remarkable benefit to the nation and constitutes a prime feature of the FluView Reports that the CDC issues weekly during the influenza season from October to May.

Figure 1. Five principle categories for influenza surveillance.
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Despite its undeniable merits, however, ILINet has shortcomings, too:

• The fact that contributions from sentinel sites are voluntary, often delayed, or incomplete
• Reporting delays that often extend to two weeks, and are often revised weeks later as additional results become available\(^7\).
• Heavy reliance on clinical criteria alone (limited specificity; many respiratory conditions mimic symptoms of influenza infection)\(^9\)
• Variability in clinical knowledge, background, and experience among outpatient care centers.\(^10\)

**CDC’s nondigital laboratory-based surveillance**

Understanding the shortcomings of surveillance methods based largely on clinical criteria alone, the CDC has begun to collect and analyze laboratory data from a variety of sources. The U.S. World Health Organization Collaborating Laboratories System, in conjunction with the National Respiratory and Enteric Virus Surveillance System (WHO/NREVSS), collects weekly records of the numbers and results of diagnostic tests for influenza from approximately 100 public health laboratories and 300 additional clinical laboratories representing all fifty states. During the 2017-18 influenza season, nearly 1.2 million test results were submitted by WHO/NREVSS laboratories.\(^11\) These efforts have highlighted a path for improved and more accurate influenza surveillance and prompted additional undertakings.

The CDC is now working diligently with state public health agencies and other laboratories to seek and incorporate more laboratory data directly into its evolving surveillance program. With advances in both molecular assays and rapid antigen detection tests (RADT) (including new FDA standards for RADT performance\(^12\)), time to result and clinical accuracy may be improved, and, with expanding data procurement from clinical and state laboratories, the needed analyses may be executed more quickly and efficiently and with greater precision. In turn, this developing program should provide a more reliable estimation of the prevalence and magnitude of illness in a community than have previous efforts. However, deficiencies remain in these approaches as well:

• There is a lack of standardized testing method(s) or reporting structure due to variability in state regulations.
• There is variability in testing methodologies among participating laboratories.
• Eight states are not presently participating.
• Technology costs and resource allocation present challenges to many laboratories and public health entities.
• Reporting delays still occur, usually one week.
• Insufficient state and federal budgets impede implementation.

**Nonlaboratory digital surveillance**

Given some of the acknowledged deficiencies of current surveillance systems, especially in the timely delivery of data, efforts to use digital technology to alleviate or overcome some of the continuing challenges have evolved. Five basic categories have been identified,\(^13\)\(^-\)\(^16\) four of which are nonlaboratory-based: participatory surveillance systems; internet news data systems; search query systems; and social media systems. To varying extents, these systems rely heavily on non-standardized information originating in nonlaboratory settings. They involve the capture and use of information from the internet that is based on single messages, word queries, references in news bulletins, self-assessment of illness by members of the public, and comments on social media platforms. Such data are potentially unreliable.

Several such entities are currently in use. In an effort to improve their specificity and overall accuracy,\(^17\)\(^,\)\(^18\) some supplement their data and conclusions with publically available information that is provided by FluView and other state and county public health agencies. Despite their handicaps, these non-laboratory digital surveillance systems hold promise to provide meaningful contributions to the nation’s influenza surveillance as system capabilities and fail-safe mechanisms advance.

**Instrument-based digital surveillance**

The fifth digitally-based surveillance system pertains to diagnostic instrument-based systems, an increasing number of which are used in diagnostic laboratories across the nation. Different diagnostic companies are introducing diagnostic instruments with their own versions of digital or wireless surveillance, including the transmission of influenza results through the LIS systems in medical centers and hospitals.\(^19\)\(^,\)\(^20\) Other systems feature the wireless transmission of test results to clouds for subsequent analysis and deployment to public health or participating healthcare facilities. Notably, these functions are outside the control or guidance of the CDC and other public health agencies, but they are capable of addressing some of the shortcomings of existing efforts by public health and other digital systems mentioned above.

Transmittable data, depending on source, may include positive and negative test results, names of operators, precise instrument locations, QC results, instrument calibration results, regional trends, and comparisons of results from different facilities in the same or different geographic or demographic settings. These data enable trend comparisons by period (week, month, and year) and can serve to help laboratory managers anticipate labor and test kit needs and other materials required for their operations. Results are generally transmitted in near real-time within seconds or minutes. Transmitted results are HIPAA-compliant and are untraceable back to the patient. Providing all test results in near real-time, these instrument-based systems overcome the major shortcoming of ILINet and other public health efforts. Their results are timely and comprehensive and give a reliable indication of disease prevalence in a region, as both positive and negative results are transmitted. In turn, near real-time data and subsequent analysis allow for expedited response by public health officials in the midst of a rapidly evolving respiratory season.

Some systems also provide pre-programmed analyses available to laboratory staff immediately upon accessing. Recently, some systems have been modified to automatically forward QC results and/or regional and national test results on a frequent basis; this automatic delivery of near real-time surveillance (updates available on a daily basis) greatly enhances their utility and appeal to healthcare stakeholders, including laboratory management and staff, physicians, and hospital...
administrators. Some digital systems now include activity maps, providing the locations from which influenza results are emanating, the magnitude of testing, and the percentage of positive test results—that is, a direct indication of regional disease prevalence.

Like all surveillance systems, these also have their shortcomings: Many lack comprehensive geographic coverage (dependent on commercial placements); any variability in clinical knowledge, background, policy, and experience at outpatients and/or point-of-care centers may affect testing patterns; the reliability of results depends on the clinical accuracy and performance capabilities of commercial tests being used; the reliability also depends on adherence to assay procedure by operators. Additionally, although these systems provide great value for assessment of disease spread, prevalence, and potentially even severity, they do not necessarily facilitate the delivery of specimens to public health agencies for characterization of circulating influenza strains.

Evolution of influenza surveillance

Given advancing efforts to develop and deploy instrument-based digital systems (including molecular and immunoassay systems) which may be integrated into current and future surveillance programs, industry is likely to work with public health and other government agencies in the future to help provide an overall benefit to the public. Ease of use and reliability of this technology will continue to improve. With expanding geographic coverage, such comprehensive real-time data could have a profound effect on epidemiology research in general and, importantly, could impact the efforts of computational biologists and sophisticated statisticians to forecast influenza accuracy and severity.20-22 As advanced computational methods on high-capacity computers become more broadly available, it seems likely that hybrid systems will be developed that will use digitally-based big-data from diverse sources and exploit the unique advantages of each system.23 Instrument-based systems employed in laboratories will be a key element in such efforts.

The need for influenza surveillance has driven much of the development of these digital systems. Given the rapid advances in development and application of these platforms, it is very likely that such systems will be applied to other infectious diseases, especially those with seasonal features like RSV, group A strep, and Lyme disease.

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Sushrut K. Reddy, BS, serves as Manager of Strategic and External Affairs for Quidel Corporation. He has specialized in characterization of novel infectious disease applications for point-of-care diagnostic devices, with primary focus on Sofia FIA diagnostic platform.
A deadly influenza season offers lessons for the community

By Hollis Batterman, MD

The influenza season of 2017-2018 was marked by widespread influenza activity across the United States. The powerful H3N2 strain, which was the biggest culprit of influenza infection, was reported in almost every state—a first in the 13 years that the Centers for Disease Control and Prevention (CDC) has been monitoring influenza activity in the country. This past influenza season was arguably one of the worst on record. Tens of thousands of people were hospitalized with influenza, and scores of deaths occurred.

Now that the next influenza season is rapidly approaching, we in the medical and laboratory communities must reflect upon lessons learned to ensure that we are well prepared and armed with insights to make the best decisions for our patients.

Lesson 1: Be mindful of vulnerable populations

Influenza infection rates vary widely among populations with different characteristics. Populations at higher risk for influenza infection include the elderly, pregnant women, and children. Individuals may also be at increased risk of influenza complications as a result of such medical factors as chronic heart, kidney, liver, or lung disease; certain blood disorders (such as sickle cell disease); extreme obesity; metabolic disorders (such as diabetes); or neurologic or neurodevelopmental conditions.

According to the CDC, most people with influenza will have mild illness, will not need medical care or antiviral drugs, and will recover in less than two weeks. However, vulnerable populations are more likely to have influenza complications that can result in hospitalization and sometimes death. For these patients, it is important to consider a more aggressive approach to testing and treatment. Each individual is unique, so the care should be, too.

Lesson 2: Confirm with testing

While many clinicians may treat patients who present with an influenza-like illness empirically, there are many test choices available, and there are compelling reasons to consider testing. Several types of influenza tests are available to clinicians, with varying strengths and limitations. Choosing the right test enables clinicians to provide the best possible care to each patient. Options include viral cell cultures; immunochromatographic assays, known as rapid influenza diagnostic tests (RIDTs); and molecular tests.

In viral cell culturing, specimens are collected by swab or other methods as bronchial wash. The specimens are then incubated in a cell-based culture system over a period of several days, while being monitored for cellular response to viral infection. Viral cultures can distinguish between influenza A and B. They generally take three to 10 days to produce a result, which makes them less than optimal for immediate treatment decisions, especially in vulnerable populations.

RIDTs are immunochromatographic assays designed to detect the viral antigens in a patient’s respiratory specimen resulting from an immune response to infection with the influenza virus. These tests can be conducted at the point of care, and results are typically available within 30 minutes. However, not all RIDTs can distinguish between influenza A and B, nor distinguish among the various strains of influenza A. Clinicians who choose to use RIDTs should understand the strengths and limitations of the test prior to use.

Molecular tests, which are recommended in current testing guidelines, are also performed on nasopharyngeal swab specimens, or specimens from other respiratory sources such as lower respiratory sources, and are intended to detect the presence of influenza viral RNA in those specimens. Molecular tests are the most sensitive and specific tests for detecting influenza viruses. Molecular test sensitivity for influenza A and B can be as high as 100 percent, and test specificity for influenza A and B ranges from 99.3 percent to 100 percent.

Lesson 3: Don’t rely solely on RIDTs

Although RIDTs offer some value for everyday clinical practice, using them as the sole diagnostic for influenza in patients carries risks. While the specificity of RIDTs generally falls in the range of 90 percent to 95 percent, the sensitivity of RIDTs is often much lower, ranging from 50 percent to 70 percent. This can result in substantial numbers of false negative results occurring more commonly than false positive results during active influenza season.

Because of the known low sensitivity of RIDTs, the CDC recommends that clinicians consider follow-up negative results with confirmatory tests (molecular or viral culture) if a laboratory-confirmed influenza diagnosis is desired.

Molecular testing that utilizes reverse transcription polymerase chain reaction (RT-PCR) has the highest degree of sensitivity and specificity, and is now considered by many to be the “gold standard” for influenza testing. In addition, molecular testing based on PCR amplification technologies has been shown to be the most cost-effective option for guiding the initiation of antiviral therapy in older adults.

However, RT-PCR has its drawbacks. It requires sophisticated expertise and laboratory technology typically reserved for hospital and academic settings and commercial diagnostic companies. And while some rapid molecular tests can provide results in one hour, patient specimens must typically be transferred to these specialized laboratories for processing. When it comes to influenza, both speed and accuracy of diagnosis are vital. There is no overestimating the value of an accurate diagnosis—as was tragically evident in reports of deaths of some individuals, including children, who were falsely diagnosed as influenza-negative during the 2017-2018 influenza season.

Lesson 4: Don’t over-treat

Treating for influenza without concurrent testing to confirm an influenza diagnosis can put individuals who do not actually have influenza (for example, those with respiratory syncytial virus) at increased risk for side effects from unwarranted treatment with antiviral agents. Treating without a confirmed diagnosis can also result in delayed or missed treatment for
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Choosing diagnostic tests to determine the viral cause of influenza-like illness

By Caroline Hentzen, PhD

Viruses causing influenza-like illness (ILI) can result in overlapping symptomology that makes accurate diagnoses challenging if based on clinical presentation alone. For more definitive diagnoses of patients with ILI, clinical diagnostic testing must be undertaken, and molecular diagnostic assays offer an ideal combination of accuracy, sensitivity, and speed for achieving this purpose.

Without clinical testing, patients with symptoms of fever of 100°F/37.8°C or higher and a cough and/or sore throat without a known cause other than influenza may be preliminarily diagnosed with ILI. Common viruses known to cause ILI include adenovirus (AdV), influenza (flu), human metapneumovirus (hMPV), parainfluenza virus (PIV), respiratory syncytial virus (RSV), and rhinovirus (RV).

Of the three types of influenza that infect humans, only types A and B cause pandemics and therefore require readily available diagnostic tests. Although all four types of PIV (1-4) commonly infect children, PIV can cause ILI in adults as well. Infections by the different PIV types may vary in clinical and epidemiological features, and testing for each type is recommended.

Benefits of molecular diagnostics

An accurate and rapid diagnosis of the agent responsible for a given case of ILI is crucial for directing appropriate treatment of patients and executing precautions to prevent the spread of infection. Turnaround time for laboratory tests is, therefore, a vital consideration when choosing tests to support clinical decision making regarding patients with ILI. Diagnostic capabilities have evolved in recent years. In vitro molecular diagnostic tests, particularly automated tests, provide results more rapidly than traditional culture methods, typically within hours of a sample being extracted, rather than days to weeks.

Although rapid influenza diagnostic tests provide results in approximately 15 minutes, these immunoassays have limited sensitivity compared with molecular or culture-based tests; therefore, a negative result does not exclude actual influenza infection in patients with ILI, particularly when community prevalence of influenza is high.

Additional benefits of timely and correct diagnoses of the causal ILI virus include decreased total costs of care, reduced inappropriate use of antibiotics which might lead to antimicrobial resistance, and surveillance of circulating viruses for public health authorities.

Considerations for choosing viral tests

Laboratories in various settings now have access to a broad array of options when selecting molecular tests for respiratory viruses. Some broad-based panels contain tests for 20 or more pathogens, whereas other manufacturers offer individual tests for each agent or small panels with two or three analytes.

Unless justified by clinical need (e.g., immunocompromised patients), testing with a comprehensive panel of ILI-causing viruses may not be cost-effective. For reimbursement purposes, only testing for the most likely agents may be deemed medically necessary, and laboratories that employ only large, multiplexed panels may incur costs associated with running tests for which they receive no reimbursement.

The likely suspects for causal virus may be narrowed through considerations of epidemiology, patient characteristics, and clinical data. For example, although AdV and RV circulate all year, flu, hMPV, PIV, and RSV have a winter seasonal peak. During known outbreaks or peak season, diagnostic tests can be chosen to reflect the potential etiologies. Immunocompromised patients, plus the very young or old, are more likely to host RSV infections than patients without these characteristics, which can be confirmed with testing. In addition, AdV, flu, hMPV, PIV, RSV, and RV impose significant risks of morbidity and mortality on immunocompromised and immunosuppressed patients, which may warrant molecular testing if such infections are suspected in this subset of patients.

Clinicians may be able to take other factors into account, such as specific symptoms (e.g., bronchiolitis, which usually results from RSV) or repeated presentation of similar cases during a seeming outbreak, to choose the most likely viral cause of a patient’s ILI for subsequent confirmation by molecular testing.

Although molecular assays are designed to detect highly conserved targets in the viral genome, mutations in these assays, such as assays for the flu itself. Thus, the introduction of higher-sensitivity assays designed to alleviate issues associated with mutation detection would be of great utility for clinicians and laboratory managers.

The value of flexibility

Based on clinical and epidemiological data, a physician may select specific diagnostic tests for an individual patient with ILI. Cost considerations may limit the choice of tests to those that are medically necessary. Laboratories would, therefore, be well advised to consider flexibility in choice of assays to save money and time by reducing the number of results to review.

In addition, the need for prompt results from these tests to achieve maximum clinical benefit suggests the use of automated molecular diagnostic tests, which generally are available as assays for multiple viruses or viral types. Platforms with multiple assay choices and well-grouped assay analytes, such as by season, provide physicians and laboratory managers with added value beyond speed. The flexibility regarding which assays to use, therefore, is a valuable component of the choice of diagnostic panel as well as the automated platform. As definitive diagnoses become more common and dictated by guidelines, the benefit could also extend to the broader healthcare system, including public health surveillance.
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Influenza continued from page 26

conditions that should have been treated with antibiotics. A thoughtful approach that includes diagnostics testing will result in the best health outcomes for the individual patient and larger population. A negative or positive result needs to be assessed in conjunction with the patient’s clinical findings and risk factors.

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Caroline Hentzen, PhD, serves as a Manager of Scientific Affairs at Hologic Inc., manufacturer of the Panther Fusion system, an automated molecular diagnostics platform, and the Panther Fusion Respiratory Assays, including Panther Fusion Flu A/B/RSV, Panther Fusion AdV/hMPV/RV assay, and Panther Fusion Paraflu assay.

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1943
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1983
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1999
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2004
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- **2009**
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- **2016**
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INR self-testing option create new opportunities for laboratorians

by Corinne R. Fantz, PhD, DABCC

Laboratorians in modern healthcare organizations are under sustained pressure to keep improving the quality of the care they provide while maximizing every dollar they spend. Yet current industry trends may limit the clinical lab’s ability to operate at peak efficiency while supporting the delivery of personalized care.

Advancements in technology now allow sophisticated testing, once unique to the lab, to be performed in point-of-care (POC) settings or even at home. Laboratorians can embrace these changes as opportunities to help the system gain efficiencies and provide the personalized care that patients desire.

One of the best examples of this trend is INR (international normalized ratio) testing for patients who need long-term oral anticoagulation management. For many years, warfarin has been the only option for those patients. Because warfarin has a narrow therapeutic window, warfarin patients require close monitoring with INR testing. Recently, several direct oral anticoagulants (DOACs) have appeared on the market, offering new choices for patients without the need for monitoring and providing newfound freedom from scheduling appointments, lab testing, and clinic visits. However, these drugs may not be appropriate for everyone on long-term oral anticoagulation therapy.

In addition, the availability of a self-testing option has made INR monitoring much more convenient for patients who must or prefer to remain on warfarin. It’s important for laboratorians to educate themselves about each available testing option — lab, point-of-care, and self-testing — in order to offer sound recommendations to caregivers and healthcare administrators, demonstrating value to both health systems and patients.

Background on INR self-testing
Part of the World Health Organization Model List of Essential Medicines, warfarin remains a relevant tool in the overall scope of oral anticoagulation therapy. According to recent prescription data for all anticoagulants, nearly half of patients who are prescribed oral anticoagulants use warfarin. For this group, monitoring is required to ensure achievement of a therapeutic INR—typically, between 2.0 and 3.0. INR monitoring can occur at a lab, at the POC during a clinic visit, or in the patient’s home.

Similar to patients with diabetes mellitus who perform their own blood glucose testing, patients on warfarin have the ability to remotely monitor their INR using a finger-stick blood sample and a handheld meter in the home. A caregiver can perform the test, or patients can perform the test themselves. Results are then forwarded via various communication methods, including phone and wireless Bluetooth, to a provider who can quickly determine whether medication dosage adjustments are needed.

Patients with diabetes can use their blood glucose test results to self-manage their own medications and treatment, but warfarin patients who self-test must still rely on advice from a provider to make changes.

The practice of self-testing at home to monitor warfarin patients isn’t yet commonplace, although it is in a position to become more mainstream. Several providers offer INR self-testing (that is, they furnish FDA-cleared handheld meters and strips, receive test results from patients, and relay results to physicians), and the services are often covered by private insurance and Medicare.

Advantages of self-testing
Many warfarin patients find the ability to monitor their own INR levels appealing for several reasons. First, the convenience of being able to test at home, at work, on vacation or anywhere else with a finger stick as opposed to a venous blood draw reduces the need for repeated visits to a provider’s office or lab, saving time, discomfort, and transportation-related expenses. As with in-office testing, doctors are able to receive the results quickly, making it easier for patients to immediately comply with dosage adjustments as needed.

Self-testing empowers patients with the tools and support they need to take a proactive role in their own healthcare with increased convenience and improved satisfaction. Data show that self-testing can improve a patient’s time in therapeutic range, an important factor in measuring compliance and the success of warfarin therapy.

DOACs vs. warfarin
While DOACs do offer value for many patients by eliminating the need for INR monitoring, there are some patients for whom warfarin remains the more appropriate course of action. Certain medical conditions, such as valvular atrial fibrillation, leading to the need for oral anticoagulant use, may make some patients ineligible for DOACs, resulting in the continued need for warfarin therapy.

Additionally, some patients find personal comfort and reassurance in being able to know and monitor their own INR, or they may be unable to tolerate a DOAC. Pricing can be another consideration. Warfarin is available as a generic alternative, but currently DOACs are not, limiting those patients who are on DOACs to brand-name products and potentially higher out-of-pocket costs. A recent study using a model to simulate cost of care of a DOAC versus warfarin treatment suggests that warfarin is the most cost-effective oral anticoagulation treatment in the prevention of stroke and systemic embolism in patients with atrial fibrillation with a high risk of bleeding and who can achieve a TTR (time in therapeutic range) of at least 70 percent with warfarin.

What self-testing means for labs
As the practice of INR self-testing becomes more common, it will create new opportunities for laboratorians. Some labs may view INR self-testing as competition, but in reality, lab testing remains an indispensable component of patient care. Further, lab testing for the inpatient population isn’t going away. For warfarin patients specifically, lab testing...
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Corinne R. Fantz, PhD, DABCC, serves as Director of Medical and Scientific Affairs, Point of Care Testing, for Roche Diagnostics Corporation.

The National Blood Clot Alliance web site (stoptheclot.org) is an excellent patient resource for information about self-testing options for warfarin patients.

The future of oral anticoagulant self-testing

Today, self-testing is only performed in approximately five percent of U.S. patients treated with warfarin. The option is much more widely used in Europe, primarily in Germany and Italy where 25 percent and 20 percent of warfarin patients, respectively, are currently self-testing to monitor their INR. The difference may lie in the fact that a number of U.S. providers may be unaware that patient self-testing is an option for their warfarin patients.

Recent technology advances, such as handheld INR self-testing meters that incorporate Bluetooth technology, could lead to more interest in self-testing. Laboratorians play a vital role in helping clinicians deliver the best patient care possible. There is a large population of patients who will continue to rely on warfarin therapy, and laboratorians can demonstrate their value by collaborating with providers to identify the best testing options for patients.

Please visit mlo-online.com for references.

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Current anticoagulation monitoring and measurement practices

Paul Riley, PhD, MBA

Clinical laboratories are often on the front lines when new pharmacologic therapies are implemented, and utilization of already available specific assays can help to improve patient outcomes. The landscape is changing for patient anticoagulation.

Therapeutic alternatives for VTE

Patients with acute or ongoing risk of venous thromboembolism (VTE), also known as thrombosis, are prescribed anticoagulant blood-thinning therapies. Therapeutic options for outpatients at risk of VTE have greatly expanded in recent years with the introduction of direct oral anticoagulants (DOACs). Of the DOACs, dabigatran was the first introduced to the market for nonvalvular atrial fibrillation (NVAF) patients at risk of stroke. Rivaroxaban and apixaban closely followed dabigatran to the market; they were first indicated for NVAF patients, and then were approved to use in patients at risk of thrombosis following orthopedic surgery, and for thrombosis prevention and treatment in other patient types. Edoxaban is another recent entry to the market, intended for NVAF and orthopedic patients. It was followed by betrixaban, which is intended only for inpatients with thrombotic risk.

With the exception of betrixaban, the DOACs were approved for NVAF patients after demonstration of noninferiority to vitamin K antagonist (VKA) therapy, or warfarin, in large-scale clinical trials. Similar noninferiority trials comparing DOACs to other mainstays of anticoagulant therapy were conducted to gain approval for the other indications. Unlike warfarin, which acts against many factors within the coagulation cascade, dabigatran is a specific, small molecule inhibitor targeting thrombin, just one component in the coagulation cascade. Similarly, rivaroxaban, apixaban, edoxaban, and betrixaban target a different key enzyme in the cascade, factor Xa. For those confused by the generic DOAC names: for the DOACs directed against factor Xa, “xa” is included in the name of the drug, which is “banning” the activity of factor Xa.

Benefits and limitations of DOACs

Compared to VKAs, DOACs have the perceived benefits of no routine monitoring required, faster onset and offset of action, fewer interactions with food and other medications, and less complex dosing requirements. On the other hand, DOACs utilize the renal system for clearance from the body, and patients with kidney failure or borderline function will require maintenance with VKA therapy. Mechanical heart valve patients also require VKA therapy, as DOACs do not exert enough of a multifactor anticoagulant effect compared to VKAs. We can expect to see additional indications for DOACs in the future for patients with acute coronary syndrome (ACS) and cancer-associated thrombosis and for pediatric patients.

Often, newly diagnosed thrombotic risk patients receive DOAC prescriptions, whereas patients with historical successful maintenance on VKA probably will not be transitioned to DOACs. A lack of specific antidotes and laboratory measurement assays cleared by regulatory bodies in the United States has produced concerns for clinicians. Regardless of those concerns, however, prescription trends have shown strong growth since the introduction of DOACs. Of the DOACs, apixaban has received more attention, due to superior outcomes in large-scale clinical trials with respect to prevention of bleeding and clotting events. Specific antidotes for several DOACs are now available, with idarucizumab available to reverse the action of dabigatran, along with andexanet alfa for reversal of rivaroxaban and apixaban.

Impact on the clinical lab

Clinical laboratories have been on the front lines of the changing anticoagulation landscape, often observing unpredictable effects on routine and specialized laboratory coagulation assays from DOAC presence, and they may have trouble implementing specific DOAC measurement assays if requested by clinicians. In the literature, along with clinical practice outside the U.S., DOAC tests such as the ecarin-based chromogenic assay (ECA) or dilute thrombin time (dTT) are useful for measurement of dabigatran levels. Similarly, the chromogenic anti-Xa assay is useful for measurement of rivaroxaban, apixaban, and edoxaban levels.

Unlike traditional anticoagulants such as VKAs and unfractionated heparin (UFH), which require monitoring, DOACs do not require routine monitoring. Instead, on-therapy levels may be useful to rule out their presence before surgery or other invasive procedures, especially if the patient has taken the drug in the previous 24 hours (or longer if creatinine clearance is < 50 mL / min). In addition, DOAC tests could be useful for identification of sub- and supratherapeutic levels in cases of patients currently taking other drugs known to affect pharmacokinetics; if patients are underweight, are obese, have deteriorating renal function, or require assessment of compliance if bleeding or clotting happens while on therapy; or if overdose is suspected. DOAC tests could also be used to monitor anticoagulation reversal, especially with the recent approval and implementation of andexanet alfa.

Laboratory diagnostics manufacturers are in the process of developing DOAC measurement assays, but no assay has yet been cleared by regulatory authorities in the U.S. market. Of the DOAC assays in development, the chromogenic anti-Xa assay is of strong interest for accurate and precise measurement of all “xabans.”

The anti-Xa assay

The anti-Xa assay is an automated ready-to-use, calibrated chromogenic assay, which works by adding a citrated patient
plasma sample to a mixture of buffer, chromogenic substrate, and excess factor Xa. With the competition between the chromogenic substrate and the anticoagulant of interest with anti-factor Xa activity (that is, any of the xabans, UFH, LMWH, or fondaparinux), an inverse relationship is established between the optical density readout from the instrument and the exact anticoagulant level. Traditional screening coagulation assays such as the prothrombin time (PT) and activated partial thromboplastin time (aPTT) are not suitable to rule out DOAC presence due to interassay variability in sensitivity and potential patient interferences from changes in factor levels and lupus anticoagulants.

To be clear, the anti-Xa assay is not a newcomer to the clinical laboratory, with its use widely implemented to measure the parenteral, antithrombin-dependent anticoagulants UFH, low molecular weight heparin (LMWH), and fondaparinux, all of which possess inhibitory activity towards factor Xa. The anti-Xa assay has shown utility as an alternative to aPTT for measuring UFH, with strong evidence demonstrating the capability of anti-Xa-based dosing nomograms to establish therapeutic anticoagulation faster and maintain therapeutic levels better than aPTT-based nomograms. In addition, aPTT-based heparin therapeutic ranges (HTR) are technically demanding to validate. When anti-Xa-based nomograms are used, fewer dosing changes and fewer tests are run on inpatients receiving UFH, freeing up nursing, phlebotomy, and laboratory time to focus on critically ill patients. Potential length-of-stay benefits have also been observed, delivering economic benefit to enable hospitals to optimize reimbursement and incrementally improve quality of patient care.1

In this way, the chromogenic anti-Xa assay is a versatile anticoagulation monitoring and measurement assay with automation capability and ease of use to support widespread routine use. Hospitals where anti-Xa has already been implemented as the standard of care in pharmacy UFH dosing nomograms and the laboratory are well positioned for the future, as DOAC measurement assays and new DOAC reversal agents move through the stages of regulatory approval.2

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The digital footprint in transfusion medicine and the potential for vein-to-vein management

By Jerry A. Holmberg, PhD, MT(ASCP)SBB

The digital footprint from physician order entry to the Transfusion Service, through the various decision matrices within the blood supply chain, has not progressed as fast as those in other ancillary healthcare support areas (for example, pharmacy). This may change with the evolving impact of Integrated Delivery Networks (IDN), Clinical Integrated Networks (CIN), and Accountable Care Organizations (ACO) on modernizing efficient healthcare delivery by placing requirements on blood suppliers.

Numerous technological advances in immunohematology and blood banking have been made in the last 70 years, but the most significant change has been the acceptance of transfusion medicine (TM) as a medical discipline focusing on the patient to determine appropriate therapy. In the early years of this century, an economic downturn in the United States placed greater emphasis on patient blood management (PBM) and cost recovery, putting a damper on the nation’s blood system. During this time, TM refocused on the patient through therapeutic guidelines to ensure that every blood product transfusion was appropriate and, if possible, that alternate therapies were considered to reduce risk to the patient. As a result, blood usage, especially red cell transfusion, has decreased over the last 10 years. Reimbursement coverage, “never event,” and penalties for poor quality healthcare performers are shaping a drive for a better digital footprint, especially in transfusion medicine.

Going LEAN

As integrated health delivery evolves, efficient suppliers, including blood establishments, must become LEAN and practice healthcare Kaizen (otherwise known as, “continuous improvement”). LEAN has often been inappropriately branded by some as Less Employees Are Needed, but that is not the case as in most Kaizen approaches. Efficiency is the primary goal, but not necessarily at the expense of staff. A LEAN approach which embraces stewardship is key. That is, driving efficiency, safety, patient satisfaction and lower cost through a better blood safety digital footprint.

Errors in blood banks and blood centers are very rare, as most facilities overcompensate based on risk mitigation and build numerous checks in the system. The greatest risks are known to be “clerical,” and most happen post-blood bank. That is, most errors occur either by or within the healthcare facility with “wrong blood in tube” for specimen testing and wrong blood administered at the bedside. ABO blood group system incompatibility and errors resulting in transfusion adverse events are among the “never events” not covered by reimbursement, thus a financial liability of the hospital.

With today’s emphasis on stewardship of the healthcare dollar and the constraints of reimbursement, the question of how to create healthcare efficiency in a managed-cost environment is crucial. The blood supply chain, including blood establishments and TM, is not solely a supplier of blood products as a commodity for the healthcare system but a value service providing the best product for the appropriate patient at the appropriate time, within a scheduled cost structure. The future of the blood supply chain to the healthcare system will be dependent on LEAN operations providing value through an integrated blood safety and availability digital network.

Transparency, V2V, RFID

To achieve this, the blood bank digital footprint, either integrated or separate from the hospital information system (HIS), must become more transparent in data sharing, including supply chain management within
the blood establishment. A shift to a transparent inventory has the potential to move the transfusion services blood supply within the IDN (integrated delivery network) to a vendor-managed inventory within the hospital. Transparency is critical to build the confidence of the IDN that its needs will be met for unexpected emergencies. A vein-to-vein (V2V) digital footprint with automation is needed to ensure both blood safety and availability (Figure 1). Acceptance of a blood safety and availability digital footprint is dependent on an “open” architecture based on common industry standards of data elements for all essential processes within the blood bank supply chain and to its final administration to the patient. Of course, cybersecurity will be of prime concern, and protection of patient/donor information will be paramount.

A V2V digital footprint within TM will require processes that may be facilitated by artificial intelligence (AI). This should include donor recruitment and selection as well as data obtained during the collection process. Checks and balances among expected needs as well as automation elements for greater efficiency are envisioned in component preparation, testing, labeling, and distribution. Management of the blood component, its labeling, and the specimens for testing, could be managed through radio frequency identification (RFID). Automating current manual processes with “minimal manual touch” is envisioned with RFID.

For example, imagine the digital footprint using automation and RFID to direct specimens for centrifugation or directly delivered to an instrument as whole blood. Imagine replacing multiple-person labeling practices compliant with Good Manufacturing Practices (GMP). The digital footprint could even streamline blood product ordering and establish logistics for delivery efficiency, ensuring the right blood at the right time to the correct location, all while reducing technical manpower and errors.

On the hospital side, the digital footprint could reduce errors when completing a physician order using AI and RFID for specimen identification and appropriate tracking. Reducing specimen labeling errors and errors of transfusion potential could create significant financial savings through an integrated V2V system. The future for TM within a changing healthcare system depends on defining a digital footprint involving both the supplier and the healthcare provider.

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Laboratory automation is no longer optional

By Rita White, MT(ASCP)SH

A shortage of skilled laboratory workers has been decades in the making—the result of a retiring workforce and a shrinking number of accredited training programs. With a growing population sending more samples to the laboratory and a shortage of staff to handle those samples, lab managers consequently are facing a number of challenges. From maintaining control over the influx of samples and finding ways to improve workflow to deliver patient results in a timely manner, to identifying growth opportunities to generate new revenue to make up for decreasing reimbursement rates, the pressure on lab managers to sustain their laboratory operations is mounting. This article will explore the evolving staffing crisis, stakeholders’ views on laboratory technology, and the impact that automation can have on both laboratory operations and the overall health system to drive outcomes that matter to patients.

State of the crisis and other challenges

The Bureau of Labor Statistics expected medical laboratory technologist and technician employment to grow by 13 percent between 2010 and 2020.¹ According to the American Society for Clinical Pathology’s (ASCP) 2016-2017 Vacancy Survey of Medical Laboratories, retirement rates of laboratory professionals across all major departments are at their highest since 2012.² Yet the data also suggest that the number of students graduating from accredited training programs is not sufficient to meet the demand.

The main concern in the laboratory workforce, according to the study, is staffing the laboratory with qualified laboratory professionals. These respondents also indicated an extremely low number of applicants compared with the number of personnel retiring. Further adding to the deficit, the number of laboratory training programs available to students interested in pursuing this field also has decreased, by nearly 25 percent since 1990.³

The Baby Boomer population will continue to age and the demand for testing will rise, but the number of laboratorians with the training required to run IVD tests remains stagnant.

While the staffing shortage and aging population are challenges that have long been on the horizon, the rising trend of healthcare facility consolidation as well as recent policy initiatives have hastened the need for solutions that will sustain laboratory operations long-term. Most recently, with the Centers for Medicare and Medicaid Services’ implementation of the Protecting Access to Medicare Act (PAMA), clinical laboratories large and small have been experiencing the most significant reduction in reimbursement in decades. PAMA is forcing laboratories to reduce costs, maximize revenue, and figure out ways to increase testing volume to make up for lost revenue. Private insurers are expected to follow suit and decrease their reimbursement rates, too.⁴ All of these challenges equate to an increasing workload—in the context of an imperative not to sacrifice turnaround time—with less financial and staffing support.

The rise of automation

Recognizing the impending challenges on the horizon, IVD manufacturers have begun rolling out automated solutions with varying capabilities to support laboratories and their growing operations. Increasingly, labs are transitioning from buying individual analyzers to purchasing total solutions from a single trusted partner. Total solutions encompass a variety of offerings, including equipment for sample management, a broad menu of assays, IVD analyzers, automation systems, and informatics. Taken together, such total solutions are designed to anticipate and address the emerging needs of clinical laboratories.

Recognizing that total lab automation can be a significant investment for any lab to undertake all at once, manufacturers have deployed a number of resources and affordable solutions to help laboratories transition into automation. Innovative instrument features such as automated quality control and calibration, sophisticated vision systems, intelligent sample management and test scheduling, and bidirectional magnetic sample transport technology optimize the workload for highly skilled operators. Less hands-on time for routine tasks maximizes existing resources to help refocus skilled attention elsewhere in the lab and reduces the need for additional operators as laboratory operations grow.

Optional becomes must-have

Automation offers laboratories standardization and consistency—two benefits that can no longer be overlooked, because the consequences of overlooking them are increasingly detrimental to patient safety. Stakeholders agree. During a recent study to determine the value of the lab to the health system, research that involved more than 300 U.S. lab directors, internists, and emergency room physicians, more than three-quarters of doctors and lab directors agreed that labs play a vital role in healthcare systems and are a critical component of patient diagnosis and treatment. Additionally, more than half of the physicians and internists noted that investments in lab technology would be very impactful on improving diagnoses, and about half of physicians and internists thought that such investments would be very impactful on improving patient safety and patient outcomes.⁵

As further support for the case for automation, an ASCP study revealed that the increasing workload in
the laboratory is compelling laboratory managers to hire lower-level applicants immediately after graduation or candidates with bachelor’s degrees but not laboratory training. Lack of training exposes patients to significant risks—for example, failure to recognize critical results. With more than 70 percent of clinical decisions being guided by test results, the laboratory must progress to continue delivering quality results. With the right infrastructure and software behind it, automation can improve workflow efficiency and turnaround time and reduce errors.

Lobbying for the lab
Hospital lab directors claim that their biggest challenges include financial constraints related to operations, investments in lab technology, and automation. Laboratory technologies often are deprioritized over other expenses that are thought to more directly impact patients. The direct and indirect impact of laboratory diagnostics, however, is undeniable. These technologies play a pivotal role in the patient’s experience and outcomes and in the hospital’s reputation. This value often goes unrecognized by hospital decision makers because, without visibility beyond the laboratory silo, lab managers often are not equipped with the information they need to argue for investment dollars.

IVD tests play a critical role in detecting, diagnosing, and monitoring disease, providing undeniable value to both patients and the healthcare system in general. The financial value is not lost on hospital workers. The majority of emergency medicine physicians (73 percent), hospital lab director/pathologists (81 percent), and internists (60 percent) agree that increased investment in technology for IVD labs can lead to overall hospital cost savings and increased revenue.3

Armed with that evidence, following are three strategies that can help support lobbying efforts for new technology for your lab:

Consider a workflow consultant: The most successful lab transformations occur as a result of staff input, alignment, and adaptability—all of which require communication. Consider the help of a workflow consultant. A workflow consultant is an expert trained to methodically analyze a laboratory’s productivity objectively and offer solutions for improvement. This professional adds value to the project team by conveying to decision makers cost justifications for modifications based on process improvement methodologies and case studies from other projects with similar goals.

Utilize a project manager: A project manager is an expert certified to coordinate the technical and physical aspects of implementation, resources management, and third-party management. The project manager works hand-in-hand with the workflow consultant and is responsible for validating project milestones and timing, and for adhering to budget compliance.

Implement change management: Change management helps you develop a plan that will assist you in leading the successful implementation of new technology in conjunction with optimized workflow processes. By focusing on the human side of automation, this process allows you to overcome resistance to change and lead a successful change initiative.

A change management initiative helps determine which key stakeholders are part of the core project team, how to manage the transition of an active lab automation system with minimal disruption to operations, and how to maintain workflow during the transition.

The long view
Investing in advanced technology can contribute to financial savings for healthcare institutions down the road. Hospitals in the United States that incorporated innovative medical technologies have Medicare Spending per Beneficiary (MSPB) scores below the national average. Sixty-five percent of top technology hospitals, as defined by U.S. News & World Report, have an average MSPB score below the national average, compared with 56 percent of nontechnology hospitals.4,5

More broadly, the escalating staffing crisis and other challenges that contribute to an increasing workload are demanding innovation to keep up with rising test volumes. Data collected from stakeholders across the health system reveal that stakeholders are supportive of investment in laboratory automation technology, but competing projects may deprioritize investing in new laboratory services and technologies, causing opportunities for workflow efficiency, physician satisfaction, and improved patient experience across the entire health system to be missed. To turn interest into implementation, leveraging the help of a trusted partner, you can develop a strategy that will focus stakeholders’ attention on the impact automation can have on both laboratory operations and the overall health system to help reprioritize funding appropriately.

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Rita White, MT(ASCP)SH, serves as Marketing Director for Automation and Informatics, North America, Siemens Healthineers.
Using automation to help address the laboratory workforce shortage

By Kathryn Richards, BSc, MSc, and Ann Ludwig, BS

For more than 30 years, stakeholders in the clinical laboratory profession have been calling attention to the growing shortage in personnel, and rightly so. Every year, more than four billion medical laboratory tests are performed in the United States. Laboratory diagnostic testing is the largest single medical activity in terms of volume, and those tests have a critical role to play in healthcare as approximately 70 percent of the interactions that physicians have with patients are influenced by test data run through a diagnostic laboratory.

About 60 percent of the healthcare workforce in the U.S. is made up of clinical laboratory professionals running those very tests. Yet at the same time that new tests are being developed to aid diagnoses and monitor health conditions, the number of people available to perform these tests is falling rapidly.

While much of the conversation has focused on ways to recruit and retain clinical laboratory professionals, the developers of hardware and software diagnostic technology also have a responsibility to assist laboratories with these challenges. Clinical lab directors should expect the medical device industry to look at laboratory automation through a new paradigm and consider where the laboratory's workflow can be served by innovative ideas and approaches.

The scope of the shortage

In 2016, the U.S. Bureau of Labor Statistics forecast demand for 12,000 new clinical laboratory professionals each year to meet rising demand for their services. However, according to The American Society for Clinical Laboratory Science (ASCLS), just 5,000 laboratory professionals are entering the workforce on an annual basis.

Making the situation even more difficult is that increasingly, newer generations of potential clinical laboratory professionals are choosing other professions instead. The average age of the clinical laboratory workforce has been increasing. According to ASCLS, as far back as 2004, the average age of a certified medical technologist was 43 years old, and the profession was aging faster than the U.S. labor market as a whole.

In an April 19, 2018, story in Biotechnology Focus, the Canadian Society for Medical Laboratory Science (CSMLS) reported that the most serious shortage is in rural and remote communities, but with 50 percent of clinical laboratory professionals becoming eligible for retirement in the next 10 years, the shortage could easily spread to more populated areas.

Many reasons for the shortage

According to the American Association for Clinical Chemistry (AACC), multiple forces are contributing to today's staffing challenges. Retirement rates among clinical laboratory professionals are increasing, the number of new students graduating from clinical laboratory programs is declining, schools are closing, and the number of training programs has dropped more than 15 percent. Nevada, Vermont and Wyoming each have only one National Accrediting Agency for Clinical Laboratory Sciences (NAACLS)-accredited laboratory educational program. Some medical laboratory science programs could accommodate more students but are unable to because of difficulties in finding clinical placements for students to complete their training.

Beyond capacity and institutional challenges, an even tougher problem looms: a combination of lack of interest and awareness among college students to enroll in clinical science programs. According to a Walden University study, college students are less aware of careers in clinical laboratory sciences, and as a result, historical stereotypes about the profession offering low pay, limited career growth, and little impact on patient care prevail.

Some institutions have reduced requirements for medical technology students. According to the AACC, the University of Minnesota's Center for Allied Health Programs reduced the time that students in its medical laboratory sciences program spend on trials from 22 weeks to 12 weeks. This reduction was due to inadequate staffing at healthcare organizations to support 22 weeks of training, and further reductions to eight weeks were being considered.

Hardware and software partners

Streamlining training requirements, better marketing, and more effective career and vocational information and materials are all meaningful and constructive solutions. But an obvious contributor to solving these challenges seems to be consistently omitted: the companies that develop, market and support the medical devices and software that clinical laboratory professionals rely on. The diagnostic industry has a responsibility to embrace the challenge of the shrinking workforce and find solutions that will help modernize the day-to-day workflow of clinical laboratory professionals and help them work smarter, not harder.

A decade ago, a good portion of a laboratorian's day was dedicated to necessary, manual tasks, such as sample archiving and system maintenance. But students don't invest four to eight years learning the complexities of pathology to then sort thousands of tubes or troubleshoot equipment.

Technology partners owe it to laboratory professionals to help them focus their expertise on what ignited their passion for the profession in the first place—the diagnostic part of their work. Specifically, they should work with their customers to look for ways to automate tasks along the diagnostic workflow—to help today's smaller workforce to do more with less, or, more grammatically speaking, do more with fewer—fewer staff members.

Consistency, efficiency and reliability

Hardware and software should be reducing the need for manual intervention. Clinical lab directors need to be bold and think big. Just imagine:

- Loading a sample onto an automation line and not having to touch it again until it is ready to be discarded
- End-to-end ethylenediamine tetra acetic acid (EDTA) automation
- Encapsulating complete blood count (CBC) analysis, complete with a six-part white blood cell count (WBC) differential
• Blood smear preparation and staining
• Digital image analysis
• Glycated hemoglobin (HbA1c) analysis and sample sorting and archiving.

What if the CBC analyzers could calibrate themselves every time a Quality Control (QC) was processed and make technical support staff aware of instrument issues in real time? If this can be combined with multi-disciplinary track connectivity, total laboratory automation starts to become a reality.

Solutions for laboratory generalists
Discipline specialists are becoming a thing of the past, yet much of the technology on the market is still geared toward the specialist. The future of laboratory professionals is about generalists. In that context, laboratorians should be able to not only flag the sample result from instrument A, but automatically direct it to instrument B, increasing the sensitivity and specificity of the final result. Additional modules should be included, such as an automated slide maker and stainer, complete with an integrated digital image analysis. Laboratorians should ask their vendors not only how much can be automated, but how much can be automated on the sample’s first pass through the instrument.

QC, maintenance and training
While we often think about automation in terms of day-to-day tasks performed by a clinical laboratory professional, automating the QC, calibration, and maintenance of laboratory hardware presents another world of possibilities. By utilizing cutting-edge “internet of things” connectivity, technology can be leveraged to provide innovative solutions:
• What if quality monitoring could be flexibly displayed on any platform or web browser, providing the lab with a snapshot of its instruments’ QC status on a single screen?
• What if an instrument could be calibrated every time a QC was processed?

But let’s not stop there. What if the instrument not only alerted the customer to the health of the instrument, but alerted technical support staff to instrument issues in real-time, who in turn provided proactive support? Clinical lab directors also should expect vendors to be innovative in their approach to training laboratory staff on the use of their instruments. New technologies can take the very best of conventional training, such as live, instructor-led learning, sharing information and performing hands-on exercises, and real-time Q&A with expert instructors, and combine it with streaming high-definition, high-quality live video over the internet from studios equipped with the same instruments that staff are learning to use in their laboratories.

That’s the kind of reinvention that the lab should look for from vendors as part of the response to staffing shortages. Between staffing difficulties and constant downward pressure on reimbursement rates, the new normal has to be a continuous focus on advancing and increasing automated processes, removing opportunities for error and increasing speed.

All of these innovations will not only help address the staff shortage that clinical laboratories face, but will also allow laboratory professionals to concentrate on the diagnostic and analytical work that they do best.

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HFAP is the cost-effective, educational laboratory accreditation alternative. Contact us at info@hfap.org or 312.202.8258. We’re here to help.
Medical laboratory science scholarship awardees make a difference

By Robin E. Stombler

Ten years ago, the American Proficiency Institute (API) created a scholarship program to award college students with ability and interest in medical laboratory science. Through its scholarship awards, API supports the next generation of laboratorians. At least five scholarships are awarded each year, and more than 50 awards totaling over $100,000 have been presented during the last decade.

What impact have these awards had? What became of these promising students: did they enter the laboratory profession, or find another career path? Thirty-one past recipients were contacted to find some answers.

Joining the profession

Kaitlyn Schmidt, a 2014 API Scholarship recipient, now works as a clinical laboratory scientist at Lutheran Hospital in her hometown of Fort Wayne, Indiana. “I absolutely love what I do,” she explains. “This is an interesting field and it constantly intrigues me.”

Michelle Horstman (2013) is a clinical laboratory scientist at St. Elizabeth Hospital in Appleton, Wisconsin. This past year she accepted a lead role in hematology and support services for the laboratory, and she has also served for two years on the ASCLS-Wisconsin Board of Directors. “This has been such a great experience,” she says. “I am able to drive positive change for the lab and our patients. I hope to continue serving the community I live in and helping make healthcare a better product for each patient.”

With degrees in molecular/cellular biology and biochemistry, Casey Penland (2015), now a clinical laboratory scientist at Children’s Hospital Colorado, shares that sentiment. “It’s my goal to continue to provide quality results to the kids and families we serve,” explains Penland.

Sharie Mae Gonzales David (2015), a clinical laboratory scientist specializing in blood banking at the Johns Hopkins Bayview Medical Center in Maryland, is considering her future options, including the pursuit of a master’s degree as a pathologist assistant or becoming a Blood Bank Specialist. “Future medical laboratory science students should strive to reach their goals,” she says. “Whether we work directly or indirectly with patients, it is important to know our worth in the field: without a diagnosis, there is no prognosis.”

Diego Solano (2008), now administrative laboratory director at Abrazo Arizona Heart Hospital, outlines his goals as a lab leader. “I plan to continue to lead the laboratory I work for to provide high-quality results for patients using the current best practices and leading technology.”

One of the most recent API Scholarship recipients, Heather Hansen (2017), a junior at Texas State University, sums up: “I am a hero in training.”

Creating a lasting impact

Some awardees ultimately pursued different career paths—but they are quick to say that their training and education in clinical laboratory science helped them in their chosen careers and created a lasting impact in their professional lives.

Aaron J. Lin, a scholarship recipient in 2012 who graduated from Louisiana State University Health Sciences Center (LSUHSC) in New Orleans with a bachelor’s degree in medical technology, talks about the arc of his career and about that impact. Lin is now in his fourth year of medical school at the LSUHSC School of Medicine. “Though I spent some time getting to know the specialties that are intimately involved in the workings of the lab like pathology, hematology, oncology, infectious diseases, and internal medicine, I’ve ultimately decided to specialize in something quite different. I’ll be going into Physical Medicine and Rehabilitation.”

“I wear my clinical laboratory scientist pin on my white coat,” notes Lin. “I think the field is highly underappreciated. Many training physicians don’t understand or respect the lab for what it does to ensure patient safety. I will always remember my roots and speak up for the lab when I can.”

Lindsay Jolly (2009) added a master’s in public health to her medical technology degree. Jolly is a microbiologist for the Tennessee Department of Health. She also serves as the Infection Control Officer and holds a seat on the Biosafety Committee for the Laboratory Services Division of the department. Committed to giving back to the community, Jolly works with the Tennessee State Training Coordinator. She participated in a roadshow of the Laboratory Response Network, informing others in locations across Tennessee about hepatitis.

Expressions of gratitude

On one point the 31 recipients were unanimous: all expressed heartfelt gratitude to API for helping to pave their way. “I remember the phone call I received when I was named a recipient,” notes Kaitlyn Schmidt. “I teared up—it meant so much to me! Not only did I feel special to be one of five students in the U.S. to be chosen, but financially it helped me out tremendously. This scholarship gave me a jump start in a career that I am extremely passionate about, and I am forever thankful for the opportunity.”

Jessie VanderLaan (2015) from East Lansing, Michigan, adds, “Receiving the scholarship from API was an honor. Not only did the scholarship help me financially; it reinforced my confidence to persevere and advocate for this profession.”

“We had no expectations of these students other than to help support their education,” explained Daniel C. Edson, API President. “To discover what they have achieved to date is heartening.”

Robin E. Stombler is president of Arlington, Virginia-based Auburn Health Strategies, LLC, a firm that provides strategic and business development services to health and science organizations.
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The role of Six Sigma in a modern quality management strategy

By Edward Hill, BSc

In their groundbreaking 1999 report, “To Err is Human,” Kohn and colleagues estimated that up to 98,000 deaths per year worldwide could be directly attributed to medical errors. This fact, coupled with evidence that 60 percent to 70 percent of all medical decisions are based on laboratory results, shows that consistently accurate laboratory outputs are of paramount importance in reducing patient risk.

Laboratories play a pivotal role in patient care, and this role, now more than ever, is increasingly receiving the recognition it deserves. Therefore, laboratories are becoming busier, and with the increase in workloads, it stands to reason that the rate of error will also increase.

It is important to remember that errors are not necessarily restricted to the laboratory itself and that they can occur at any stage throughout laboratory testing. Therefore, it is important to note all potential sources of error, from sample analysis to interpretation of test results, and even at the sample collection stage.

Consequently, it is imperative that laboratories implement a quality management strategy (QMS) that will put measures in place to reduce the risk of error. A major development in improving quality was the implementation of Six Sigma methodologies, originally developed by Motorola in the mid-1980s. These methodologies have recently risen to prominence within the healthcare sector due to their application in laboratory quality control.

Six Sigma (or Sigma Metrics), continues to be applied by laboratories, external quality assurance (EQA) programs, software vendors, and manufacturers, quite simply because it is useful. But what exactly is Six Sigma?

Defining Six Sigma
Six Sigma is a method of process improvement which focuses on minimizing variability in process outputs. Variation in lab processes leads to wasted time and resources, in re-running tests and altering standard operating procedures (SOPs), for example. Reducing variation will ultimately reduce costs, improve performance and increase profitability. Sigma is an effort to measure, to quantify, errors, and then to reduce their number as much as possible.

The Sigma model looks at the number of standard deviations (SD) that fit within the quality specifications of a process. In the clinical laboratory, the quality specifications relate to the Total Allowable Error (TEa) for each test. Simply put, the higher the number of SDs that fit within the limits, the higher the Sigma score, and therefore the more robust the process/method.

(Figure 1)
In the lab, a Sigma score of three (3) is considered the minimum accepted performance, while a score of six (6) is considered the “gold standard.” This is, unsurprisingly, almost impossible to achieve, but a lab with a Sigma score of 6 will experience approximately 3.4 errors (defects) per one million QC test runs—thereby highlighting the accuracy and reliability of a Six Sigma test.

Calculating Sigma
Within the settings of the clinical laboratory, Sigma is most commonly calculated by measuring variation.

The imprecision (CV) and inaccuracy (Bias) are routinely calculated for each test, and those metrics can be used in Sigma calculations, in conjunction with the TEa. The TEa for each test can be located from numerous sources; for example, CLIA, RilBAK and Biological Variation provide TEa limits for each test, and are commonly used by laboratories worldwide.

Sigma is calculated using the following equation:

\[
\text{Sigma} = \frac{\text{TEa} - \%\text{Bias}}{\%\text{CV}}
\]

• TEa is Total Allowable Error.
• Bias is the deviation (%) between obtained mean and the reference value or peer group target.
• CV is imprecision of the data (%).

As an example, a laboratory is running aldosterone and wants to evaluate whether it is performing close to Six Sigma. The lab checks the CLIA database, which
shows that aldosterone has a TEa of 36.7%. The laboratory then calculates the %Bias of their aldosterone assay when compared to its peer group and finds that it is running with a Bias of 5%. The aldosterone assay also has a CV of 10%. Using the calculation outlined above, we see that:

\[ \text{Sigma} = \frac{(\text{TEa} - \%\text{Bias})}{\%CV} \]

\[ \text{Sigma} = \frac{(36.7\% - 5\%)}{10\%} \]

\[ \text{Sigma} = 3.17 \]

In this instance, the aldosterone assay is running just above three Sigma, which is around the minimum acceptable performance. The laboratory will need to make efforts to decrease its %CV and %Bias to improve the overall Sigma Score for the assay.

**Benefits of Sigma**

By incorporating Sigma calculations into your quality management strategy, your laboratory can reap benefits. One of the main functions of calculating Sigma is to give labs a quantitative indication of the approximate number of failed quality control (QC) results per million tests. In simpler terms, as the Sigma score increases, the approximate number of failed QC results will decrease. Figure 2 highlights the probability test results that will be within acceptable limits in relation to Sigma score.

Table 1 shows the percentage accuracy and approximate number of failed tests per million QC runs. Once

<table>
<thead>
<tr>
<th>Sigma level (with a 1.5 sigma shift)</th>
<th>% Accuracy</th>
<th>Failed QC Results per million</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30.9%</td>
<td>697,700</td>
</tr>
<tr>
<td>2</td>
<td>69.1%</td>
<td>308,700</td>
</tr>
<tr>
<td>3</td>
<td>93.72%</td>
<td>66,810</td>
</tr>
<tr>
<td>4</td>
<td>99.4%</td>
<td>6,210</td>
</tr>
<tr>
<td>5</td>
<td>99.98%</td>
<td>233</td>
</tr>
<tr>
<td>6</td>
<td>99.9997%</td>
<td>3.4</td>
</tr>
</tbody>
</table>

**Table 1.**

labs are able to quantify their approximate number of QC failures, they can identify any poor performing tests and take steps to improve their performance.

The benefits of a more dynamic QC strategy include reduced cost and time implications in the long-run, as well as greater levels of error detection, thereby drastically reducing risk to the patient. In the 2018 paper “Analytical Sigma metrics: A review of Six Sigma implementation tools for medical laboratories,” Westgard concludes that through the assessment of Sigma metrics laboratories can specify the number of control rules, the number of control materials, and even the necessary frequency of running those controls. Sigma metrics are providing a gateway to designing a customized, optimized QC strategy for the method.4

**Where should you start?**

Implementing Six Sigma methodologies, along with root cause analysis (RCA) and ongoing quality improvement evaluations, is an exhaustive (and exhausting!) process. For this reason, it may not be time-efficient to implement Six Sigma practices for all tests in the lab right away. It would be better to identify a few tests which you know are performing poorly and carry out the following steps:

1. Calculate %Bias, %CV and TEa for selected test(s).
2. Carry out the calculation \( \text{Sigma} = \frac{(\text{TEa} - \%\text{Bias})}{\%CV} \) to determine Sigma scores for each test.
3. Make efforts to identify the potential sources of error which could be negatively influencing the accuracy and precision of your test(s).
4. Once improvements have been made to your quality system, recalculate Sigma using your new imprecision and inaccuracy values.
5. Monitor Sigma performance over time, which should be improving as a direct result of improved quality practices.

**The reward of vigilance**

Clinical laboratories are rapidly evolving, and in such a dynamic marketplace, the old “one size fits all” model of quality management is not sufficient to meet the time and cost-saving requirements of the new modern laboratory. Innovative solutions are needed, along with a constantly vigilant approach to QMS optimization.

Sources of error can permeate every facet of the laboratory. However, Six Sigma is an effective and proven way of identifying goals, using metrics to establish current performance, critically evaluating all processes, identifying and implementing potential solutions, and evaluating results. The laboratory’s entire testing process can be quantified using Sigma metrics, and steps can be taken to implement continuous process improvement.

Every lab, no matter how big or small, should be invested in the quality of its processes and, therefore, the quality of its results.

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Edward Hill, BSc, serves as QC Product Specialist for Randox Laboratories, provider of laboratory Quality Controls, peer group reporting software, and other diagnostic solutions for clinical, food/wine testing, veterinary, forensic, and molecular laboratories.
Enhancing QC protocols through automation
Emerging technologies advance care and efficiency by streamlining QC maintenance.

By Anthony M. Barresi, BS, MBA

The modern-day laboratory is a fast-paced environment with high demands and stretched resources. Industry-wide, laboratory managers balance fewer skilled staff and greater budgetary constraints with an upswing in testing demands. With continuing innovation and attention to better disease prevention, diagnosis, and management, the clinical laboratory is increasingly at the front and center of healthcare. Because of this, the need for fast, accurate, efficient results delivery has never been so acute, and a vigilant quality control (QC) program is essential to ensuring this need is met.

In QC management, laboratories apply various levels of rigor. Some QC procedures employ paper-based protocols, which requires storing printed documentation. This type of system necessitates extreme diligence on the part of the laboratory staff and has left laboratory managers to question QC procedural compliance. In an effort to close gaps and reduce variation in QC programs, industry innovators have posed another question: “How do we advance QC management to drive consistency and efficiency?” They have found an answer in automated middleware solutions.

Automated middleware solutions
Middleware technology takes manual laboratory QC procedures into an automated environment to ensure that processes meet defined standards 24 hours a day, seven days a week. With middleware solutions, laboratories gain increased confidence in reported results and identify instrument and control irregularities faster.

Today’s advanced middleware technology gives laboratories the ability to establish two types of QC monitoring protocols—a control protocol and a patient protocol. A control protocol—including rules-based QC management features—analyzes data from commercial control materials to ensure quality. A patient protocol performs statistical analyses—such as those based on patient moving averages—using patient results to provide insight into potential future QC failures.

An aggregate graphical display of statistical data facilitates communication in the laboratory by allowing laboratorians to readily visualize and share results and print reports. These advanced solutions offer features that promote significant advantages:

- Streamlining QC maintenance to help laboratories monitor, manage, and act through enhanced QC; stopping autovalidation based on a single parameter, per CAP requirements
- Ensuring all QC runs are on schedule, using a timeout feature
- Identifying system issues proactively and ensuring quality results between QC runs through the use of exponentially weighted moving averages.

Streamlining QC maintenance
Actionable visual cues. Because laboratories are tasked with delivering excellence in patient care, while achieving operational efficiency, instrument manufacturers are continually identifying ways to elevate results quality and streamline workflow. One way to accomplish this is to give laboratorians at-a-glance information and visual parameter cues from which they can quickly take action. If QC protocols are met, tests can be run; if not, early attention can be given to gaps. Flags against individual analytes inform laboratorians about QC status and guide corrective actions, if needed, to increase confidence in results. Such flags may appear when a protocol is in error or a result is blocked.

Rules-based QC management. Pre-programmed or user-defined rules ensure consistent performance throughout workflow processes, helping laboratories deliver quality results regardless of time of day or staff skill level. With advanced middleware solutions, laboratorians can set rules, defining QC protocols for each analyte based on QC metrics such as Westgard rules. Trained laboratory staff members can set middleware rules that inform all staff of QC issues, or automatically stop autovalidation. These system notifications ensure that necessary actions are taken based on pre-identified rules. Because rules can be defined by the user, they can be created to meet a laboratory’s individual requirements, and they can be written by laboratory staff trained in these systems, without the need for IT involvement.

Electronic audit trail. One major benefit of an automated system is the analytics it provides for greater insight into laboratory operations. Unlike a paper-based system, automated QC management gives the user the ability to look back at QC trends. If desired, the user can research specific issues and determine what actions were taken and by whom. This assists laboratories in optimizing QC, by addressing recurring issues and confirming compliance with all protocols.

Timeout feature
New middleware solutions prevent the release of erroneous data by helping laboratories ensure QC is run within specified time frames. Using a timeout feature, data is not released if the QC is not run as indicated. This halts error reporting and promotes peace of mind for laboratory leaders and staff members, assuring them that every QC material test scheduled to run on a given day was completed.

Exponentially weighted moving averages
Minimizing release of erroneous data. Statistical analysis is at the core of QC management. A moving average is a mean calculated for a specified number of patient results. An exponentially weighted moving average (EMWA), available in newer technology, provides a moving average weighted to consider the age of the results.

continued on page 50
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Depending on how the protocol is defined, EWMA can warn the laboratory to shut-off autoverification automatically to prevent the release of potentially erroneous results and eliminate the need for retesting, physician notification, and other corrective actions. It can also alert the system to stop sending test requests to a specific instrument. This round-the-clock real-time insight keeps laboratories in control of their results and provides a proactive tool to ensure results quality by monitoring portions of the laboratory that may not be normally monitored and by adding an additional level of quality assurance. It also helps to promote better patient care, as it provides early detection of system issues to reduce false high or low results.

Ensuring consistent results between QC runs. Users of these enhanced features have reported shortened turnaround times (TATs), as specimens can be processed without waiting for the completion of QC verifications. Because reviewing laboratorians are alerted to any drifts in QC values in real time, operators can be assured that, if any QC value is not within the appropriate range, test results will be blocked from autovalidation, mitigating erroneous reporting. This allows laboratories to run specimens on the instrument sooner—reducing TATs—with a high level of confidence in diagnostic test results.

Beyond the lab: impacting patient care
Today’s tools aim to assist laboratories with the critical and often laborious task of QC management. Enhanced system features enable laboratories to move many patient samples through with accuracy and efficiency—in some cases, with shortened TATs. Advanced analytics give insight into issues that can affect results delivery—such as pre-analytical sample integrity and the order-to-collection process. The actionable data can be used to facilitate conversations with clinical partners—including Emergency Department staff members—to mitigate factors that may affect test quality or TAT.

As the demand for accurate and timely results continues to rise and as technology becomes increasingly sophisticated in all market segments, clinical diagnostics innovators will look for creative, beneficial ways to improve laboratory instrumentation. Building on already-established laboratory-enhancing technologies, these innovations will further boost efficiency through time-saving features, facilitate collaboration among all healthcare partners through actionable data, and advance patient care through quality results.

Anthony M. Barresi, BS, MBA, serves as Global Product Manager, Clinical Informatics, for Beckman Coulter, Inc.
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Don’t rely *solely* on Sigma values to determine QC frequency

They are just one factor that comes into play.

By John C. Yundt-Pacheco, MSCS, and Curtis A. Parvin, PhD

Laboratories know that appropriate quality control (QC) rule selection depends on the in-control performance of a test method (the Sigma value). Higher performing tests may allow “easier” rules, while lower performing tests require more powerful rules. In recent years, QC frequency has undergone a shift in thinking and approach related to patient risk-based QC design. That is, what we are asking now is, what is an appropriate QC frequency to assure that the risk of patient harm from an erroneous reported patient result is acceptable?

In that context, is the Sigma value for a test method all that is needed to determine an appropriate frequency for QC testing to adequately mitigate patient risk? The simple answer is no: having two different analytes with the same sigma value does not necessarily mean the same QC frequency is warranted. The Sigma value is an important and necessary piece of information, but it is not sufficient to appropriately mitigate patient risk. There are at least four other factors that should influence decisions about the appropriate QC frequency for a test method:

1. The reliability of the test method;
2. The expected length of time between reporting a patient result and its being acted on;
3. The likelihood that an erroneous reported patient result will lead to an inappropriate medical decision or action; and
4. The expected severity of patient harm if an inappropriate decision or action occurs.

**Test method reliability**

The Sigma metric measures the ability of a test method to limit the number of erroneous patient results produced when the test method is performing in its stable in-control state. However, patient risk not only depends on the likelihood of producing erroneous results when the test method is performing in its stable in-control state, but also on the increased likelihood of producing erroneous results when test methods are out-of-control. Therefore, knowing how often a test method goes out-of-control (the reliability of the test method) is an important consideration when assessing an appropriate frequency for QC testing in order to adequately manage overall patient risk.

An out-of-control condition that produces a single erroneous albumin result that occurs only once every two years would be acceptable. What if the same out-of-control condition produced a single erroneous result every month? That might be of concern. What if the same out-of-control condition happened every two days, so the lab would release about 15 erroneous albumin results each month? Depending on test volume, this may be acceptable—or it may be completely unacceptable. What is clear is that out-of-control conditions occurring every two days have a very different impact than out-of-control conditions occurring every two years.

**Time until clinician acts**

Even if the QC rules are powerful enough to detect a significant out-of-control condition at the first QC event after the condition occurs, if patient results are being reported as soon as they are produced and verified, then there is the possibility that a number of erroneous patient results will have been reported between the occurrence of the out-of-control condition and its detection. If those erroneous results are not identified and corrected before they are acted on, then the risk to those patients has not been mitigated. How likely is it that the lab will be able to identify and correct erroneous patient results already reported will depend on the expected length of time between the lab’s reporting of the result and its being acted on. No matter how capable the test method, if the time between QC events is too long relative to the time needed to correct results before they are acted on, then patients will be at increased risk of harm any time an out-of-control condition occurs.

**Inappropriate medical decisions**

The amount of actionable information contained in a patient result depends on the analyte. Some analytes are critical to the medical decisions and actions taken; others are peripheral. Therefore, for some analytes it is much more likely that an erroneous reported patient result will lead to inappropriate decisions or actions. For analytes where the likelihood is low that erroneous reported results will lead to inappropriate actions, the lab can tolerate reporting more erroneous results without significantly increasing patient risk. In this case, less frequent QC testing may be acceptable. Conversely, for analytes where the likelihood is high that erroneous results will lead to inappropriate actions, the lab needs to be much more stringent in not allowing erroneous results to be reported, and more frequent QC testing is advised.

For instance, compare troponin to albumin. Troponin results form a significant part of the clinical diagnostic decision. While other parameters are considered, most of the decision about what to do with a patient presenting with chest pains relies on the troponin result. If there is a credible, positive troponin result, chances are very high that clinical action will be taken because of it. So it is unlikely that a lab will have the same tolerance for erroneous troponin results that it has for erroneous albumin results. Laboratories are more likely to establish tighter QC programs for troponin than they might.
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Molecular analysis of the individual microbiome

By John Brunstein, PhD

When we hear of next generation sequencing (NGS) methods in the context of clinical applications, most of us probably first think of it as applied to an individual’s nuclear genome—his or her innate chromosomal DNA, carrying information relating to inherited diseases, drug metabolism, and other aspects of “personalized medicine.” However, NGS can also be applied to the analysis of microbiomes (that is, the identities and relative numbers of different microorganisms) specific to both the individual and the sampling site. As we’ll review in this month’s installment of “The Primer,” there are a number of valuable clinical applications.

NGS in action

Here’s a quick reminder of how NGS systems work as applied in this use. A sample is diluted into microscopic reactions in such a way that each tiny reaction has a single template molecule. There are a number of other steps too, collectively known as “library generation,” which include fragmenting the nucleic acids to be analyzed into short pieces suitable for analysis by the chosen NGS chemistry and platform and ligating on various “barcodes” and adapters required for the process, but for today’s purpose that’s all pretty much behind the scenes. So too is the tiling process (where all of the individual short reads from each microscopic reaction are examined, areas of obvious overlap identified, and longer contiguous reads assembled out of these).

If we’re interested in the microbiome, there’s also going to be a first pass bioinformatics step which identifies and removes all of the human-derived sequences in our results, and then a second pass bioinformatics step which identifies the remaining microbial species. Because the NGS approach works by dilution to single templates, if we’ve done this on DNA, we’re also able to determine at least relative abundance of the represented species; assuming this sampling is a purely stochastic process, if DNA fragments attributable to Organism A occur 10 times as often as fragments originating from Organism B, we can assume that there’s 10 times as much Organism A as Organism B genetic material in the sample.

To convert this to something more meaningful, we’d also want to know what the relative genome sizes are; in this example, if Organism A has a genome twice as large as Organism B, then the actual relative abundance would be 5A:1B as expressed in GEq (Genome Equivalents, which is the molecular analogy to CFUs (Colony Forming Units) where one such unit equates essentially to one discrete organism. The caveat there is needed because unlike a CFU, a GEq doesn’t necessarily equate to a viable organism; for instance, if the specimen is from a patient recently treated with antibiotics, the CFU values might be significantly lower than GEq values.

Because we’re using an NGS approach here, we can at least in theory extract other information such as the presence or absence of particular antibiotic resistance markers or genes for specific toxins or virulence factors in each organism. While there are simpler, cheaper, faster molecular methods such as qPCR for direct interrogation of a sample for the presence of these kinds of markers, they’re not tremendously informative in the context of mixed microbial populations, as it may not be possible to know which organism(s) host which resistances. (It’s also worth bearing in mind that, strictly speaking, antibiotic resistance is defined on a phenotypic level at pre-established drug concentration “breakpoints”; the presence of a particular antibiotic resistance gene marker is a prerequisite for such resistance but not strictly a proof that it is expressed to a level meeting the formal requirement for being considered resistant. In many cases, however, presence of the associated markers is used to direct therapy choices, as the correlation between marker presence and functional resistance is very good.)

In the clinical setting

What are some of the clinical settings where this molecular approach to microbiome analysis is used? One obvious example is in the setting of cystic fibrosis, where classical culture methods on airway samples have been historically used to monitor disease progression and to inform therapeutic choices. This is a notoriously microbiologically diverse setting, including not just the “usual suspect” pathogens Pseudomonas aeruginosa, Staphylococcus aureus, and Burkholderia cepacia but also many anaerobic species. Obtaining accurate quantitative loads across this diversity with classical methods is challenging to say the least, as well as time-consuming.

By contrast, NGS methods will detect and enumerate readily cultured organisms as well as more fastidious ones, allowing for what is probably a less biased and more accurate representation of actual relative populations. The applicability of molecular methods in this specific application was immediately obvious, and indeed some of the earliest publications on NGS applications to clinical microbiology are found in the CF field. The utility of the method extends well outside of just the CF background, however, including, for example, the impact of respiratory microbiome on response to viral infections.1

Another obvious microbiome of significance is that of the GI tract. Aside from the not-so-subtle expressions of this that are familiar to travelers—particularly those with a predilection for purchasing exotic local delicacies from questionable vendors—there is a constant and very complex web of interactions between gastrointestinal microbiota and overall immunity (for
example see reference 2) and even neurological function (the so-called "gut-brain axis"); publications in this vein have examined impacts of gut microbiota on everything from mood to Parkinson’s disease). In fact because of this complexity, it’s probably fair to say that at present we can’t generally make much immediate clinical use of gut microbiome data—not because there isn’t a lot of valuable data there, but because we currently lack enough information and correlative observations to see the useful information amid the bulk data. This is certain to change as further research is done, and it would not surprise this author if in five years or a decade from now, we see gut microbiome workups as a common diagnostic component of a range of conditions, some of which won’t be directly digestive in overt nature.

Beyond these two very obvious microbiome sites, there are of course a range of other sampling sites and types which are likely to yield information. These include skin, upper airway (as opposed to deeper respiratory), various surface-exposed mucosal sites, and the reproductive tract. While the oft-quoted “statistic” that there are many more bacterial cells than human cells in the average person has been shown to be inaccurate, best estimates are that it’s at least in the range of 1:1, with perhaps a slight bias towards the bacteria (30 trillion human cells to 39 trillion bacterial cells in a hypothetical 170 cm tall, 70kg, 20 to 30-year-old male). So perhaps it’s high time we realize that we’re more ambulatory communities than unitary organisms, and begin giving more attention to the impact of our unicellular tenants.

Aside from the kinds of applications touched on above, are there other ways in which NGS microbiome sampling could be of medical use? There are, with one being the search for potential etiological agents of orphan diseases. Analyses of microbiomes in disease cases versus controls can be used to identify what appear to be significant changes in composition (species present and/or relative numbers), although they provide no information as to whether this is causal or purely correlative in nature. Combination of this short list of candidate organisms with testable mechanistic hypotheses and model systems can then be applied toward fulfillment of Koch’s Postulate in actually proving or disproving causal linkage, with potential for impacts on treatment strategies.

Another application, but one which would likely only come into use if some sort of “microbiome snapshot” becomes a more routine part of a diagnostic workup, would be in the tracking and tracing of outbreaks. Molecular methods have been applied in this context for years; for example, in an outbreak of Salmonella cases, molecular fingerprinting has been used to ensure that the cases being tracked are indeed all likely from a common source, and not just unrelated statistical anomalies. If large pools of relevant microbiome data were being collected and available for public health scrutiny, we’d probably be in a position to have faster and more comprehensive detection of food-associated outbreaks and faster tracking of root sources.

**It’s becoming more feasible**

The impediments to all of these and other possible applications of NGS microbiome analysis of human samples remain ones of basic cost, throughput, time, and return on investment. Advances in methods and devices continue to bring NGS costs down, however, while simultaneous gains in computational capacity per unit cost assist on the bioinformatics side. As these costs come down and our appreciation for the value of the data increases, the ROI metric will begin to tip in favor of broader application of the method.

Has all of the above whetted your appetite for a deeper look at clinical applications of NGS for microbiomes? As further reading, you might turn to reference 4, a fairly recent review with a broad focus.

**REFERENCES**

What’s the “buzz” in software?

The Lean approach
Increased regulations and reimbursement cuts for Anatomic Pathology Services have forced AP labs to scrutinize options in reducing their operating costs. Lean Process Improvement is becoming a popular methodology, or a structured approach, that is used to obtain cost-reduction goals. It is a belief held by everyone in the organization that, however efficient the lab is operating, there is always opportunity to improve operational efficiency. It is a way of life, a philosophical approach, and a continual commitment by all to eliminate waste in a way that improves the financial health of the lab, streamlines internal processes, and improves efficiency, while enhancing patient care.

Critical to the Lean approach is the ability to retrieve, analyze, and report on data relevant to the processes within the lab. Software programs, referred to as "Business Intelligence Tools" (BI Tools), are commercially available to aid in meeting this real-time need for information. Ideally, the BI Tool and the Lean Process Improvement methodology should be tightly integrated into, or part of, the Anatomic Pathology LIS, combining streamlined workflow, business intelligence, and the commitment of the lab to continuous process improvement and financial efficiency.

Scalable IT solutions
Laboratorians, when evaluating new instrumentation, often focus on physical attributes and analytical capabilities such as higher throughputs, faster TATs, and/ or analyte specificity. Analyzer software was there to provide the basic information around system operation, calibration, and patient test result access. Though that is still true today, users have come to expect much more from their analyzer’s software and user interface. They expect that the analyzer software will help them to actively manage instrument performance and laboratory data.

Software of the future should help the laboratory by creating a product offering that utilizes the same look and feel so that user familiarization is shorter. Software should provide information to users beyond just a patient’s results to include the process it took to get the results. Software should provide users with access to 24x7 support if their processing is impeded. The software package should have state-of-the-art security to prevent possible disruptions in the service it supports. The software package should offer flexibility to integrate not just into the laboratory’s workflow, but also into its data systems.

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continued on page 58
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Cloud-based data management solutions
The future of the clinical lab lies with integrated, cloud-based laboratory information management systems (LIMS), designed to respond to an increasingly complex scientific environment. Today, labs are challenged with collecting, storing, and analyzing unprecedented volumes of data, while also complying with stringent regulatory requirements. There is a real need for digital solutions, such as LIMS, that can be seamlessly integrated with analytical instrumentation, and simultaneously manage data from multiple sources, which can be securely shared with remote collaborators.

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Unpacking Medicare’s final policy on next-generation sequencing for patients with advanced cancer

Samuel K. Caughron, MD, FCAP

This spring, the Centers for Medicare and Medicaid Services (CMS) released its final National Coverage Determination (NCD) for next-generation sequencing (NGS) for Medicare beneficiaries with advanced cancer. Considering the unclear and potentially harmful language in the preliminary draft version, the final NCD policy should be considered a major success for clinical laboratory professionals, academic medical centers, leading cancer institutions, patient advocacy groups, and, most importantly, cancer patients across the country. While our collective efforts to share expertise and educate stakeholders ultimately helped convince CMS to make significant improvements to the policy, many important questions still remain unanswered. Clinical laboratory professionals are now intently focused on understanding how this policy will be operationalized and implemented.

I currently chair the Economic Affairs Committee (EAC) for the Association for Molecular Pathology (AMP). AMP is a global organization representing more than 2,400 physicians, doctoral scientists, and medical technologists who are among the early adopters of molecular testing in clinical settings. Our members are committed to ensuring broad patient access and coverage for the thousands of high-quality, clinically-proven NGS-based tests that are currently recognized as the standard of care in oncology diagnostics.

When the preliminary policy was released, the EAC and AMP members actively engaged congressional offices on both sides of the aisle to express concerns and share success stories of how NGS-based tests, including laboratory-developed procedures (LDPs), are being used to benefit Medicare cancer patients every day. During the open comment period for the proposed coverage determination, AMP’s EAC submitted detailed recommendations with supporting evidence to refocus the scope of the final policy, highlighting significant inconsistencies with current coverage and coding structures for molecular pathology procedures utilizing NGS-based platforms.

We are encouraged that CMS considered our feedback and made important changes. Specifically, the final NCD aligns with AMP’s recommendations in two major ways:

First, AMP recommended that the final NCD apply only to FDA-approved NGS-based in vitro diagnostics. The coverage was authorized as part of the parallel review process and therefore appropriately addresses FDA-reviewed tests. However, as originally drafted, the policy went significantly further and excluded coverage for all other NGS-based testing for cancer patients. NGS-based LDPs provide clinically significant information for cancer patients and have already been designed and validated to meet or exceed Clinical Laboratories Improvement Amendment (CLIA) standards, and/or other federal, state, and professional accreditation organizations’ standards. The final NCD acknowledged these existing, time-tested LDP oversight entities and focused the national policy limitation primarily on FDA-reviewed NGS-based assays.

Second, AMP recommended that coverage for other appropriately validated NGS-based tests should continue to be determined by Local Coverage Determinations (LCDs) administered by Medicare Administrative Contractors (MACs). The broadly restrictive preliminary NCD would have superseded existing LCDs with established evidence-based coverage policies, thereby reducing patient access to these valuable tests. The policy would have disrupted the current high-quality patient care provided by many academic hospitals, leading cancer institutions, and community medical centers across the country.

Now that the final NCD has been released, the task of operationalizing its directives is underway. Within the coming months, CMS is expected to provide coding and implementation instructions to the MACs. These instructions will reveal CMS’s true intent. Hopefully, the final instructions will provide further positive developments in the form of patient-centered interpretive directives. In the meantime, laboratories are left with unanswered important questions. AMP is now working to obtain clarity on specific aspects of the NCD via direct communication with CMS, including:

• How will the new NCD align with the patient criteria outlined in both existing and new LCDs? For example, will MACs be able to provide coverage in LCDs that is broader than the NCD criteria, such as coverage in stage 2 patients?
• Is the specific terminology used to describe staging for advanced cancer in the final NCD meant to encompass all advanced malignancies? If so, how should the terminology be understood? Additionally, how should the NCD be interpreted for cancers that do not utilize traditional staging terminology?
• As science evolves and/or new indications are added to FDA labeling, how will the NCD be updated?

With the finalizing of the NCD, AMP believes the most significant issues with the policy were avoided. However, many questions about what the NCD means for individual laboratories remain. Because most molecular testing is provided at the local level, AMP members in those laboratories are sailing in the proverbial uncharted waters.

AMP is committed to working with policymakers to ensure appropriate implementation of the national policy that maintains access to NGS-based testing by laboratories across the country. Moving forward, members will continue to share our collective expertise, provide specific examples, and work with key stakeholders to further improve Medicare coverage and overall quality of patient care. We remain intently focused on preserving broad access to all of the accurate and reliable procedures, including the thousands of successful laboratory-developed testing procedures that benefit patients every day. Without precision diagnostics, there is no precision medicine.

Samuel K. Caughron, MD, FCAP, serves as Chair of Pathology & Laboratory Medical Director for Shawnee Mission Medical Center (Kansas), and Managing Partner & Director of Molecular Lab for MAVD Pathology Group.
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EUROIMMUN, www.rsleads.com/808-154

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EXECUTIVE SNAPSHOT :: BY ALAN LENHOFF, EDITOR

Sarilyn Johnson-Carter fuels innovation as Bio-Rad U.S. Clinical Diagnostics Sales Director

Please describe the career path that has led you to your current position. I started by being a lab customer, and I think that is the experience that has been the most valuable for me. Then, as my career developed further, I worked in technical, operations, and commercial roles. I’m most proud of the impact I’ve made managing and building highly functioning teams.

Professional
I have been with Bio-Rad as Sales Director, U.S. Clinical Diagnostics Group, for approximately two years. Prior to Bio-Rad, I worked for Abbott for more than 25 years, primarily in Diagnostics, but in several of their other medical business franchises as well.

Education
I have a BS degree in Microbiology from Louisiana State University (LSU), advanced coursework in Biomedical Sciences from LSU Health Sciences Center in New Orleans, and I have multiple leadership and business certifications.

Personal
I have been an active supporter of various community organizations in places where I have resided and relocated with my family, including Louisiana, Texas, California, Illinois, and Puerto Rico. My interests and hobbies include sports, music (jazz), and travel. I am grateful to a large network of friends, mentors, colleagues, and family, who have given my life purpose, supported my career progression, and kept me on track over the years.

The output includes improvements in efficiency, customer satisfaction, sales growth, new products launches, product and solution development, and enhanced business relationships.

What are some of your primary responsibilities? I am responsible for U.S. sales, representing Bio-Rad’s Clinical Diagnostics Group, leading a team of more than 125 sales, technical, and business development professionals. Our team delivers highly valued and market-leading quality control, autoimmune, immunohematology, diabetes, newborn screening, and other products and services to laboratories across the United States.

In your view, what skills, professional and interpersonal, are vital for a manager in a position like yours? How can “leadership” be defined and measured? The most important interpersonal skills that I have are passion and open/direct communication. My energy and passion come from being authentic, loving what I do, and being a champion for change to achieve the best personally, with our team, and with our customers. People respect my honesty; they hear exactly what I am thinking and my expectations, perceptions, and ideas. I think that the three most important skills for effective leadership in this position are, first, strategic planning, to serve our customers better and grow and launch new products; second, communication, to drive alignment with the needs of our customers across our organization and inspire and motivate our employees to achieve our vision; and third, learning and collaboration to improve our capabilities by driving change.

What role do you play in managing product launches? Can you give examples? My role in managing product launches involves the execution. For example, after the R&D stage and obtaining FDA approval for a product, our marketing team will have a launch strategy for commercial execution of the product launch. The four essential elements to first-year launch success are being: 1) technically prepared; 2) well-aligned with customer needs; 3) flexible with contingency plans; and 4) consistent in messaging multi-channel promotion and communication.

The clinical lab industry is facing regulatory, reimbursement, and other challenges today. How do these impact your efforts on behalf of Bio-Rad and its customers? The clinical laboratory industry continues to face price and laboratory consolidation pressures every year. These challenges impact a diagnostics company’s ability to justify the value of higher-quality products as customers seek lower prices and sometimes compromise their criteria due to budgetary constraints. In this type of environment, technical differentiation becomes more challenging. And companies like Bio-Rad may find it more difficult to gain a return on investment for newly developed technologies and products.

One challenge the industry faces is the aging lab workforce and the resulting shortage of skilled laboratorians. How can current and future technologies address this problem? Most IVD companies are deploying technology that does a good job of automating many of the manual, labor-intensive processes, as well as managing the replenishment of consumables and anticipating any potential issues that might be faced when a less experienced labor force may be operating equipment. Additionally, the evaluation, analysis, and management of test results across sites and methods can be enhanced with advanced IT solutions.

Future technologies will need to be even more user-friendly, error-proof, and adaptable to fit the needs of all access points to healthcare including physician office, direct-to-consumer, point-of-care and laboratories. And more focus on risk management, through enhanced quality assurance programs, may also be required to minimize the potential for an incorrect result to be reported by less skilled workforces.

This interview continues online at www.mlo-online.com.
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