MLO-online.com

MARCH 2019 ■ Vol 51 ■ No 3

MEDICAL LABORATORY OBSERVER

MLO®

The Peer Reviewed Management Source for Lab Professionals since 1969

Procalcitonin serial testing for sepsis

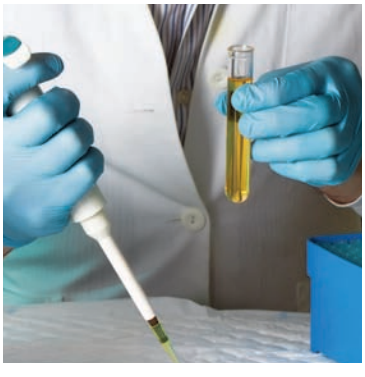
Automated immature granulocyte count

SMH lab techs talk automation

EXECUTIVE SNAPSHOT

Kristine Russell
EVP, Group Publisher
Endeavor Business Media

Urinalysis automation for a new level of standardization and workflow efficiency



Even today's most advanced urinalysis laboratories are only getting partial results from their urinalysis analyzers. Fluorescent flow cytometry is a highly effective screening tool but often requires review of abnormal patient samples. Imaging alone requires review and interpretation of these images on all samples tested. By combining urine flow cytometry with digital image analysis, Sysmex offers a highly standardized, reliable and accurate process for urine sediment analysis. Flexible user-definable rule settings and innovative, integrated technologies allow your laboratory to reach new levels of control, quality assurance and efficiency. Less manual microscopy. More time to focus on the scientific expertise laboratory professionals provide.

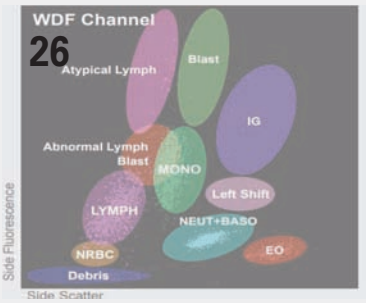
Learn more today at www.sysmex.com/UA

RAISE THE BAR.

- **UF-5000™ FULLY AUTOMATED URINE PARTICLE ANALYZER**
  Eliminate time consuming hands-on review by screening for samples with pathological elements
- **UD-10™ FULLY AUTOMATED URINE PARTICLE DIGITAL IMAGING DEVICE**
  High-quality digital camera provides detailed images of urine particles
- **SOFTWARE SOLUTIONS**
  BeyondCare℠ Quality Monitor (BCQM) Quality control — simplified.

sysmex | Lighting the way with diagnostics

MEDICAL LABORATORY OBSERVER
MLO®
The Peer Reviewed Management Source for Lab Professionals since 1969



4 From the editor

6 The observatory

CONTINUING EDUCATION

8 Procalcitonin serial testing to inform treatment of sepsis
By Chris Ann Dague, BSMT

12 CE Test
Tests can be taken online or by mail. See page 12 for testing and payment details.

CLINICAL ISSUES

14 The shifting spectrum of emerging infectious diseases
By Linda L. Ross, MS, MLS (ASCP)^{cm} SM and Linda L. Williford Pifer, PhD, SM (ASCP), GS (ABB)

LAB MANAGEMENT

20 Sarasota Memorial Hospital laboratory techs talk automation
By Editors Lisa Moynihan and Janette Wider

24 Leveraging automation as a strategy to overcome today's laboratory challenges
By Rita White

SPECIAL FEATURE

26 Advanced clinical parameters: achieving efficiency with the automated immature granulocyte count
By Mary Anne Loafman, MS, MT(ASCP)SH

EDUCATION

32 Accelerating cancer biomarker development using the latest mass spectrometry tools and techniques
By Yue Xuan, PhD

THE PRIMER

38 Limits of detection—is not detected always synonymous with not present?
By John Brunstein, PhD

BEST PRACTICES

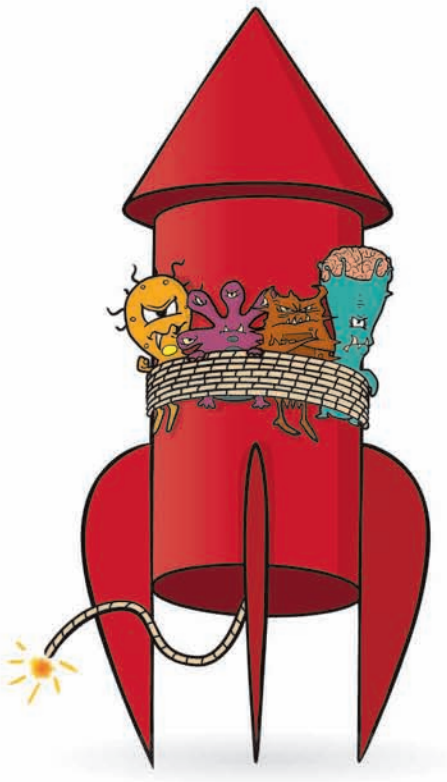
40 AI and interpretive algorithms
Obtaining accurate and efficient results in clinical MDx
By Susan Sharp, PhD

EXECUTIVE SNAPSHOT

44 A conversation with Kristine Russell on the ongoing history of *MLO*
By Janette Wider, Editor

Boost lab performance.

Better lab results and patient outcomes with syndromic infectious disease testing from BioFire.



Having the right tools at your disposal makes your lab invaluable to the hospital and physicians. The ability to consistently provide fast, reliable test results helps ensure better patient outcomes down the line. The BioFire® FilmArray® System utilizes a syndromic approach—simultaneously testing for different pathogens that can cause similar symptoms—to deliver actionable results in about an hour. Plus, the footprint is small and user-friendly with a streamlined workflow to improve productivity.

Fast: Rapid turnaround time facilitates efficient diagnosis and treatment decisions.

Easy: With just 2 minutes of hands-on time, the BioFire System is easily used by any tech, on any shift, and at any size institution.

Comprehensive: One test to check for a broad spectrum of pathogens—viruses, bacteria, parasites, fungi, and antimicrobial resistance genes.

Learn more about solutions from the leader in syndromic testing at **biofiredx.com**.

BioFire® FilmArray® Panels

Tests available for your lab:

- **Respiratory**
  1 Test / 21 Targets / 45 Minutes
- **Blood Culture Identification**
  1 Test / 27 Targets / 1 Hour
- **Gastrointestinal**
  1 Test / 22 Targets / 1 Hour
- **Meningitis/Encephalitis**
  1 Test / 14 Targets / 1 Hour
- **Pneumonia**
  1 Test / 33 Targets / 1 Hour

BIO FIRE®

A BIOMÉRIEUX COMPANY

Syndromic Testing: The Right Test, The First Time.

A round of applause for the laboratorians

By Janette Wider
Editor

Your job as a laboratorian may often feel thankless. Perhaps the doctors and nurses at your facility take for granted what you do. And maybe your friends and family don't even *know* what a medical laboratory technologist *is*. So, here at *MLO*, we want to take the opportunity in our 50th anniversary edition to say:

Thank you for everything that you do!

Medical laboratory scientists are an amazing breed, that has an aptitude for science, and utilize their critical thinking skills day in and day out. You put your life at risk by working in an environment where there are biohazardous materials like blood, urine, and tissue samples. Many of you have long hours, due to the lab being open 24/7, which means overnights, weekends, and holidays. You all surely spend a large portion of the day on your feet, which can lead to physical repercussions.

But you do it all for the patients.

Laboratorians play such an integral role in the healthcare system. Your job is to assist physicians in the diagnosis and treatment of diseases—these test results are where the patient who's been waiting for some answers can finally begin to see the light. For a patient who is waiting on a cancer diagnosis, they are depending on you, whether they know it or not.

My co-editor and I recently had the opportunity to tour Sarasota Memorial Health Care System's laboratory (read the article on page 20) and could *not* have received a warmer welcome into their workspace. I can't remember one tech that didn't have a huge smile on their face when we were chatting. As we all know, any kind of work comes with frustrations, but the group truly seemed cheerful and positive, despite any of the day's obstacles.

A lot of the article is about the shift toward automation in the lab. There's no question that troubleshooting analyzers is a tough job, but no one really complained. They just stated they wanted to do the best job they could (saying they may need more training on fixing equipment or need more practice) for the hospital, the physicians, the nurses, and of course the patients. Which, honestly, is the most selfless attitude that I've ever seen at any place I've been invited into to conduct interviews. To me, it finally seemed like I was interacting with a group that wasn't about the dreaded *bottom line*.

My background is mostly in healthcare information technology, so it was interesting to hear the old-school techs discuss laboratory information systems and joke about when file cards were all they used. A major change like computers could have turned a lot of staff off the whole field, but it was clear to me that all of them pushed through, learned the new technology, and most importantly…embraced it.

To wrap things up, I thought it was only fitting to dedicate this editorial in our 50th anniversary edition to all the laboratorians who read *MLO*. Thank you again, for everything you do. Your profession may not be the most well-known, or glamorous (how could anything involving urine samples be?) but know that the staff at *MLO* and your fellow laboratorians, all recognize your hard work, dedication, and loyalty to the job.

Janette Wider

MEDICAL LABORATORY OBSERVER

MEDICAL LABORATORY OBSERVER Vol.51, No.3

Publisher/Executive Editor
Kristine Russell
krussell@mlo-online.com

Editor
Lisa Moynihan
lmoynihan@mlo-online.com

Editor
Janette Wider
jwider@mlo-online.com

Graphic Artist
Patti Connors
pconnors@endeavorb2b.com

Audience Development/List Rentals
Laura Moulton
lmoulton@endeavorb2b.com

Ad Traffic Manager
Norma Machado
nmachado@endeavorb2b.com

eProduct Coordinator
Mary Haberstroh
mhaberstroh@endeavorb2b.com

ADVERTISING

East Coast/Midwest Sales (except IL)
Classified/Recruitment Advertising
Carol Vovcsko
(941) 321-2873
cvovcsko@mlo-online.com

South/West Coast/Illinois Sales
Lora Harrell
(941) 328-3707
lharrell@mlo-online.com

CORPORATE TEAM

ENDEAVOR BUSINESS MEDIA

Chris Ferrell, CEO
Patrick Rains, COO
Scott Bieda, EVP
Kristine Russell, EVP
Tracy Kane, VP, General Counsel

2477 Stickney Point Rd., Suite 221B Sarasota, FL 34231
Phone: (941) 388-7050 Fax: (941) 388-7490
www.mlo-online.com

VERIFIED AUDIT CIRCULATION

MLO - MEDICAL LABORATORY OBSERVER
(ISSN: 0580-7247). Published monthly, with an additional issue in August, by Endeavor Business Media, LLC., 2477 Stickney Point Rd, Suite 221B, Sarasota, FL 34231 (941) 388-7050. Subscription rates: $127.60/year in the U.S.; $154.88 Canada/Mexico; Intl. subscriptions are $221.43/year. All issues of *MLO* are available on microfilm from University Microfilms International, Box 78, 300 N. Zeeb Rd., Ann Arbor, MI 48106. Current single copies (if available) $15.40 each (U.S); and $19.80 each (Intl.). Back issues (if available) $17.60 each (U.S.); $22.00 each (Intl.). Payment must be made in U.S. funds on a U.S. bank/branch within the continental U.S. and accompany request. Subscription inquiries: subscriptions@endeavorb2b.com. *MLO* is indexed in the *Cumulative Index for Nursing and Allied Health Literature* and *Lexis-Nexis*. *MLO* Cover/CE, Clinical Issues, and Lab Management features are peer reviewed. Title® registered U.S. Patent Office. Office of publication: Periodicals Postage Paid at Sarasota, FL 34276 and at additional mailing offices. **Postmaster:** Send address changes to **MLO MEDICAL LABORATORY OBSERVER,** 2477 Stickney Point Rd, Suite 221B, Sarasota, FL 34231.
Printed in U.S.A.

Save More Lives.

by screening for colorectal cancer.

OC-Auto® 80 MICRO

Automated FIT (Fecal Immunochemical Test)

- Only FDA cleared automated FIT
- Recommended FIT by the USPSTF - "The OC-Light and the OC FIT-CHEK (OC-Auto) family of FITs (Polymedco, Inc., Cortlandt Manor, NY) have the best test performance characteristics (i.e., highest sensitivity and specificity)."[1]
- 1 patient sample
- Completely closed sampling bottle
- Convenient patient take home packs and absence of dietary restrictions for maximum patient compliance

epi pro colon®

Blood Test for Colorectal Cancer Screening

- FDA Approved for colorectal cancer screening for people who are unwilling or unable to be screened by recommended methods.
- Epi proColon is a molecular test that detects methylated Septin 9 DNA in blood.
- DNA methylation of the SEPT9 gene is increased in colorectal cancer.
- Methylated Septin 9 DNA can be found in tumor DNA that has been shed into the bloodstream from proximal and distal colon and rectal sites, making it a differential biomarker for the early detection of colorectal cancer.

"Increasing screening rates to 80% by 2018 would prevent 277,000 new cases of colon cancer and 203,000 deaths within 20 years."[2]

POLYMEDCO

www.polymedco.com
info@polymedco.com
800-431-2123

1. http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/colorectal-cancer-screening2
2. http://www.cancer.org/cancer/news/news/impact-of-achieving-80-by-2018-screening-goal

FAST FACTS

Measles

Measles is a highly contagious, serious disease caused by a virus. Here are some interesting statistics:

1963

is the year the measles vaccination was introduced.

110,000

is the number of measles deaths in 2017, globally.

85 percent

of the world's children received one dose of measles vaccine by their first birthday in 2017.

21.1 million

estimated deaths were prevented by the measles vaccination from 2000-2017.

95 percent

of measles deaths occur in countries with low per capita incomes and weak health infrastructures.

10-12 days

after exposure to the virus is usually when a high fever begins.

4 days

prior to the onset of the rash—to 4 days after the rash erupts—is the amount of time the virus can be transmitted from an infected person.

2 hours

is the amount of time the virus remains active and contagious in the air or on infected surfaces.

• **Source:** https://www.who.int/news-room/fact-sheets/detail/measles

Assays

New blood test to help identify Ara h 6 peanut sensitization. A new test from Thermo Fisher Scientific helps allergists and other medical providers better predict which patients may be at risk for life-threatening sensitization to Ara h 6, a protein component in peanuts that can cause severe allergic reactions in certain individuals. Thermo Fisher's ImmunoCAP Specific IgE blood test for Ara h 6, part of a line of assays for detecting specific peanut allergen components, has been cleared by the U.S. FDA for in vitro diagnostic use.

Results from Ara h 6 ImmunoCAP testing can act as an aid to help specialists and other clinicians better understand patients' risk factors as part of a tailored allergy treatment or management plans. In some cases, it could reduce the need for oral food challenges, a testing method where a healthcare professional feeds a patient food in measured doses to see if it triggers an allergic reaction.

Advanced diagnostic capabilities for peanut allergies can contribute to better outcomes for allergy sufferers, especially young children. Patients should consult with their healthcare professional or healthcare provider to get tested for individual peanut components. This knowledge helps the clinician understand potential risks, leads to more informed allergy management, and provides renewed peace of mind for patients and parents.

The newest addition to the ImmunoCAP line of component allergy tests also includes assays for cross-reactive carbohydrate determinants (CCD) and profilins, which are both allergens contained in various plants, pollens, and foods. Sensitization to CCD and/or profilin usually does not cause any symptoms but is due to cross-reactivity with certain plants and pollens.

ImmunoCAP blood testing is the most widely used specific IgE blood test, and its accuracy has been documented in more than 4,000 peer-reviewed publications. The tests can identify allergic sensitization to common environmental allergens—seasonal and perennial, indoor and outdoor—as well as common food allergies such as peanuts, eggs, and milk. ImmunoCAP tests, which are available in most major U.S. laboratories, can be ordered for patients of any age regardless of skin condition, current medication, symptom, disease activity, or pregnancy status.

Immunotherapies

Study links psoriasis treatment and improvement in heart artery disease. Researchers have found that treating psoriasis with biologic drugs that target immune system activity can reduce the early plaque buildup that clogs arteries, restricts blood flow, and leads to heart attacks and stroke. The findings highlight how immunotherapies that treat inflammatory conditions might play a role in the reduction of cardiovascular disease risks. The study was funded by the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health (NIH).

Researchers provided first in-human evidence that treatment of a known inflammatory condition with biologic therapy, a type of drug that suppresses the immune system, was associated with a reduction in coronary artery disease, in particular of rupture prone plaque which often leads to a heart attack.

Psoriasis, a common skin disease affecting 3-5 percent of the U.S. population, is associated with heightened systemic inflammation, which elevates risk of blood vessel disease and diabetes. Inflammation occurs when the body's defensive mechanism kicks in to ward off infection or disease, but this mechanism can turn against itself when triggered, for instance, by excess low-density lipoproteins (LDLs) that seep into the lining of the arteries.

The resulting inflammatory response can cause blood clots, which block arteries and can lead to heart attack and stroke. Inflammation puts 20-30 percent of the U.S. population at risk for these kinds of events. People with inflammatory diseases such as rheumatoid arthritis, systemic

lupus erythematosus, and psoriasis have a much higher rate of cardiovascular events.

Those high rates make worse already troubling numbers: more than 15 million Americans, and many more worldwide, suffer from atherosclerotic cardiovascular disease. Heart attack occurs in 750,000 individuals every year in the U.S.; globally, more than seven million people had heart attacks in 2015.

Opioids

FDA finalizes policy on new buprenorphine treatments for opioid use disorder. The U.S. FDA issued a final guidance, "Opioid Use Disorder: Developing Buprenorphine Depot Products for Treatment," which outlines the FDA's current thinking about drug development and trial design issues relevant to the study of buprenorphine depot products, such as modified-release products for injection or implantation. The guidance includes minor changes to the draft document published in April 2018.

Improving access to prevention, treatment, and recovery services, including the full range of medication-assisted treatment (MAT), is a focus of the FDA's ongoing work to reduce the scope of the opioid crisis and one part of HHS' Five-Point Strategy to Combat the Opioid Crisis.

There are currently three FDA-approved drugs for MAT—methadone, buprenorphine, and naltrexone—that have been demonstrated to be safe and effective in combination with counseling and psychosocial support to treat opioid use disorder (OUD). Regular adherence to MAT with buprenorphine reduces opioid withdrawal symptoms and the desire to use opioids, without causing the cycle of highs and lows associated with opioid misuse or abuse. At proper doses, buprenorphine also blocks the pleasurable effects of other opioids, making continued opioid abuse less attractive.

When combined with the right treatments and supports, novel formulations or delivery mechanisms described in the FDA guidance—including passive-compliance formulations such as sustained-release depots and implants—can provide effective treatment of OUD, and may result in less misuse, abuse, or accidental exposure compared to self-administered formulations such as transmucosal tablets and films.

The guidance outlines ways that companies can more efficiently advance innovations in buprenorphine depot products—from the data needed to support approval, to the specific review pathways that are available to help streamline how sponsors consider their development plans. It also details the types of studies the FDA recommends for buprenorphine depot products that are similar to an approved depot product, as well as buprenorphine depot products with novel features relative to approved depot products.

HIV

Ending the HIV epidemic: a plan for America. Robert R. Redfield, MD, Director, Centers for Disease Control and Prevention (CDC) made the following statement regarding ending the HIV epidemic in America:

"I'm excited that CDC is part of this unprecedented opportunity to end the HIV epidemic in America. The Administration's plan will deploy the people and key prevention and treatment strategies needed to reduce new HIV infections by 75 percent over the next 5 years, with the hope of a 90 percent reduction within 10 years.

We have the tools to end new HIV infections in this Nation, but they must be applied now. The most recent data suggest that progress in reducing new infections has plateaued, and many communities remain vulnerable to HIV infection. Under this proposed initiative, we will focus on four key strategies to meet the needs of communities with the highest HIV burden: diagnose new HIV infections; treat those with infection rapidly and effectively; protect people from being infected through access to comprehensive prevention and treatment, including medications that can prevent infection; and respond quickly to and stop new outbreaks. To accomplish this, we will accelerate our work with state and local health departments. We will establish HIV elimination teams—for 'boots-on-the-ground' support—to ensure communities with the greatest burden make progress. We will listen to people living with HIV, and to public health partners in the most-affected communities, so we reach those in greatest need.

CDC is proud to have been part of the fight to prevent HIV from the very beginning, and we are honored to continue to work with our HHS colleagues on this important initiative. I thank the President and Secretary Azar for their visionary leadership in seizing this opportunity. The time to end the HIV epidemic is now. I have always believed in seeing the possible. Embracing the possible, we will do it together."

EBV

Binding Site offers recombinant EBV antigens for research and IVD manufacturing applications. Binding Site's Immunological Group announced the addition of five new recombinant Epstein-Barr Virus (EBV) antigens to its broad offering of products for in-vitro diagnostic (IVD) manufacturing and research applications.

The EBV Capsid Antigen P18; EBV Capsid Antigen P23; EBV Early Antigen P138; EBV Early Antigen P54; and EBV Nuclear Antigen EBNA1, P72 have all been expressly designed for use as integral components within solid phase enzyme immunoassay test procedures, especially ELISA.

All antigens offered are *E. coli* source-derived recombinant proteins which exhibit exceptional purity levels as a result of exclusive chromatographic manufacturing techniques, while demonstrating exceptional lot-to-lot consistencies and high degrees of activity and specificity. All feature a shelf life stability claim of ten years from the date of manufacture and are offered in a standard-sized 1.0mg filled vial, with larger, bulk packaging configurations available.

Procalcitonin serial testing to inform treatment of sepsis

By Chris Ann Dague, BSMT

Sepsis, also known as blood poisoning or septicemia, is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] Sepsis continues to be the leading cause of death in U.S. hospitals, representing around 25 percent of patients.[2-3] According to the CDC, of the 1.7 million American adults that develop sepsis, 270,000 die each year.[4]

The primary infections that lead to sepsis are respiratory (35 percent), genitourinary (25 percent), gastrointestinal (11 percent), and infections of the skin (11 percent).[2,4] The average length of hospital stay for patients with sepsis is considerable, at around 9 days.[4] With an annual cost of hospital care for sepsis patients estimated at around $24 billion in the U.S., the condition places a significant burden on the healthcare system.[5] However, with rapid diagnosis and treatment, as many as 80 percent of sepsis deaths could be prevented.[3]

LUMIPULSE G1200 fully automated immunoassay instrument; image courtesy of Fujirebio.

Antimicrobial resistance contributes to sepsis mortality rates

Effective treatment for sepsis requires timely administration of a suitable antibiotic to prevent a rapid, often fatal deterioration in a patient's clinical condition. However, the emergence of antimicrobial resistance (AMR) renders many antibiotics ineffective. Fueled by poor antibiotic stewardship—administering antibiotics unnecessarily or prescribing the wrong antibiotic at the wrong dose, and for the wrong duration—AMR has considerable potential to impact sepsis mortality rates.[6]

CDC estimates that 20-50 percent of acute-care hospital antibiotic prescriptions and 30 percent of outpatient antibiotic prescriptions in the U.S. are unnecessary, mostly caused when antibiotics are inappropriately prescribed for viral infections. Furthermore, it is approximated that more than 70 percent of the bacteria responsible for the two million infections acquired in U.S. hospitals each year are resistant to at least one commonly used antibiotic.[7] Unless effective measures are put in place to limit the development of AMR, these numbers are likely to rise.

Associated risks of antibiotic overuse include increases in disease severity, disease length, health complications, rehospitalization, and the need for medical treatment of health problems that may be resolved on their own. These factors can have a considerable impact on patient quality of life and contribute significantly to added healthcare costs.[7] To improve patient outcomes and antibiotic effectiveness, diagnostic and prognostic testing to aid antibiotic therapy decision-making has an essential role.

Antibiotic misuse contributes to *Clostridium difficile* infection

The incidence and severity of *Clostridium difficile* infection (CDI) has increased dramatically within the past two decades, making the *Clostridium difficile* bacterium the most common cause of nosocomial infections in developed countries. Responsible for almost half a million infections in the U.S. each year, CDI is associated with significant morbidity and mortality.[8]

Patients at increased risk of CDI include those receiving antibiotic therapy or patients who are immunocompromised through chemotherapy treatment or HIV infection.[9] Due to resultant diarrhea and the development of potentially life-threatening complications such as sepsis, CDI represents a substantial clinical burden.

It has been estimated that excess healthcare costs related to CDI could be as much as $4.8 billion for acute-care facilities alone.[10] In a meta-analysis, the average CDI-attributable cost per case was $20,085 for community-acquired CDI and $34,149 for hospital-acquired CDI. These figures were associated with an average length of stay of 5.7 days for community-acquired CDI and 7.8 days for hospital-acquired CDI.[11]

An average 20.9 percent recurrence rate has been reported for healthcare-associated CDI, resulting in an estimated 61,400 first recurrent infections.[10] Given the challenges of treating recurrences, and because almost all antibiotics are associated with an increased risk of CDI, initiatives aimed to reduce CDI incidence should target reduced antimicrobial exposure through effective antibiotic stewardship programs.[12]

Current methods to identify systemic bacterial infections require improvement

Signs of bacterial and viral infections frequently overlap, including elevated body temperature, heart rate, respiratory

Earning CEUs

See test on page 12 or online at www.mlo-online.com under the CE Tests tab.

LEARNING OBJECTIVES

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

1. Discuss the burden that sepsis places on the U.S. healthcare system.
2. Describe the past biomarkers used for sepsis determination and their limitations.
3. Discuss how procalcitonin (PCT) represents a superior biomarker for sepsis.
4. Recall the importance of PCT serial testing and how it applies to antibiotic stewardship programs.

rate, and leukocyte count. Although these parameters can be monitored easily, they are often inadequate to determine the nature of the infection. Further information can be gained by culturing urine, cerebrospinal fluid (CSF), bronchial fluid, or blood. However, such tests are time-consuming (up to 48 hours for urine, CSF, and bronchial fluid, 50-60 hours for blood) and negative cultures do not exclude infection.[2,13] Since time is crucial when treating sepsis, measurement of a relevant biomarker is far more appropriate.

Common biomarkers of sepsis include c-reactive protein (CRP), lactate, and the cytokine interleukin-6 (IL-6).[14] However, all of these have limitations. Relevant elevated CRP levels cannot be measured until 6 to 12 hours after an infectious challenge and takes 24 to 48 hours to peak adding considerable time to diagnosis.[15] Lactate is not specific to bacterial infections but instead poor tissue perfusion. Lactate is also elevated in individuals with acute myocardial infarction, hypotension, and heart failure, reducing its utility as a sepsis biomarker.[16] Cytokines such as IL-6, tumor necrosis factor-α (TNF-α), IL-1β, and IL-10 show low specificity for bacterial infections and increase only briefly or intermittently.[2,14] Furthermore, the variability in the course of time and individual patient kinetics for secretion of cytokines limits their use for diagnosis.

Procalcitonin (PCT) is a superior biomarker of systemic bacterial infections

Due to its improved sensitivity, specificity, and kinetics as compared to CRP, lactate, and IL-6, PCT is the preferred biomarker of sepsis. PCT is a 14.5kDa prohormone encoded by the CALC-1 gene, belonging to the calcitonin super-family of peptides. The production of calcitonin is exclusive to the parafollicular cells (C cells) of the thyroid. In healthy

LUMIPULSE G1200 B·R·A·H·M·S PCT Immunoreaction Cartridges; image courtesy of Fujirebio.

individuals, PCT is produced only in the thyroid, but in the presence of an infection may be produced by extra-thyroidal tissues.[2,25] In healthy individuals, circulatory PCT levels are very low (0.05ng/mL).[2,17]

In the presence of bacterial infection, PCT expression is induced in virtually all tissues and organs. This occurs either directly via microbial toxins or indirectly through a humoral or a cell-mediated host immune response. Since non-neuroendocrine parenchymal tissues lack the ability to cleave PCT to calcitonin, a dramatic increase in serum PCT levels result.[2] This can be detected approximately four hours after the bacterial challenge, peaking at 12 to 24 hours—a far earlier response than provided by CRP.[17] With viral or parasitic infections, serum PCT levels are less likely to increase.[15] In contrast, CRP is positive for infectious and non-infectious reasons whenever inflammation is involved and is elevated in the presence of a viral infection.[14]

In a study comparing IL-6 to procalcitonin as a biomarker of sepsis, PCT demonstrated a far greater specificity of 97 percent vs. 67 percent, and a negative predictive value of 88 percent vs. 39 percent providing substantial support for its utility as a sepsis biomarker.[18]

In addition to the early and highly specific diagnosis of severe systemic bacterial infection and sepsis, PCT affords the ability to monitor the patient response to antibiotic therapy and the course of the disease.[19] Remaining elevated until the bacterial infection resolves, PCT levels have a half-life of 25 - 30 hours[2,19] providing physicians with a means to assess the therapeutic effect of treatment.

PCT has utility as a diagnostic guide

Since its identification as a reliable biomarker of sepsis, PCT has been studied in a wide range of infections. These include respiratory infections, post-operative infections, and ventilator-associated pneumonia. Importantly, PCT has also demonstrated proven utility to distinguish bacterial from viral meningitis[17] and has been used to evaluate the severity of CDI and other bacterial infections.[20,21]

A further advantage of PCT over other sepsis biomarkers is its use to diagnose bacterial infection in neutropenic patients.[17] Measurement of PCT levels can also be employed to distinguish sepsis from non-infectious systemic inflammatory response syndrome (SIRS) since normal or very low PCT plasma concentrations have a high negative predictive value to rule out SIRS.[22] Finally, PCT can be used in the differential diagnosis of urinary tract infections and urosepsis, as well as diagnosing catheter-related bloodstream infections (CRBSI) in critically ill patients.[20, 23]

PCT serial testing is essential for accurate results

For PCT testing to be effective, a baseline reading followed by serial measurements at 24-hour intervals is necessary. Although the baseline measurement can be used to indicate the presence of a systemic bacterial infection—prompting the initiation of antibiotic therapy—it should not be used in isolation to make clinical decisions. Serial measurements of PCT are essential.[24]

With effective antibiotic therapy, PCT, with a half-life of 24-hours, should show an approximate reduction of 50 percent with each day of treatment. PCT levels measured daily over the 72-hour treatment regimine should show a decline of 80 percent or more from the initial baseline.[21]

Antibiotic discontinuation is encouraged when PCT levels have dropped by 80 percent from baseline or are between 0.25 and 0.5 ng/mL, or when levels are >0.5 ng/mL and have dropped by <80 percent from baseline. Discontinuation is *strongly* encouraged when PCT levels are <0.25 ng/mL or have dropped by 90 percent from baseline reading. Using these FDA-cleared algorithms to guide antibiotic treatment, it has been possible to decrease antibiotic exposure without increasing adverse clinical outcomes for sepsis.[21]

Empowering physicians to assess the severity of sepsis, PCT serial testing appears to be an effective tool to guide clinical decision-making. Because clinical decisions are based upon serial measurements of PCT, it is important to use an immunoassay with high precision and sensitivity. This is especially pertinent when patients exhibit only low levels of the prohormone upon presentation.

PCT serial testing represents a major innovation for antibiotic stewardship

Due to its capacity to differentiate between bacterial and viral infections better than other biomarkers, PCT is an extremely powerful diagnostic assay. In initiating early antibiotic treatment or making an antibiotic switch where necessary, PCT serves as a good prognostic marker in sepsis to predict patients at risk of deteriorating.[26] In combination, these features enhance clinical decision-making to promote responsible antibiotic stewardship.

As well as contributing to antibiotic effectiveness, serial monitoring of PCT levels helps improve patient outcomes and reduce adverse effects, such as CDI, AMR, and lower respiratory tract infections (LRTI) through more efficacious treatment. In addition, PCT serial testing positively impacts healthcare utilization and cost-effectiveness for sepsis. This is achieved by reducing antibiotic therapy days, days in the ICU, and days spent on a regular ward, all lowering hospital costs by an estimated 20-30 percent.[27]

Proven efficacy of PCT serial testing

With a pressing need for hospitals to provide early, effective antibiotic treatment while reducing unnecessary treatment days, high sensitivity and precision are fundamental to serial PCT testing. This is especially important in the lower ranges of PCT, where critical medical decisions to initiate an antibiotic protocol are to be made. A retrospective study of 2,152 patients in a center with an antibiotic stewardship program assessed the impact of incorporating a PCT algorithm to guide antibiotic management, publishing the results in 2017.[21] The cohort with PCT testing experienced:

- 47 percent reduction in median days of antibiotic therapy, from 17 to nine days, with an associated reduction in costs of antibiotics
- 50 percent reduction in all-cause 30-day readmission rate, from 22.4 percent to 11.1 percent
- 50 percent reduction in adverse drug events from antimicrobials, from 16.2 to 8.1 percent
- 62 percent reduction in all-cause hospital mortality, from 7.6 to 2.9 percent deaths
- 64 percent reduction in CDI, from 2.5 to 0.9 percent

Although serial PCT testing requires upfront investments such as equipment, supplies, and staff education, these costs are more than offset by downstream savings which do not compromise patient outcomes.[27] Incorporating PCT algorithms for antibiotic treatment may be useful in decreasing hospital spending per patient by reducing the number of hospital days, the number of blood cultures, and days on antibiotic therapy.

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), JAMA, 2016;315(8):801-10.
2. Jin M, Khan AI. Procalcitonin: use in the clinical laboratory for the diagnosis of sepsis. Lab Med. 2010;41(3):173-177.
3. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence. 2013;5(1):4-11.
4. Centers for Disease Control and Prevention. Data & reports for the public: making health care safer. CDC website. https://www.cdc.gov/sepsis/datareports/index.html (Last accessed 2/9/2019)
5. Torio CM, Moore BJ. National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2013. Healthcare Cost and Utilization Project (HCUP). https://www.hcup-us.ahrq.gov/reports/statbriefs/sb204-Most-Expensive-Hospital-Conditions.jsp?utm_source=AHRQ&utm_medium=AHRQSTAT&utm_content=Content&utm_term=HCUP&utm_campaign=AHRQ_SB_204_2016 (Last accessed 2/9/2019)
6. Pradipta IS, Sodik DC, Lestari K, et al. Antibiotic resistance in sepsis patients: evaluation and recommendation of antibiotic use. N Am J Med Sci. 2013;5(6):344-52
7. Center for Infectious Disease Research and Policy (CIDRAP). Overuse and overprescribing of antibiotics. CIDRAP website. http://www.cidrap.umn.edu/asp/overuse-overprescribing-of-antibiotics. (Accessed 2/9/2019)
8. Centers for Disease Control and Prevention. Nearly half a million Americans suffered from *Clostridium difficile* infections in a single year. CDC website. https://www.cdc.gov/media/releases/2015/p0225-clostridium-difficile.html (Accessed 2/9/2019)
9. Baggs J, Jernigan JA, Halpin AL, et al. Risk of Subsequent Sepsis Within 90 Days After a Hospital Stay by Type of Antibiotic Exposure. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America. 2018;66(7):1004–1012.
10. Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. N Engl J Med. 2015;372(9):825-834.
11. Zhang S, Palazuelos-Munoz S, Balsells EM, et al. Cost of hospital management of *Clostridium difficile* infection in United States—a meta-analysis and modelling study. BMC Infect Dis. 2016;16(1):447.
12. Brown K, Valenta K, Fisman D, et al. Hospital ward antibiotic prescribing and the risks of *Clostridium difficile* infection. JAMA Intern Med. 2015;175(4):626-633.
13. Lin GL, McGinley JP, Drysdale SB, Pollard AJ. Epidemiology and Immune Pathogenesis of Viral Sepsis. Front Immunol. 2018;9:2147.
14. Blomkalns AL. Sick or not sick?: evolving biomarkers for severe bacterial infection. Emergency Medicine Cardiac Research and Education Group. https://pdfs.semanticscholar.org/1f67/eb51f3f9d88c83af59b0fbaf01a4ef237eeb.pdf?_ga=2.42132389.1009923110.1549572011-1693079622.1549572011 (Accessed 2/7/2019)
15. Simon L, Gauvin F, Amre DK, et al. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis. 2004;39(2):206-217.
16. Lazzeri C, Valente S, Chiostri M, Gensini GF. Clinical significance of lactate in acute cardiac patients. World J Cardiol. 2015;7(8):483-489.
17. El-Azeem AA, Hamdy G, Saraya M, et al. The role of procalcitonin as a guide for the diagnosis, prognosis, and decision of antibiotic therapy for lower respiratory tract infections. Egypt J Chest Dis Tuberc. 2013;62:687-695.
18. Harbarth S, Holeckova K, Froidevaux C, et al. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med. 2001;164(3):396-402.
19. Castelli CP, Pognani C, Meisner M, et al. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. Crit Care. 2005;8(4):R234-R242.
20. Sugimoto K, Adomi S, Koike H, Esa A. Procalcitonin as an indicator of urosepsis. Res Rep Urol. 2013;5:77-80.
21. Broyles MR. Impact of procalcitonin-guided antibiotic management on antibiotic exposure and outcomes: real-world evidence. Open Forum Infect Dis. 2017;4(4):ofx213.
22. Anand D, Das S, Bhargava S, et al. Procalcitonin as a rapid diagnostic biomarker to differentiate between culture-negative bacterial sepsis and systemic inflammatory response syndrome: a prospective, observational, cohort study. J Crit Care. 2015;30(1):218.e7-12.
23. Ozsurekci Y, Oktay Arikan K, Bayhan, C, et al. Can procalcitonin be a diagnostic marker for catheter-related blood stream infection in children? Jornal de Pediatria. 2016;92(4):414–420.
24. Rey Galán C. Biomarkers of severe bacterial infection: do they help in clinical practice? An Pediatr (Barc). 2016;84(5):247-248.
25. Schuetz P, Maurer P, Punjabi V, et al. Procalcitonin decrease over 72 hours in US critical care units predicts fatal outcome in sepsis patients. Crit Care. 2013;17(3):R115.
26. Shiferaw B, Bekele E, Kumar K, et al. The role of procalcitonin as a biomarker in sepsis. J Infect Dis Epidemiol. 2016;2(1):1-4.
27. Kip MM, Kusters R, IJzerman MJ, Steuten LM. A PCT algorithm for discontinuation of antibiotic therapy is a cost-effective way to reduce antibiotic exposure in adult intensive care patients with sepsis. J Med Econ. 2015;18(11):944-953.

Chris Ann Dague, BSMT, Product Manager,
Fujirebio US, Inc.

RANDOX
QUALITY CONTROL

ACUSERA

TRUE THIRD PARTY CONTROLS

Our Acusera range of true third party controls offer complete test menu consolidation. With more than 390 analytes available across the Acusera range of multi-analyte controls, and a wide range of formats providing flexibility and choice, we have the right QC solution to suit you, saving time and money whilst delivering reliable results you can trust.

CONSOLIDATION

The Acusera range of multi-analyte controls are designed to reduce the number of individual controls required to cover your test menu, ultimately reducing costs, preparation time & money.

FLEXIBLE OPTIONS

With an extensive range of assayed or unassayed, liquid or lyophilized and single or multi-analyte controls, the Acusera range has a solution to fit all laboratory requirements.

CLINICALLY RELEVANT LEVELS

The presence of analytes at key decision levels not only ensures accurate instrument performance, but maximizes lab efficiency by eliminating the need for low/high level controls at an additional cost.

COMMUTABILITY

Acusera controls are designed to mimic patient samples, helping to meet ISO 15189:2012 requirements whilst minimizing inconvenient and costly shifts in QC results when a reagent batch is changed.

randoxqc.com
marketing@randox.com
Visit randoxonlinestore.com to buy directly from Randox today

TEST QUESTIONS

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

1. **What percentage of patients that develop sepsis die during their hospitalization?**
   - a. 5
   - b. 10
   - c. 25
   - d. 50

2. **Which of the following infections lead to sepsis?**
   - a. lung, skin, genitourinary, and wound
   - b. gastrointestinal, wound, eye, and respiratory
   - c. ear, skin, genitourinary, and eye
   - d. gastrointestinal, skin, genitourinary, and respiratory

3. **As many as _____ percent of sepsis deaths could be prevented with rapid diagnosis and treatment.**
   - a. 50
   - b. 70
   - c. 80
   - d. 90

4. **Poor antibiotic stewardship is caused by**
   - a. unnecessary administration of antibiotics.
   - b. administrating the wrong antibiotic.
   - c. administrating the wrong dose or duration.
   - d. all of the above

5. **Of the nosocomial infections in the U.S., what approximate percentage of bacteria are resistant to at least one commonly used antibiotic?**
   - a. 25
   - b. 70
   - c. 80
   - d. 95

6. **Which bacteria is responsible for being the most common cause of nosocomial infections?**
   - a. *Clostridium difficile*
   - b. *Staphylococcus aureus*
   - c. *Escherichia coli*
   - d. *Streptococcus pneumoniae*

7. **Signs and symptoms of bacterial and viral infections overlap and are inadequate to determine the nature of the infection.**
   - a. True
   - b. False

8. **What is/are common biomarker(s) being used in the determination of sepsis that have proven limitations?**
   - a. lactate
   - b. IL-6
   - c. CRP
   - d. all of the above

9. **What biomarker is now considered preferred due to its improved sensitivity, specificity, and kinetics?**
   - a. lactate
   - b. PCT
   - c. IL-6
   - d. CRP

10. **Where is PCT converted to calcitonin before it is released into the circulatory system?**
    - a. thyroid gland
    - b. pituitary gland
    - c. liver
    - d. adrenal glands

11. **About four hours after a patient responds to a bacterial challenge, PCT levels rise because**
    - a. non-neuroendocrine parenchymal tissue cannot cleave PCT to calcitonin.
    - b. the liver destroys the calcitonin bound to PCT.
    - c. it is secreted by the thyroid gland.
    - d. none of the above

12. **Serum PCT is superior to CRP levels because CRP**
    - a. has a higher negative predictive value.
    - b. is elevated when the patient has a viral infection.
    - c. increases whenever any form of inflammation is present.
    - d. both b. and c.

13. **When comparing serum PCT to IL-6, PCT has been shown to have _____ specificity and _____ negative predictive value.**
    - a. lower; higher
    - b. higher; higher
    - c. lower; lower
    - d. higher; lower

14. **PCT levels remain elevated until the bacterial infection resolves and therefore, does not provide physicians the capability to assess the therapeutic effect of treatment.**
    - a. True
    - b. False

15. **The use of PCT as a diagnostic tool has been shown to aid in**
    - a. diagnosing bacterial vs. viral meningitis.
    - b. evaluating the severity of CDI.
    - c. diagnosing UTI vs. urosepsis.
    - d. all of the above

16. **A baseline reading of PCT levels and serial measurements at _____ is necessary for proper clinical decisions to be made.**
    - a. six hours
    - b. 12 hours
    - c. 24 hours
    - d. 48 hours

17. **Antibiotic therapy for sepsis will prove to be effective when the PCT level shows a reduction of _____ compared to the previous day during the first four days of treatment and a decline of _____ or more over four days from the initial baseline level.**
    - a. 50 percent; 80 percent
    - b. 80 percent; 50 percent
    - c. 50 percent; 90 percent
    - d. 80 percent; 55 percent

18. **Antibiotic discontinuation is strongly encouraged when PCT levels are below _____ ng/ml and have dropped by _____ percent from the baseline reading.**
    - a. 0.5; 90
    - b. 0.5; 80
    - c. 0.25; 80
    - d. 0.25; 90

19. **The retrospective study cited in the article on antibiotic stewardship concluded overall reductions by 47 percent or higher in**
    - a. median days of antibiotic therapy.
    - b. 30-day readmission rates and hospital mortality rates.
    - c. adverse drug events from antimicrobials.
    - d. all of the above

Tests can be taken online or by mail. Easy registration and payment options are available through NIU by following the links found at www.mlo-online.com/ce.

PLEASE PRINT CLEARLY

NAME _____ MAILING ADDRESS _____ ☐ HOME ☐ WORK

CITY _____ STATE _____ ZIP _____ INSTITUTION/FACILITY _____

PHONE _____ E-MAIL ADDRESS _____

Send your $20 check payable to Northern Illinois University with this form to: University Outreach Services, Northern Illinois University, DeKalb, IL 60115-2860 Phone: 815-753-0031

FEE NOT REFUNDABLE OR TRANSFERABLE

P = Poor; E = Excellent

1. **To what extent did the article focus on or clarify the objectives?**
   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
3. **How will you use the CE units?**
   ☐ state license ☐ employment ☐ recertification ☐ other

CE Licensure Information for FL and CA:

FL: Your FL license number: _____
(required for CE credit)

CA: Accrediting Agency: 0001
(for use in submitting your CE credits to CA)

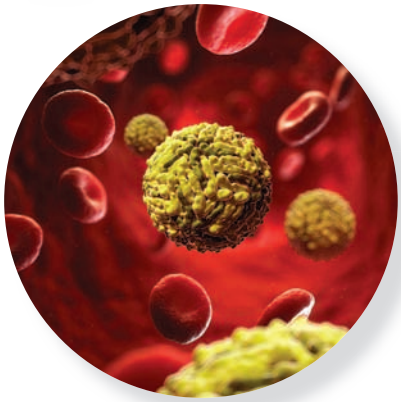
MLO and Northern Illinois University (NIU), DeKalb, IL, are co-sponsors in offering continuing education units (CEUs) for this issue's CE article. CEUs or contact hours are granted by the College of Health and Human Sciences at Northern Illinois University, which has been approved as a provider of continuing education programs in the clinical laboratory sciences by the ASCLS P.A.C.E.® program. Approval as a provider of continuing education programs has been granted by the state of Florida (Provider No. JP0000496). Continuing education credits awarded for successful completion of this test are acceptable for the ASCP Board of Registry Continuing Competence Recognition Program. Readers who pass the test successfully (scoring 70% or higher) will receive a certificate for 1 contact hour of P.A.C.E.® credit. Participants should allow three to five weeks for receipt of certificate. The fee for this continuing education test is $20. **This test was prepared by Amanda Voelker, MPH, MT(ASCP), MLS, Clinical Education Coordinator, School of HealthStudies, Northern Illinois University, DeKalb, IL.**

INTRODUCING

FUJIREBIO LUMIPULSE® G1200 B·R·A·H·M·S PCT ASSAY

One PCT test is NOT enough...

Serial testing is critical to patient care.



- Can reduce unnecessary antibiotic exposure
- Aide physicians in antibiotic treatment decisions
- Helps reduce unnecessary antibiotic treatment days

Visit us at www.fujirebio-us.com for more information and to see our entire line of assays for the LUMIPULSE® G1200.

LUMIPULSE G® B•R•A•H•M•S PCT assay should be used in conjunction with other laboratory findings and clinical assessements

Reagent developed in collaboration with Thermo Fisher Scientific. Lumipulse is a registered trademark of Fujirebio Inc. B•R•A•H•M•S PCT is a registered trademark of Thermo Fisher Scientific and its subsidiaries.

FUJIREBIO

The shifting spectrum of emerging infectious diseases

By Linda L. Ross, MS, MLS (ASCP)cm SM and Linda L. Williford Pifer, PhD, SM (ASCP), GS (ABB)

In 1962 Nobel laureate (Medicine/Virology) Sir Frank Macfarlane Burnet remarkably stated that, "To write about infectious disease is to almost write of something that has passed into history."[1] Fifty-seven years ago in the United States, we crushed smallpox, polio, measles, diphtheria, typhoid and were armed with powerful antibiotics that had experienced virtually zero resistance from microbes. We held a shining sword of power over disease and death. Vaccines and antibiotics were its two cutting edges.

However, although Burnet had lived through the "Spanish influenza" of WWI that killed more than 50 million people (nearly one in 20 worldwide) he had no way of foreseeing HIV/AIDS, Ebolavirus, Legionnaire's disease, etc.[2] The idea of emerging infectious diseases was unknown, as was the concept of the immunocompromised host. We have learned many humbling lessons since those days of audacious innocence at our perceived height of power over the microbe.

We have learned that the unseen microbial world is never to be underestimated. *All* living things have a vigor to exist and will withstand extreme stressors to the limits of physical tolerance to live and reproduce.

Emerging arthropod-borne outbreak in LA

Who could have imagined flea-borne murine typhus in downtown Los Angeles on Sunset Blvd.? Thus far, there have been over 100 confirmed cases. Six of the downtown LA cases were in homeless people. Trash and debris generated by their make-shift dwellings create the perfect environment to support rat populations. The disease is caused by *Rickettsia typhi*, which is transmitted by fleas whose feces, bearing the bacteria, enter scratches and skin abrasions in human skin. Symptoms include chills, fever, body aches, muscle pains, loss of appetite, nausea, vomiting, cough, and a rash appearing at about day five. Most recover without treatment (Doxycycline is preferred) but severe organ damage can occur. Test results require weeks so empiric treatment will usually be started upon report of flea bites and report of pathognomonic symptoms. Fleas most often originate from rats, cats, and opossums in the Western U.S. (CA, TX, HI).[4]

Overall, according to the CDC, vector borne diseases are extremely important causes of illness and death on every continent. In the U.S., Rocky Mountain spotted fever and Lyme disease are most commonly transmitted by ticks. West Nile virus and Zika virus are spread by mosquitoes, although the latter has not become indigenous. A recent CDC study showed that the number of annual reports of tick-borne bacterial and protozoan diseases (*Babesia microti* and Cytauxzoonosis) have more than doubled between 2006 and 2014 from >22,000 to >48,000.[5]

Zoonotic bacteria, prions, and viruses

An emerging zoonotic cause of sepsis, endocarditis, and meningitis is *Capnocytophaga canimorsus*, a Gram (-) bacterium first named in 1989.[6] The organism is found in the mouths of most healthy dogs (74 percent) and cats (57 percent), but can cause lethal infections in up to about 30 percent of cases when individuals are asplenic, heavy users of alcohol or otherwise immunocompromised.[6] A lick on a scratch by his puppy nearly cost a young WI boy his life—he lost his fingers and toes to *C. canimorsus* sepsis.[7] A 58-year-old S. Milwaukee woman died only two days after admission to hospital with *C. canimorsus* pneumonia after having been nipped by her new puppy.[8] A 48-year-old WI man lost parts of all four appendages, part of his nose, and lower lip—and very nearly his life—because his open scratch was licked by his dog.[9] Finally, a case report of a 70-year-old woman without immune dysfunction, who presented neither scratch nor bite, but who survived *C. canimorsus* sepsis suggests that "the lick of death" alone may transmit the infection.[10, 11] Weakened immunity may well present an invitation to *Capnocytophaga* whether skin is visibly intact or not.

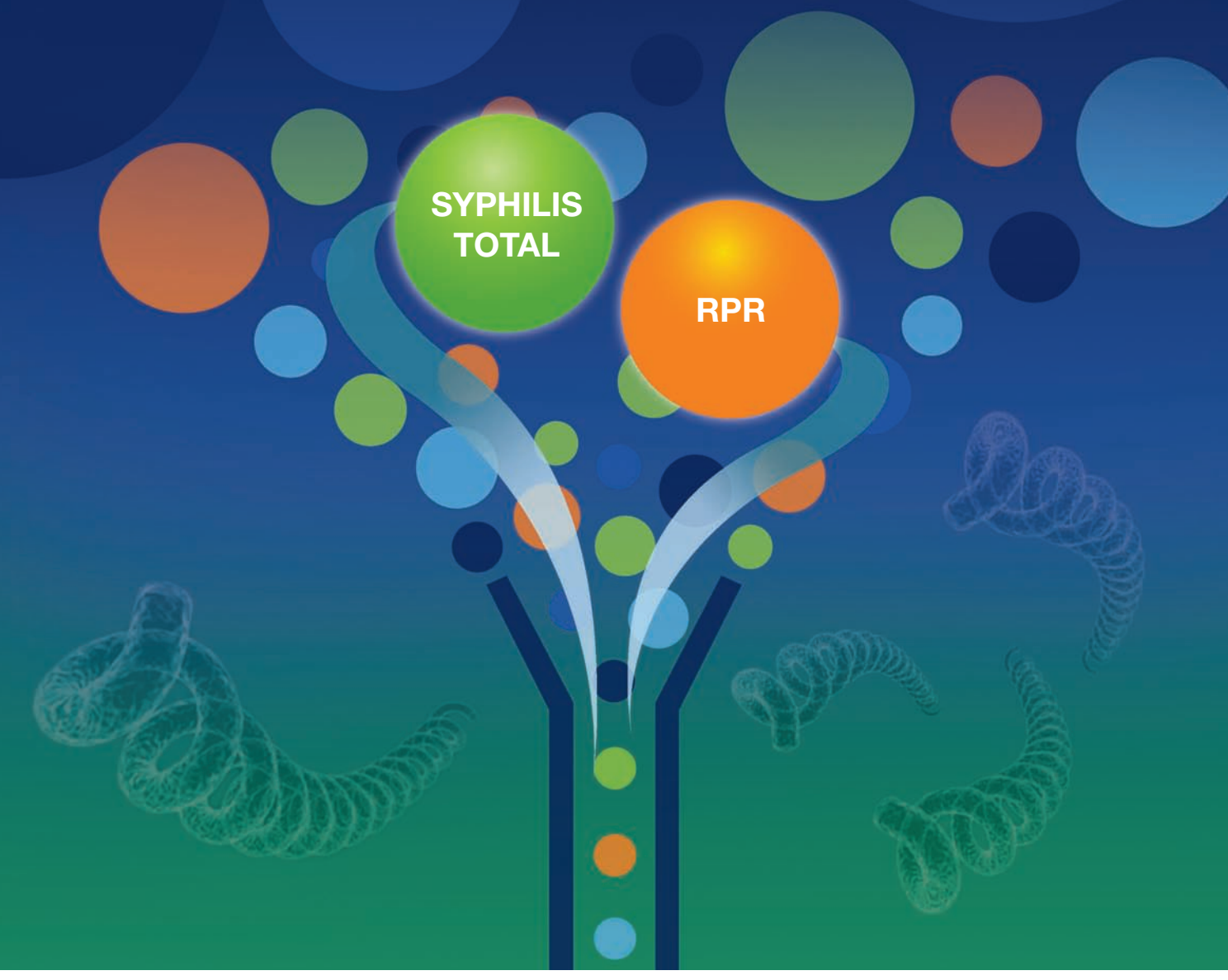
A prion-associated death is suspected in a NY hunter with a history of squirrel brain consumption[12] (considered a delicacy in some parts of the U.S.). In 2015, a 61-year-old man entered a hospital in Rochester, NY with declining mental abilities, confusion, and inability to walk. His MRI scan was consistent with those seen in patients with variant Creutzfeldt-Jakob disease (vCJD), one of the spongiform encephalopathies caused by prions, which are rogue infectious proteinaceous particles. Variant CJD is a progressive neurological degenerative disorder for which there is no treatment and is always lethal.

In Western KY, definite or probable vCJD was seen in five patients with histories of consuming squirrel brains. Variant CJD is one of a number of inheritable or acquired prion diseases which are progressive, incurable, and fatally affect the brain and central nervous system. In this area and others, squirrel brains are used in preparing "burgoo" which is a traditional vegetable and game stew. The authors note that confirmation of the apparent association will be required with a larger population of subjects, but avoidance of consumption of this dish would be well advised.[13]

Recently, three individuals in the U.K. and an Israeli living in the Port Harcourt area of endemic southern Nigeria have been diagnosed with monkeypox virus which originated in Nigeria. At least one of the U.K. residents contracted the virus in the U.K., and smallpox vaccinations were offered to those present in the physician's office on the same day on which the affected individual was present.[14] Smallpox (variola) has been extinct as a naturally transmitted infectious disease since 1979, thanks to the success of worldwide application of vaccine.

Fortunately, cross-immunity exists between smallpox virus (variola), cowpox (vaccinia), and monkeypox. The latter is far milder and exhibits symptoms of headache, fever, chills, muscle aches, followed by a rash on the face followed by blisters, pustules, and scabs that eventually cover the entire body. Since September 2017, there have been 115 confirmed cases, and there have been 37 at the time this article was written in 2018.[15] The lesson here is that exotic viruses are as near as the next transcontinental flight. Travel, immigration, climate change, deforestation, war, changing human social habits, and many other societal and environmental factors have both subtle and dramatic impacts upon the changing spectrum of emerging and re-emerging infectious diseases.

SIMPLIFY YOUR SYPHILIS TESTING
WITH AN AUTOMATED ONE-STEP METHOD



One test. Two results.

The BioPlex 2200 Syphilis Total & RPR Assay eliminates the need to maintain multiple methods for syphilis testing. Our automated dual treponemal/non-treponemal immunoassay offers laboratories both Syphilis Total and RPR results from a single test.

BioPlex 2200 System
More Results, Less Effort.

Visit info.bio-rad.com/bioplex-syphilis to learn more or contact your Bio-Rad sales representative.

BIO-RAD

Record increase in STIs in CA

Sexually-transmitted infections (STIs) such as syphilis, gonorrhea, and chlamydia have reached a never-before recorded high (a 45 percent increase in past five years) in California, particularly in Orange County, LA.[16] Cuba, Thailand, and Belarus are presently doing a better job at controlling syphilis. According to the CA Dept. of Public Health, this has led to an unprecedented surge in cases of congenital syphilis. The crisis has been blamed on the deterioration of the health infrastructure beginning in 2008 and budget slashes that occurred ten years ago that were never restored to their original level.[16]

Health officials have also coupled the rise of STIs with homelessness, poverty, substance abuse, and mental health problems. According to Dr. H. Bauer of the CA STD Control Branch, the Affordable Care Act has also funneled patients away from public health services toward primary care physicians, and this is not the most effective plan. Those who depended on public clinics for STI screening, etc. may not feel comfortable talking about it with their physicians or may have no physician at all.[16] Thus, economics and government policy play a significant role in shifting patterns of infectious diseases. The sequelae include stillbirths, ectopic pregnancies, infertility, blindness, hearing loss, dementia and ultimately, vastly increased health costs—to mention a few.

Dangerous emerging mycotic infection

Who can recall the last time a CDC advisory was issued to report the isolation of a nosocomial mycotic infection? *Candida auris* has been growing in notoriety now for several years with a case count of 463 plus in the Fall of 2018. It is an emerging mycotic threat with grave consequences for three reasons: 1. Multidrug resistance; 2. It is difficult to identify and easy to mis-identify, leading to non-optimal treatment; and 3. It has caused serious outbreaks in healthcare facilities that have been difficult to eradicate.[17] It has been reported to be the cause of invasive infections (candidemia) with a high incidence of mortality (approaching 60 percent).[18]

Seventy cases of *C. auris* infections (seven invasive) occurred in the neurosciences intensive care unit of the Oxford University Hospitals, U.K., and all were associated with use of reusable skin-surface axillary temperature probes.[19]

The CDC maintains updates on the diagnosis, treatment, and environmental decontamination procedures for *Candida auris* at https://www.cdc.gov/fungal/candida-auris/c-auris-treatment.html and continues to update the site due to the insidiousness and potentially deadliness of this emerging mycotic infection.

Conclusion

Although Nobel laureates accomplish amazing breakthroughs in science and medicine, they are not necessarily gifted with foresight, as proven by Sir Frank M. Burnet. He apparently believed that infectious diseases were, in 1962, conquered things of the past. Louis Pasteur (1822-1895) who was possibly the greatest of all microbiologists once said, "Gentlemen, it is the microbes that will have the last word."[20] HIV/AIDS, the Ebola viruses, and other numerous dangerous emerging and re-emerging pathogens have proved Pasteur to be correct and that laboratory managers should best remain at the ready.

REFERENCES

1. Science News Magazine. 190:13, Dec. 24, 2016, p. 32.
2. Klain, Rod (White House Ebola Response Coordinator), Vox, Oct. 15, 2018.
3. "Flea-Borne Typhus Spreads Across L.A. Area, with at Least 57 Reported Cases." CNN Wire, Oct. 8, 2018.
4. CDC Typhus Fevers: https://www.cdc.gov/typhus/murine/index.html
5. Vital Signs: Trends in Vectorborne Disease Cases- United States and Territories. 2004-2016; MMWR, May 4, 2018, Vol. 67, No. 17.
6. Butler, T. *Capnocytophaga canimorsus*: an emerging cause of sepsis, meningitis, and post-splenectomy infection after dog bites. Eur. J Clin. Microbiol. Infect. Dis. 2015 Jul:34(7):1271-80. doi: 10.1007/s10096-015-2360-7. Epub 2015 Apr 1.
7. Wisconsin boy's mysterious illness may have been caused by dog lick. WISN News 12, Aug. 9, 2018. https://www.wisn.com/article/wisconsin-liam-young-mysterious-illness-dog-lick-saliva/22688731
8. West S. Bacteria spread through dog saliva linked to S. Milwaukee woman's death. Milwaukee Journal Sentinel, Aug. 11, 2018. https://www.jsonline.com/story/news/local/milwukee/2018/08/11/bacteria-dog-saliva-linked-death-wisconsin-woman/966203002/
9. Phillips K. The Shocking reason that this man's legs and hands were amputated: A dog's saliva. The Washington Post, July 31, 2018.
10. Marcus M.B. Woman's pet dog gave her a life-threatening infection. CBS News, June 30, 2016. https://www.cbsnews.com/news/womans-pet-dog-gave-her-life-threatening-infection/
11. Wilson J. P., Kafetz K., Fink D. Lick of death: *Capnocytophaga canimorsus* is an important cause of sepsis in the elderly. BMJ Case Reports 2016; doi:10.1136/bcr-2016-215450.
12. Prion disease update (02): United States (New York) Variant CJD Suspected, Squirrel Brain, Human Fatality, 2015, International Society for Infectious Diseases, promededr@promedmail.orghttps://outlook.office.com/owa/?realm=uthsc.edu&exsvurl=1&ll-cc=1033&modurl=0&path=/mail/search
13. Berger J.R., Weisman E., Weisman, B. Creutzfeldt-Jakob Disease and eating squirrel brains. The Lancet. August 30, 1997, DOI: https://doi.org/10.1016/S)14)-6736(05)63333-8.
14. Monkeypox–UK (05): ex Nigeria, A ProMed-mail post, Oct. 2, 2018, International Society for Infectious Diseases, https://www.blackpoolgazette.co.uk/news/health/patients-offered-smallpox-vaccine-to-protect-against-potential-monkeypox -infection-1-9375758
15. Monkeypox–Israel: ex Nigeria, A ProMed-mail post, Oct. 12, 2018, International Society for Infectious Diseases, http://afludiary.blogspot.com/2018/10/israel-moh-confirms-imported-monkeypox.html
16. Weber C. STDs reach all-time high in California. Associated Press, USA Today, May 15, 2018.
17. *Candida auris* https://www.cdc.gov/fungal/candida-auris/index.html
18. Larkin E., Hager C., Chandra J. The emerging pathogen Candida auris: growth phenotype, virulence factors, activity of antifungals, and effect of SCY-078, a novel glucan synthesis inhibitor, on growth morphology and biofilm formation. Antimicro. Agents & Chemother. May 2017, Vol. 61:5, 1-13, e02396-16.
19. Sheppard A., Madder H., Moir I. et al. A *Candida auris* outbreak and its control in an intensive care setting, N. Engl. J. Med. 2018; 379:1322-1331.
20. Louis Pasteur Quotes. https://www.azquotes.com/author/11366-Louis_Pasteur

Linda L. Ross, MS, MLS (ASCP)^{cm} SM, is a seasoned Clinical Microbiologist, as well as, an award-winning teaching Associate Professor at the **University of Tennessee Health Science Center's (UTHSC), Department of Clinical Laboratory Science** in Memphis, TN.

Linda L. Williford Pifer, PhD, SM (ASCP), GS (ABB), is a Professor at **UTHSC's Department of Clinical Laboratory Science.** She established the diagnostic virology lab at **Le Bonheur Children's Hospital** in Memphis, TN.

HOLOGIC®

FUSION SEASON

Impact patient care when needed most.

PANTHER FUSION® Flu A/B/RSV Assay

PANTHER FUSION® AdV/hMPV/RV Assay

PANTHER FUSION® Paraflu Assay

FLU SEASON *READY*

Be prepared for the flu season with the Panther Fusion® Respiratory assays: a fully automated, modular approach to syndromic respiratory testing.

PANTHER FUSION®

Puritan Medical Products: 100 Years of Innovation, Evolution, Authenticity

As important as wedding anniversaries, graduations, and birthdays are in our lives, the celebration of noteworthy milestones is of equal importance in business. As Puritan Medical Products, Co.—and MLO—celebrate exciting anniversaries this year, we reflect on this success.

What is the secret to longevity in business? For Puritan, the answer is found in these essential traits.

■ **Stewardship.** As a family-owned business, the leadership of the third generation solidly grounds the company. The organization continues to operate from its headquarters in the small town of Guilford, Maine.

■ **Stability.** The organization originated in 1919 as The Minto Toothpick & Specialty Company, manufacturing a single product: mint-flavored toothpicks. Soon after, the founders recognized an opportunity to expand into other markets. The name changed to Hardwood Products Co. and Puritan brand was created. Puritan has since evolved into a global manufacturer of single-use products for diagnostics, forensics and genetics, environmental, medical, and controlled environments. Its product line consists of more than 1,200 unique devices, including tongue depressors, swabs, specimen transport systems, molecular media, and environmental sampling products.

Throughout the years, dedication to quality—the company's heartbeat from conception—remained strong. Today, Puritan's unfaltering commitment to quality is seen in every step of manufacture from management of raw materials to labeling, all closely monitored through the combination of rigorous process and leading-edge technology.

■ **Responsiveness.** We respond to our customers. Equally important to maintaining stability is the ability to respond to evolving market changes and customer needs. Puritan's capacity to innovate is evidenced in its diverse product line and its global reach.

■ **Mutual respect.** We believe that successful businesses operate effectively by recognizing and respecting the contribution of everyone in the organization, much like a family. This concept is built into Puritan—not only is it a family-owned business, but its employee base includes many multi-generational families.

Through adherence to these traits, Puritan products are now relied upon in established systems that improve people's health, safety, and overall quality of life.

Puritan's line has developed with the times, growing steadily over the years. Today, Puritan's R&D team, with input from industry's innovators, delivers single-use devices that meet the needs of today's rapidly changing technologies. Puritan products are no longer limited to traditional healthcare—they now serve to facilitate global initiatives in clinical microbiology, environmental security, genomics, and research in every area of investigation.

Puritan's **806-WC** has long been the gold standard of basic cotton tipped applicators for use in basic patient care and industry. Spun rayon, polyester, and calcium alginate fibers were added in subsequent years to complete this line of tipped applicators.

In 1987, the technology to produce foam tipped applicators was brought online at Puritan. The foam tips, initially intended for controlled environments, found acceptance in specimen collection and remain there today.

Puritan flocked swab technology was developed in 2012. Puritan's engineering staff approached the flock swab in a new way, utilizing polyester fibers of differing lengths, and fabricating the swab through a proprietary technique. The result—Puritan's patented **PurFlock Ultra**® and **Hydra-Flock**® swabs. These offer ultimate collection and release properties. Not only in rapid POCT and research, Puritan's flock swabs are used in forensic and crime scene investigations.

Dry transport configurations are available for most of the tipped applicators Puritan manufacturers. Transport media devices became an important member of the Puritan line in 2011, when Puritans' new lab began formulating and filling Liquid Amies and UTM, complete with a Puritan swab for specimen collection and transport. These became our **Opti-Swab**® and **Uni-Tranz**® devices. Other media followed.

We were not done there—**PurSafe**® molecular preservation solution is now available, intended for research use only and proven to be a reliable transport for cellular transport.

What's next? You will tell us and we will deliver. Puritan is a fully integrated manufacturer, developing and producing the broadest line of single-use items for patient care, lab and controlled environments available. Still proudly made in the USA.

Visit www.puritanmedproducts.com to learn more.

Timothy Templet
Executive VP of Sales
Puritan Medical Products Co.
31 School St., PO Box 149
Guilford, ME 04443
800-321-2313
sales@puritanmedproducts.com
www.puritanmedproducts.com

PURITAN MEDICAL PRODUCTS
100 YEARS
QUALITY SINCE 1919

Congratulations to us!

Puritan is celebrating 100 years of innovation in swab technology and supplying lab professionals with the tools needed to make every day a success. And, **MLO is celebrating 50 years** of connecting and educating laboratory professionals – keeping them in-the-know and up-to-date on industry news, trends and product reviews.

Puritan. We'll be there. **Learn more at puritanmedproducts.com**

207-876-3311
puritanmedproducts.com
sales@puritanmedproducts.com

Puritan®
Quality since 1919

Sarasota Memorial Hospital laboratory techs talk automation

By Editors Lisa Moynihan and Janette Wider

Just five miles down the road from the Sarasota, Florida office of *MLO*/Endeavor Business Media, sits Sarasota Memorial Health Care System (SMHCS), an 839-bed regional medical center. Within its walls are over 5,000 staff, over 900 physicians, and 600 volunteers.

Humble beginnings

In 1921, faced with a growing need for organized healthcare, residents of Sarasota began raising funds to build a hospital. A yearlong fund-raising campaign was conducted, along with a "tent hospital" and a temporary six-bed facility to treat patients and emergency cases. It was said that no businessman dared to venture down Main Street without first pulling his pockets inside out, thereby making a public statement that he had no more money to give for the hospital!

The hospital is the waking reality of "the dream of many made possible by the intensive efforts of a few and the generosity of all," as the Sarasota Herald Tribune wrote in November 1925 to announce the opening of the first modern hospital, featuring 32 beds, in Sarasota County.

Sarasota Memorial Hospital

1st U.S. Siemens Aptio by Inpeco Automation Total Laboratory Automation Solution

Employing a state-of-the-art, total automation system

SMHCS has come a long way since 1925. On Friday, August 3, 2018 (approximately 93 years later), an official ribbon cutting ceremony took place for one of their most tremendous accomplishments to date—a laboratory automation line!

The Sarasota Memorial Hospital (SMH) laboratory became one of the first in the U.S. to process the majority of its patient samples from beginning to end using a new state-of-the–art, total laboratory automation system from Siemens Healthineers. The line employs the Siemens Aptio by Inpeco automation solution, performing chemistry, immunochemistry, coagulation, and hematology analysis. The fully automated process helps improve the timeliness, accuracy, and reliability of test results. As a side note, the SMH lab was designated a Center of Excellence by Siemens Healthcare Diagnostics for Automation and Chemistry in June of 2018.

As per the SMH laboratory director, "The implementation of total laboratory automation is a challenging task since the laboratory cannot stop production at any time. We had to maintain our full function during seasonal volume upswings (a Florida thing), while also completing the installation, testing, and migration to the new equipment and automation line process. Our staff did a phenomenal job adjusting to change and focusing on our patient care mission. Siemens partnered well with us, as did Sysmex for our hematology. It was truly a team sport designed to ultimately benefit patient care in our region of Florida."

Since 70 percent of all clinical decisions are based on lab results, and because SMH's lab performs more than 2.6 million tests per year, ensuring prompt, reliable results is the department's number one priority. Current services include hematology/coagulation, biochemistry (including endocrinology and therapeutic drug monitoring), immunology/serology/urinalysis, microbiology/parasitology, immunohematology/transfusion services, and virology.

Previously, the lab processed tests through multiple inputs using various modalities. The new system allows the laboratory to automate about 80 percent of its testing, including many of its most common tests, freeing up professional staff members to concentrate on the remaining 20 percent of samples, which typically come from acutely ill patients that require additional analysis and expertise.

MLO visits the lab

We had the opportunity to tour the clinical laboratory at SMCHS, thanks to the Director of Laboratory Services, Harold Vore, MS, MT(ASCP), and Laboratory Operations Manager, Dana Rickard, BS, MT(ASCP).

As we were escorted into the lab, we saw laboratorians in white lab coats going about their daily routines—hustling to run tests and keep out of each other's way with the end goal of getting results to the ordering physicians. And not just from their facility, but many other reference labs that utilize their services.

The automated equipment that wrapped around the entire lab was reminiscent of a conveyer belt found in a manufacturing facility; transporting test tubes and specimen containers from spot to spot. To outsiders, like ourselves, the equipment appeared to make the laboratorians lives a bit easier. However, we wanted to speak to those who had been in the business long enough to see the laboratory landscape evolve and to find out if automated equipment truly did

Making a Splash with Liquid Linearity and Daily QC

Over 120 Analytes Available

Introducing a new addition to our line of liquid linearity and daily QC

Linearity Drop LQ Fructosamine for Roche Systems

Levels: Five
Format: Liquid
Package Size: 5 x 2mL
Open Vial: 7 days when stored at 2-8°C
Analytes: Fructosamine
Order Number: K930M-5

Providing value to our customers through:

- A broad line of superior quality universal & analyzer specific products.
- Personalized technical support from our experienced laboratory professionals.
- AUDITOR QC, a free and easy to use online data reduction service providing “instant reports”.

AUDIT MicroControls™

866.25.AUDIT(28348) | customerservice@**audit**micro.com | **audit**micro.com

make their job easier. Who better to give us insight, other than those who live it?

Back in the day

Margaret, who has admirably worked in the SMH lab since 1995, shared that "back in the day," the laboratory was much more compartmentalized, including assigned departments and separate instrumentation, both of which resulted in more specialty technologists.

She reflected that Chemistry techs worked in the main lab every day, however, Microbiology only worked in Microbiology. Hematology had its own techs, as did Coagulation. Each department knew the ins and outs about everything in their particular department.

Even back then equipment was still pretty good, but it certainly wasn't integrated on a line. Specimens didn't get loaded to one central location. Techs had to manually load everything. And when things were done, they weren't multiuse; so they had to be sealed and physically brought to the next area. Things were much more hands-on at that time.

Not to mention, there were no laboratory information systems or electronic health records—so information was documented by hand, several techs mentioning file cards and a file card system.

Today, the lab staff is more united. There are more generalists who work all areas due to advanced technology. Most departments, like Chemistry, Hematology, Urinalysis, and Coagulation are rotated; except Blood Banking and Microbiology. Microbiology doesn't work out in the "main land" and vice versa.

Although those we spoke with unanimously concluded automation's impact has made a difference for the better, it was not without its challenges. The pros? Obtaining a patients lab results quicker and more efficiently. The cons? Learning how to fix multiple analyzers.

Troubleshooting instruments

Diane is a technical specialist in Microbiology. She shared that her department has received four new instruments within the last six months—all of which have new technology—and all of which needed validation. Her team is expected to know the machines. And if they need assistance, they're to solicit a shift super-user for guidance and troubleshooting. Then, if the issue(s) can't be resolved, a call into the 1-800-service line is in order.

We were told laboratorians not only want more in-house training, they want more training in school. Years of diagnostics training isn't preparing them for using multiple analyzers and laboratory information systems when they get on the job. Point of care is very IT oriented. Waiting until an internship to experience hands-on training is too late.

Yet, the laboratorians at SMH persevere through these challenges and their learning curve is becoming smaller each day. These skilled professionals are truly dedicated to the laboratory as well as their patients, and take their responsibility to troubleshoot the machines in stride.

Out with the old

Linda was identified to us as a laboratorian who worked her whole career at SMH's laboratory. She knew we wanted to talk to some "old-timers" and had a great sense of humor. The first thing she said when she entered the interview room was, "I heard you guys want to talk to some old people!"

After the laughter stopped, Linda told us that she had been in the field since 1971. She joked, "I started here young and single, and here I am, an old married grandmother!"

She let us know that she could barely type when they started introducing computers in the laboratory, and that she came from a small town in Indiana. When she was growing up, she said, if you were interested in medicine, "males were doctors and females were nurses." She didn't learn about the laboratory being an option until she was in college. She enjoys the hands-on aspect and the chemistry. The rest, you can say is history.

Linda works in Microbiology, which is just getting into automation at the SMH laboratory. She has a very positive outlook on things changing, stating, "I've always liked to learn new things." She hopes the move to automation in Microbiology will help standardize tasks, "I may plate something different than the next guy" she explains.

All the techs we spoke to knew the average age of a laboratorian is 58 and recruiting newcomers is challenging. Lack of education, career path information, public awareness, and soliciting the wrong demographic seems to be contributing to the lack of recruits.

Margaret, who if you recall has been in this industry for almost 25 years, openly confessed that both her family and friends don't know what a medical laboratory technician is! "I just end up telling people I'm a laboratory scientist," she said.

We were also told nurses are now being trained to do laboratory testing—taking on more and more testing in addition to what they are already doing—but it's not ideal. Nurses already carry heavy workloads, and are not trained laboratory specialists.

When we asked Linda if she'd advise her grandchildren to go into the medical laboratory field she said, "We're going to need more IT staff and engineers. We don't have to get the biochemicals anymore, that part of it isn't as integral now, it's more about running the instruments. Not to say that those things shouldn't be learned in school but being able to work with the instrument is imperative."

In with the new

The extraordinary laboratorians we interviewed could take up many more pages of *MLO*, and truly gave us a lot of thought-provoking material to write this article. One thing we did notice was that each and every tech's number one goal was getting quality test results to the physician's patient in the fastest and most efficient way possible; automation or no automation. As new technologies evolve in the workplace, it takes time for the bumps to be smoothed out, and no one was ready to throw in the towel.

Linda said it best at the end of our time with her, "I love the profession. At the end of the day, I can go home and say, 'you know, this has been accomplished and Joe will live another day because of me.'"

We agree, Linda. Thank you.

Editors' note: The names of the laboratory technicians have been changed in this story to preserve anonymity.

For more information on automation and how to apply its benefits to your laboratory, turn to page 24 to read "Leveraging automation as strategy to overcome today's laboratory challenges" from Siemen's Healthineers.

InteliQ.
Smarter, Simpler QC.

Optimize Workflow

Increase productivity and improve turnaround time by eliminating manual steps.

Increase Efficiency

Unique sample tracking and easy XML data upload of lot-specific QC values.

Improve Performance

Access Unity data management program and large peer groups.

Achieve Quality Goals

Use advanced Unity software tools to support your lab's risk management program and simplify compliance reporting.

Simplify your QC workflow with load-and-go efficiency and robust data management.

InteliQ quality controls automate your QC on next generation platforms. These barcoded, load-and-go controls reduce hands-on time and manual errors, streamlining your workflow and giving you more freedom. InteliQ controls, together with Unity's advanced data management tools, improve workflow efficiency. InteliQ. It's simply smarter QC!

How will InteliQ help you work smarter?
Visit: qcnet.com/InteliQ

BIO-RAD

InteliQ is compatible with next generation chemistry and immunoassay platforms including Siemens Healthineers Atellica Solution.

Leveraging automation as a strategy to overcome today's laboratory challenges

By Rita White

From standalone hospital labs to health systems and GPOs, different labs have different business models. Yet, they face similar operational challenges, among them finding and retaining qualified staff and identifying growth opportunities in response to declining reimbursement. These challenges, and the corresponding statistics about them, are all too familiar to many:

- The retirement rates of laboratory professionals across all major departments are at their highest since 2012.[1]
- The number of laboratory training programs has decreased by nearly 25 percent since 1990.[2]
- Due to PAMA, laboratories are experiencing the most significant reimbursement reduction in decades with private insurers expected to decrease rates as well.[3]

Meanwhile, the needs of aging patients continue to rise, resulting in higher volumes with fewer staff and resources to manage them. At the same time, organizations are increasingly measured by patient satisfaction and tasked with meeting value-based healthcare initiatives.

Multidisciplinary automation presents a strategic, tactical move organizations can make to answer multiple challenges across silos, disciplines, and staff. In fact, when tasked with faster turnaround times (TAT), consistent results, and lower costs in the face of higher volumes, laboratory automation can be instrumental to achieving necessary results—both for the laboratory and for the organization as a whole.

Gain buy-in and educate decision-makers

In the lab, technology can have a direct impact on patient experience, patient outcomes, and hospital reputation. Yet, the role the lab plays in supporting value-based healthcare goals may not always be recognized by the healthcare delivery organization's administration and decision-makers. Nearly half of the laboratory professionals polled in a recent study by Siemens Healthineers identified gaining approval from C-suite executives as the second most challenging aspect of their project. The number one challenge? Budget. Seventy-two percent of those surveyed identified this as their main challenge.[4] Ultimately, this may mean that getting support for a laboratory automation project will require buy-in from decision-makers, particularly those who can influence the project's budget.

In fact, garnering support for a lab automation project is one of the first, and often most impactful, steps that can be taken before undertaking the project itself. Ask yourself, which decision-makers need to better understand the value of automating the laboratory? More than 70 percent of clinical decisions guided by test results[5] rely on labs to consistently, and sustainably deliver high quality. Yet, a successful automation project can do much more—potentially increasing lab efficiency, improving TAT, and reducing errors. Thus, when approaching the topic with decision-makers, the goal is often increasing awareness not only about the clinical benefits of advanced technology but also the higher levels of patient safety and satisfaction that may be possible with faster, more accurate diagnoses.

In a recent study commissioned by Siemens Healthineers of 300 U.S. lab directors, internists, and emergency room physicians, more than 75 percent of respondents agreed that labs are a critical component of patient diagnosis and treatment. What's more, nearly half of those respondents agreed that investments in lab technology would be very impactful to improve patient safety and outcomes.[6] Keep in mind as well that U.S. hospitals that incorporate innovative medical technologies have Medicare Spending per Beneficiary (MSPB) scores below the national average.[7] This is an important point about how innovative technology may help to reduce the cost of patient care.

Break down silos and engage stakeholders for support

A multidisciplinary automation project can provide significant, tangible benefits to numerous stakeholders throughout an organization. To do so, however, one needs to begin by identifying which stakeholders will be directly impacted by an automation project. Stakeholders can range from lab directors and purchasing decision-makers to IT specialists, quality managers, lab technicians, disciplines managers, and others. Garnering project support and buy-in is an essential step that is often overlooked. Quite simply, this is the human side of an automation project. Who will be impacted? Who should be given the opportunity to submit concerns and ideas? By communicating with these individuals and offering them the ability to comment and participate in this process, one can energize stakeholders, excite them about the project, and potentially turn them into champions for its success.

During the planning stage, both decision-makers and stakeholders should be aware of the goals of the automation project. These goals should be specific, measurable, and feasible against the project's budget. Identify the project's scope and specific objectives, noting what will be considered outside the scope of the project. Give stakeholders and decision-makers ample opportunity to comment and participate, and excite them by demonstrating how the automation project will make their roles, the laboratory's offerings, and, ultimately, patient care, better.

Engage a workflow consultant and project manager

As you consider which stakeholders and decision-makers should be involved, a workflow consultant and project manager who can partner with you on your project may offer significant value. The best time to add a workflow consultant to the project team is during the early planning stage.

During this stage, an expert workflow consultant can conduct a thorough workflow analysis to identify process pain points and specific automation goals that can later be used to measure and validate return on investment (ROI). This methodical analysis of a laboratory's productivity provides objective insights and solutions for improvement. By using process improvement methodologies and case studies from other projects with similar goals, workflow consultants can provide cost justifications to decision-makers and other stakeholders. Additionally, as the project progresses,

informatics provided by the workflow consultant can enhance compliance and oversight capabilities for laboratorians.

Working in tandem with the consultant, an experienced project manager can coordinate the technical and physical aspects of implementation and resource management to help meet project milestones, time-related goals, and budget. During installation, the addition of project managers will help to ensure everything is in place to support a smooth implementation.

Evaluate current workflow processes and instruments

Laboratory operations performed day after day create muscle memory that will be disrupted during automation implementation. To limit this impact and ultimately improve laboratory efficiency and operations, a workflow analysis should be conducted prior to implementation.

A workflow analysis might entail evaluating the current workflow internally. Then, an experienced vendor can further evaluate the operational flow and develop suggestions for a customized solution with a full array of pre- analytical, post-analytical, and analytical systems for multiple disciplines.

Automated solutions with varying capabilities exist to support laboratories with their growing operations and to optimize the laboratory based on each facility's unique needs. Total solutions encompass a variety of offerings, including equipment for sample management, a broad menu of assays, IVD analyzers, automation systems, and informatics. Such total solutions are designed to anticipate and address the emerging needs of clinical laboratories. Automation can also help provide a single point of entry for multiple testing disciplines, allotting for future growth capabilities without having to significantly increase footprint. In addition, expanded capabilities can accommodate menu and volume growth.

Recognizing total lab automation can be a significant investment to undertake at one time. As such, manufacturers have deployed a number of resources and affordable solutions to segue laboratories 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.

Further support for the case for automation includes ASCP study results—which revealed 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.[8] Lack of training can expose 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.[5] With the right infrastructure, and software behind it, automation is meant to improve workflow efficiency, to improve TAT, and to reduce errors. By working together with an experienced vendor, laboratories can define their unique key performance indicators and automation goals, and implement proven workflows based on best practices to achieve measurable outcomes. The key is keeping communication open during implementation and beyond.

A laboratory automation project can be a complex change for an organization accustomed to operating in silos, particularly if the project will be fully integrated with IT and multidisciplinary analyzers. When implementation begins, traditional processes and muscle memory will be interrupted while the workload continues. Strong collaboration among staff, stakeholders, and decision-makers will be essential.

In fact, the success of laboratory automation hinges on detailed planning and cross-collaboration. By involving decision-makers and stakeholders throughout the process, common obstacles that result from miscommunication and/or ambiguity may be avoided. Be sure to predetermine communication channels and deliver regular updates. Once installation begins, communications will be even more essential. Determine how the team will measure success for each milestone and highlight those successes and milestones as they are achieved. Using the information provided by the workflow consultant, define how you will measure ROI to communicate the value and importance of the automation project. Be sure to continue to highlight successes as they occur both during and after implementation to continue to garner support and enthusiasm for the project.

Answer top-level goals

There will always be competing projects and initiatives within an organization that may take the focus away from the lab. Yet, when decision-makers and stakeholders recognize the impact laboratory automation can have on the quality of patient care, daily workflow efficiency, and revenue, they can become champions for the lab and its automation.

Successfully guiding a multidisciplinary laboratory automation project relies on exceptional communication, which includes identifying a measurable ROI. How to embark on these tasks will require planning, buy-in, and alignment across multiple stakeholders and decision-makers. To do so, leverage the expertise of a professional workflow consultant and laboratory project manager who can identify areas for improvement from the onset, note considerations to keep in mind, and provide informatics and insights gained from projects with similar objectives. During construction, keep in mind that local regulatory authorities and approvals vary, which can have a significant impact on the project timeline. Partnering with a vendor who is experienced in guiding laboratories through this transition will help to manage expectations, timelines, and costs. As construction and installation come to a close, be certain to initiate a change management plan to overcome resistance. An ideal plan will address the human side of automation to elevate fears, minimize disruption, and maintain workflow during the transition.

As a strategy, multidisciplinary laboratory automation can answer several clinical and business challenges. It offers the opportunity to increase accuracy and capacity, provide faster and more consistent TATs, and sustainably improve staffing efficiency. Further, improvements such as these can be critical to an organization's top-level goals, including value-based healthcare objectives—raising awareness about your lab's role in what matters most: patient care.

Please visit mlo-online.com for references.

Rita White serves as Marketing Director for Automation and Informatics, North America, **Siemens Healthineers.**

Advanced clinical parameters: achieving efficiency with automated immature granulocyte count

By Mary Anne Loafman, MS, MT(ASCP)SH

The Complete Blood Count (CBC) is one of the most frequently ordered tests in the clinical laboratory. Its use ranges from screening for infection and anemia to monitoring disease progress and treatment. The CBC test often includes a leukocyte differential to determine the types and amounts of white blood cells (WBC) present. Recent cuts to reimbursement from the Centers for Medicare & Medicaid Services (CMS) have made it necessary for labs to increase efficiency—while retaining accuracy and rapid turnaround times (TATs)—when performing this high-volume testing.

Immature granulocyte percentage

A great deal of research has focused on the utility of laboratory testing in the diagnosis of sepsis (a known or suspected infection plus systemic manifestations of infection) in the critically ill patient. Since the early 1990s, the guidelines for diagnosing sepsis, severe sepsis, and septic shock have undergone many significant alterations. However, among these guideline changes, the idea of infection being part of the underlying pathology of the condition has prevailed.[1] From the idea that sepsis always begins with an infection, additional guidelines for diagnosing sepsis have focused on the immune system's response to an infection, and in particular, a rise in the immature granulocyte (IG) percentage in patients with a normal total WBC count.

With these definitions in mind, a number of clinical studies have been conducted with the aim of utilizing laboratory testing, specifically the IG percentage, to rapidly and reliably detect infection. Initial and subsequent studies with severely ill inpatients reveal that:

- The IG fraction is a better predictor of infection than total WBC count[2]
- The IG fraction is comparable to the absolute neutrophil count (ANC) for predicting infection[3]
- An IG fraction of greater than three percent is a very specific (greater than 90 percent) predictor of sepsis.[2]

Increased IG fractions

More recent studies have focused on IG fractions in the outpatient population. In an extensive study performed in 2011, researchers at Boston Medical Center examined the clinical applications of the IG fraction in an outpatient population by relating increased IG fractions with particular illnesses and conditions relevant to outpatients.[4]

Numerous hematology analyzers have the capability to report a six-part automated differential that includes an IG fraction. The automated six-part differential data from these analyzers is usually reported in relative (percentage) and absolute (number of) units and includes the following cell types:

- Neutrophils (includes neutrophilic band cells)
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils
- Immature granulocytes (includes promyelocytes, myelocytes, metamyelocytes)

Current six-part differential technology also uses flagging algorithms as part of an interpretive program to alert users to the possible presence of abnormal cells, as well as increases or decreases in the relative percentage of normal cells in the differential. Some of these flags are generated by the analyzer software, while others are triggered at user-defined cutoffs that are reflective of the laboratory's Standard Operating Procedures (SOPs) and review criteria.

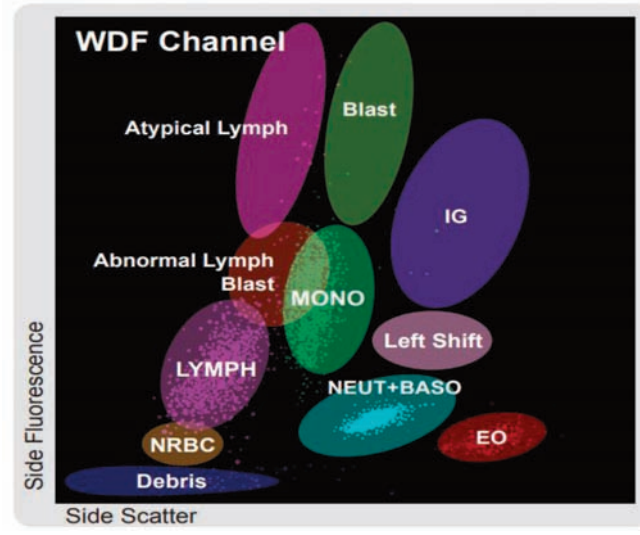


Figure 1. Flow cell scatter gram from the blood cell analyzer showing the reportable populations and Interpretive Program (IP) flagging areas. The y-axis of this scatter gram represents side-fluorescence; the x-axis indicates side-scattered light.

When immature granulocytes are present in numbers that exceed a user-defined limit, the analyzer will generate a flag message that reads "IG Present." The appearance of this flag would prompt a smear review of the results that may include correlation with the patient's history and diagnosis, or a manual examination of the

sysmex | Lighting the way with diagnostics

RESHAPING SCALABLE AUTOMATION

XN-Series™ Automated Hematology Systems

THE **XN-20** AUTOMATED HEMATOLOGY ANALYZER

Improved differentiation through the white blood cell precursor channel (WPC) provides more comprehensive patient results.

FULL AUTOMATION HAS CHANGED FOREVER

The XN-9100™ scalable and modular automated hematology system offers decreased turnaround times while optimizing staffing efficiency. Maintain high quality patient results through automatic workload balancing, hands-free rerun/reflex testing and fully automated reflexive slide preparation.

Configure your system with a variety of analyzers that include the XN-10™ and XN-20™ hematology analyzers, SP-50™ Slidemaker/Stainer, DI-60™ Integrated Slide Processing System for digital imaging, ESR and HbA1c testing, tube sorting and Sysmex WAM™ middleware for data management. Customize the right combination for your workflow and maximize your laboratory's capacity and productivity.

www.sysmex.com/us

blood film to verify the presence of immature granulocytes and any additional clinically significant features.

Smear reviews

In medical literature, much discussion debates the reliability of the 100-cell manual differential due to the minimal sample portion and the relatively low number of white cells counted.[5] In contrast, a six-part "auto-diff" that includes the IG parameter, offers the benefit of higher precision (thousands of WBCs counted), a shorter TAT[2] and the ability to detect possible infection.[4] As a result, many labs are opting to perform smear reviews, as opposed to manual differentials, to search for features that enhance the reportable automated differential such as toxic white cell changes or other abnormal white cell morphology.

The hematology analyzer in the Core Laboratory at Rush University Medical Center (RUMC) in Chicago, IL processes 800-1,000 EDTA specimens per day. Result review is performed on all samples with interpretive messages generated by the analyzer. At RUMC, the "IG Present" flag will signal the slide preparation unit to generate a blood smear. The smear (slide) is then stained and reviewed to evaluate the accuracy of the automated differential.

Along with the "IG Present" flag, other flags may be generated by the analyzer such as "Abnormal Lymphocytes?" or "Blasts?" **(Figure 1)** These additional flags, on their own, or in combination, should also trigger a slide review by the laboratory technologist.

Since many of the samples processed in this lab are STATS from the cancer center, emergency department, or inpatient critical care units, reviews are often difficult and time consuming. While a number of these samples generate multiple flags, a significant amount flag only for the presence of immature granulocytes. The "IG Present" flag contributed to an overall review rate of 15 percent per day with the first shift performing the majority of the 80-100 smear reviews each day.

As previously stated, the "IG Present" message is user-defined and intended to be in line with the review criteria set forth in the individual laboratory's SOP. At RUMC, the upper threshold for IG is set at 1.5 percent, meaning that any specimen with a relative IG count of 1.5 percent or greater will be flagged and sent to the differential bench for manual examination.

Following evaluation of the smear, the medical lab scientist will determine whether to report out the automated differential results as accurate or to perform a manual differential. This entire process often results in a significant workflow reduction as many Core Lab specimens have only the "IG Present" flag.

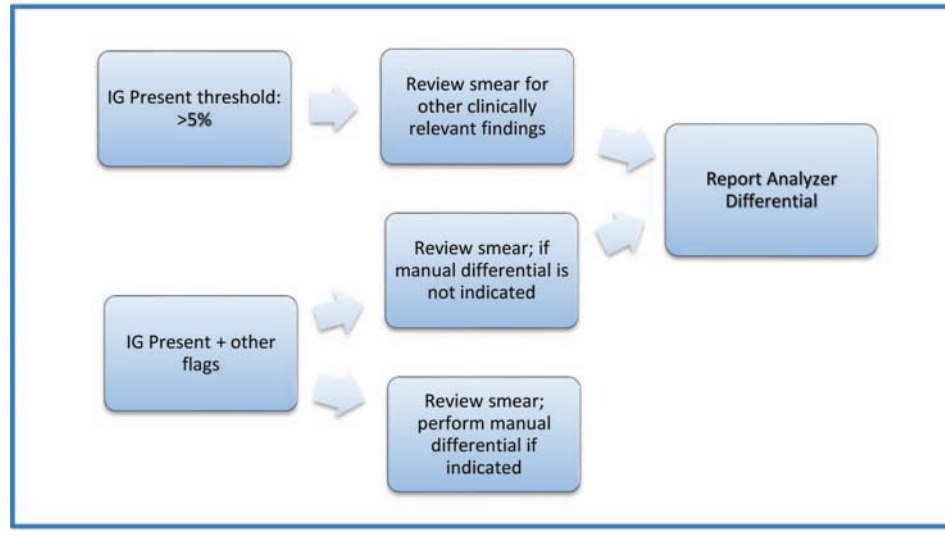


Figure 2. RUMC Core Lab's revised manual smear review flow for samples with "IG Present" flag.

RUMC Core Lab review

In December 2015, the RUMC Core Lab performed a review of 637 auto-differential reports from the hematology analyzer that contained the "IG Present" flag. This was done at the request of the hematology supervisor, and in cooperation with the pathology staff, to assess whether the IG threshold to initiate smear review was set at an appropriate level. Two hundred white blood cell, red blood cell, and platelet IP messages, as well as flag combinations, were evaluated.

The study concluded that when only the "IG Present" message was generated—or "IG Present" combined with the "Left Shift?" message—the smear review did not yield any additional clinically significant information. As a further benefit, the IG result showed no evidence of interference from toxic granulation, which had been an issue with previous analyzer technology. It was determined that the IG review threshold could be increased from the current cutoff of 1.5 percent. Subsequently, the RUMC Core Lab raised the IG review threshold on the hematology analyzers to 5.0 percent. **(Figure 2)**

To determine the impact of raising the IG threshold on workload efficiency, RUMC Core Lab examined analyzer auto-differential reports from a seven-day period. Of the 601 manual review reports investigated during this time period, 264 reports generated an "IG Present" flag, with no other accompanying IP messages. Among the 264 auto-differential reports with only the "IG Present" message, 173 had an IG fraction of greater than 1.5 percent, but less than five percent, while 91 patient reports had an IG fraction of greater than five percent.

Of these 601 auto-differential reports, 434 reports had an IG fraction of greater than 1.5 percent and 167 reports had an IG fraction of greater than five percent. This meant that by increasing the IG threshold to five percent, the lab was able to reduce the number of auto-differentials submitted for manual review by approximately 30 percent per day. Raising the IG threshold had a significant, positive impact on workflow efficiency at the differential bench.

NEW

HEPARIN-INDUCED THROMBOCYTOPENIA

HIT Testing **in Minutes.**

The on-demand solution that saves more than time.

Fast, accurate HIT antibody detection. Prompt detection of HIT antibodies is critical to selection of the most appropriate therapy. Only IL provides a fully automated HIT assay on Hemostasis testing systems, ready-to-use, 24 hours/day, 7 days/week. Complete HIT testing solutions—now on-demand for ACL TOP® testing systems.

For more information in North America, call 1.800.955.9525
or visit **instrumentationlaboratory.com**

Outside North America, visit **werfen.com**

Instrumentation Laboratory
A Werfen Company

A timed study performed in the lab revealed that it takes about five minutes for the RUMC techs to perform each smear review. Raising the flagging threshold for IG eliminated approximately 25 smear reviews each day, saving almost 15 hours of tech time each week. The decrease in workload allowed the Core Lab techs more time to focus on problem patients, training activities and special projects.

Implementing the changes to the slide review policy was simple. Upon reviewing the study data, the hematopathologist was quick to approve the new flagging limit, noting that it may even be reasonable to raise the IG threshold to 10 percent in the future. The laboratory staff had been reporting automated IGs for more than 10 years, and IG was a trusted parameter among the techs and caregivers alike. Additionally, for the past number of years, the hematology techs were directed to validate the auto-differential (in lieu of performing a manual differential) whenever possible. This practice contributed to widespread acceptance of the IG result among caregivers and made it unnecessary to communicate the SOP changes to the medical staff.

In a lab that is operating 24 hours a day, seven days a week, and serving a 700-bed hospital with an ever-expanding outpatient population, the change in smear review procedures decreased TATs enabling technologists to spend more of their time assisting with other important bench work in the Core Lab. The IG parameter is a critical part in allowing RUMC Core Lab to manage a swelling workload and at the same time, deliver quality laboratory results to healthcare providers.

REFERENCES

1. Singer M, Deutschman C, Seymour C, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016; 315(8):801-810.

2. Buoro S, Mecca T, Vavassori M, et al. Immature granulocyte count on the new Sysmex XN-9000: performance and diagnosis of sepsis in the intensive care unit. Signa Vitae. 2015; 10(2):54-64.

3. Nierhaus A, Klatte S, Linssen J, et al. Revisiting the white blood cell count: immature granulocytes count as a diagnostic marker to discriminate between SIRS and sepsis – a prospective, observational study. BMC Immunology. 2013; 14:8.

4. Ansari-Lari MA, Kickler TS, Borowitz MJ. Immature Granulocyte Measurement Using the Sysmex XE-2100. Am J Clin Pathol. 2003; 120(5):795-799.

5. MacQueen BC, Christensen RD, Yoder BA, et al. Comparing automated vs manual leukocyte differential counts for quantifying the 'left shift' in the blood of neonates. Journal of Perinatology. 2016; 36(10):843-848.

Mary Anne Loafman, MS, MT(ASCP)SH, serves as Supervisor of Hematology in the Core Lab at **Rush University Medical Center**, Chicago, IL. As supervisor in a high-volume laboratory, Mary Anne strives to employ proven technology to increase efficiency while maintaining accuracy.

THE RIGHT RESULTS, THE FIRST TIME

Avoid inefficiencies with a **93%** first-pass yield[1]

When important patient care decisions are on the line, you need results you can count on—the first time. The **DxH 900 hematology analyzer** first-pass yield enables predictable costs and maximizes staff time by:

- **Delivering accurate results with fewer reruns** using near native-state cellular characterization and DataFusion technology—a unique combination of multiple testing methods for precise, high-resolution analysis in a single run
- **Ensuring predictable costs** through industry-leading 93% first-pass throughput[1] for accurate flagging and a reduced number of slide reviews
- **Maximizing staff time by reducing** the time and supply costs related to managing systems with higher repeat rates, and simplifying workflow through a lean reagent portfolio

Learn more about how laboratories can achieve Lean practices and minimize repeat rates with the DxH 900 analyzer.

Visit www.beckmancoulter.com/dxh900-MLO

1. Percentage of samples with numerical results that do not require additional intervention or handling, such as manual smear review, spun hematocrit, dilution, or other repeat/reflex testing. DxH series side-by-side results documentation.

For more information, visit www.beckmancoulter.com/contact

AD-180261

BECKMAN COULTER

Move healthcare forward.

Accelerating cancer biomarker development using the latest mass spectrometry tools and techniques

By Yue Xuan, PhD

Cancer is the second leading cause of mortality and is responsible for an estimated 9.6 million deaths worldwide each year.[1] While the prevention of some types of cancer is viewed as a long-term goal for scientific research, an immediate priority for the research community is the improvement of patient outcomes by finding new, more effective treatment approaches and detecting the disease earlier. As such, translational proteomics has become an integral part of cancer research, playing a key role in the discovery and development of protein biomarkers that are set to revolutionize cancer diagnosis, monitoring, and treatment.

The advances in proteomics that have been made over the past two decades stem in large part from remarkable developments in mass spectrometry (MS). Ongoing improvements in the mass accuracy, resolution, and sensitivity of MS instruments are enabling the rapid and reliable detection, identification, and quantitation of proteins in complex mixtures. These techniques are opening the door to improved methods for discovering disease-specific biomarkers with the potential to support early disease detection and even individualized therapies.

Despite improvements in the technical performance of MS instrumentation, a lack of reproducible, scalable workflows has made the task of translating promising candidate biomarkers into real-world clinical diagnostic assays extremely challenging.[2] However, in recent years, advanced MS-based proteomics workflows have been developed that are enabling exceptional reproducibility, multiplexing capacity, and quantitative accuracy. These workflows are now being used in large-scale proteomics research projects, including the Cancer Moonshot initiative, with the aim of driving the successful translation of biomarkers from discovery stage research to clinical applications.

Powerful MS techniques for translational proteomics

MS has proven to be an indispensable tool for unraveling the complexities of the proteome. Its ability to characterize and sequence individual proteins with precision means it can be used to determine protein interactions, document protein expression, and pinpoint sites of protein modification. Recent advances in instrumentation have improved the sensitivity, resolution, quantitative accuracy, and acquisition speed of MS techniques, enabling high-throughput, in-depth proteomic analysis.

Fundamental proteomics research has typically focused upon analytical sensitivity and depth of coverage. However, as biomarker development progresses toward clinical application, MS requirements have become more quantitative, and factors such as reproducibility, standardization, and scalability have become more important. Biomarker verification studies are used to screen potential biomarkers to ensure only the highest quality leads from the discovery phase are progressed. These verification workflows require high throughput methods that are capable of high analytical specificity and sensitivity, require minimal sample preparation, and can provide confident protein confirmation.

Due to innate biological variability, verified candidate biomarkers need to be validated across a large number of samples by developing targeted quantitation assays. Another area of focus for modern proteomics MS workflows is the efficient, targeted analysis of as many candidates as possible across hundreds, and potentially thousands, of samples.

Biomarker discovery using multiplex labeling techniques

Biomarker discovery is the first step in the translational proteomics pipeline. Discovery proteomics workflows are used to characterize biological samples at the protein level, in order to identify potential protein markers associated with disease in small patient cohorts. As biological samples contain very large numbers of proteins, discovery workflows must facilitate comprehensive profiling to ensure no promising candidate biomarkers are overlooked. To help researchers achieve multidimensional characterization of the proteome, multiplexing tools optimized for use with high resolution tandem MS platforms are enabling more accurate and higher throughput quantitation.

While incumbent approaches were limited by the need to analyze complex samples one-by-one, isobaric labeling strategies such as tandem mass tag (TMT) workflows allow for parallel multiplexing of large-scale high-throughput quantitative experiments. Using this technique, multiple peptide samples are chemically labeled with isobaric chemical tags that covalently bind to peptide N-terminal groups or lysine residues on peptides. During MS/MS analysis, each variant produces a unique reporter ion. The intensities of the peaks corresponding to each variant are recorded and compared to determine the relative abundances of the peptide in each sample.

Multiplex approaches based on TMT workflows play an important role in cancer proteomics by detecting the subtle biological changes that contribute to the disease. For example, a TMT-based quantitative proteomics approach was recently used to identify potential diagnostic biomarkers for gastric cancer.[3] The study compared differentially expressed proteins between cancer patients and healthy control subjects, finding several up-regulated and down-regulated proteins active in antigen binding, calcium ion binding, and protein homodimerization. Used in this way, TMT workflows are proving to be highly effective in identifying differentially expressed proteins associated with cancer pathways.

A scalable approach for discovery and verification

Although TMT workflows play a vital role in discovery-stage proteomics experiments, for larger targeted

continued on page 36

When it comes to serum free light chain testing,

Freelite® on Optilite® is the Ultimate Solution

Only Freelite serum free light chain assays are FDA cleared for both diagnosis and monitoring of Multiple Myeloma and AL Amyloidosis

Only Freelite is referenced in >3,000 publications, the result of >18 years of clinical utility

Ensure the best possible performance

Both the assays and the analyzer are optimized by Binding Site

Use less reagent

Assays are designed with wide measuring ranges and large dilution steps

Capture very high Myeloma samples without manual intervention

Optilite automatically re-dilutes to end result

By running Freelite on Optilite, you're guaranteed that your results are delivered quickly, easily, and accurately.

Contact us to learn more.
Binding Site Inc.
Tel: 800-633-4484

info@bindingsite.com
www.bindingsite.com

Protein diagnostics.
Smart solutions.

Binding Site

Who Will Advance Your Laboratory Career?

Dr. Rachel Morris
BLD Graduate Program Director

SPARTANS WILL. The medical laboratory is always changing. Are you? Here at Michigan State University's Biomedical Laboratory Diagnostic Graduate Program (BLD Program), we're providing our students with the skills and expertise that they need to advance their careers in this changing environment. Our faculty's extensive professional and teaching experience allows us to provide the best educational environment for today's working laboratory professionals. The BLD Program has been training medical laboratory scientists for over 90 years, and we've been teaching online for over a decade. Utilizing the latest technology to connect with our online students, we are able to provide the academic content that you need without sacrificing the mentoring and discussion that make graduate education unique. We know that you already have a busy life balancing professional and personal responsibilities, and we provide the flexibility that you need to obtain a master's degree or to sharpen your skills with advanced coursework while managing the rest of your life. As the director of the graduate program, I can honestly say that it is our greatest joy to see our students go on to find professional success after completing our programs. We hope that you'll join us so that we can celebrate your success in the future.

Certificate Programs

Designed for working professionals who need continuing education requirements or who want to update their skills as a lab scientist. These courses are taught online. Some programs offer a week long on-campus lab experience, or an independent study at a lab near the student.

Certificate Programs Offered

- **Molecular Laboratory Diagnostics** The courses cover topics on molecular biology theory, techniques, assay design, and implementation. These courses provide a solid preparation for national credentialing examinations; however, these courses do not fulfill the requirements for eligibility for certifying exams.
- **Immunodiagnostics and Clinical Flow Cytometry** Lab technologists will be trained to apply immunologic principles to current clinical practice. Students design and assess methods in the immunology lab. Flow cytometry is introduced.
- **Advanced Flow Cytometry** Especially for flow cytometry professionals, this program introduces concepts of advanced flow cytometry assay design and analysis.
- **Clinical Mass Spectrometry** For both beginners and experienced technologists. Students learn about mass spectrometry theory and its use in the clinical lab.
- **Managing Biomedical Laboratory Operations** For working lab professionals who want to advance into leadership roles or update their management skills.
- **Transfusion Service Management** Best practices and common work themes of transfusion management are explored; ranging from theories of coagulation and hemostasis to adverse transfusion outcomes and resource management.

Master's Degree Programs

Designed to expand the skills of lab professionals by presenting new technologies and advanced concepts. A multidisciplinary approach to the lab sciences is emphasized, encouraging innovative thinking.

Master's Degree Programs Offered

- **Master of Arts in Biomedical Laboratory Science** Enhances the student's knowledge base and broadens their perspectives across the profession. A variety of science and management courses can be taken to fulfill the degree requirements. A final capstone project expands the student's knowledge of a new technology.
- **Master of Science in Clinical Laboratory Science** Emphasizes the multidisciplinary nature of the laboratory sciences, encourages research that crosses traditional laboratory disciplines, and promotes innovative thinking. Course work is tailored to the student's interests and research project.
- **Master of Science in Biomedical Laboratory Operations** For individuals with previous clinical laboratory experience who seek career advancement as managers, administrators, researchers, entrepreneurs and policymakers in the field. The core of this program resides in three major components: science, management and practice. A science/management research project is completed to develop the student's skills in their area of interest.

To hear more about our faculty and the Master's Programs follow this link to see a short video https://www.youtube.com/watch?v=vVANriMvlwc.

Biomedical Laboratory Diagnostics Program
North Kedzie Hall, 354 Farm Lane, Rm. N322
East Lansing, MI 48824-5672
(517) 353-7800
BLD.NATSCI.MSU.EDU

GO WITH THE FLOW

ADVANCED ONLINE COURSES IN FLOW CYTOMETRY FOR WORKING LABORATORY PROFESSIONALS.

ARE YOU ABLE TO VALIDATE AN ASSAY?

DO YOU UNDERSTAND THE GATES YOU SET?

DOES THE GATING STRATEGY GIVE YOU THE RESULT YOU WANT?

ARE THERE BETTER FLOUROCHROMES FOR YOUR ASSAY?

TAKE THIS COURSE TO GAIN THE CONFIDENCE YOU WANT AND THE EXPERTISE YOU NEED TO BECOME A LEADER IN THE LAB

WWW.BLD.NATSCI.MSU.EDU/ONLINE-EDUCATION

BIOMEDICAL LABORATORY DIAGNOSTICS PROGRAM
MICHIGAN STATE UNIVERSITY

MEET THE PROFESSOR

Dr. Sue McQuiston's experience in flow cytometry started in the lab for Cell Analysis at the University of California San Francisco in 1989. Dr. McQuiston joined the faculty at the Biomedical Laboratory Diagnostics Program at Michigan State University in May 2009 and has incorporated flow cytometry into all levels of undergraduate and graduate teaching.

continued from page 32

verification-stage studies, more flexible and scalable techniques are necessary. Label-free data dependent acquisition (DDA) methods have proven particularly useful at meeting this need and can be used to directly compare relative abundances of proteins across multiple liquid chromatography (LC)-MS/MS experiments without the use of isotopic tags. These methods are generally used for genome-wide protein identification studies and are very effective at extending proteome coverage while minimizing redundant peptide precursor selection. The primary advantage of this approach is that the number of sample comparisons is not limited, creating a comprehensive and scalable workflow.

Label-free protein quantitation is based on tandem MS analysis of the most abundant precursor ions. In contrast to stable isotope-labeling approaches, where differentially labeled proteins are combined and analyzed together, proteins studied using label-free approaches are measured individually. While this allows for comparison of multiple samples, any deviations arising from sample preparation or instrument use generate greater variability and reduce precision. Thus, DDA-based experiments require more repeat measurements to achieve statistical significance.[4]

The latest DDA workflow optimizations, including improvements in separation, acquisition, and data analysis, overcome the challenges around method standardization and experimental reproducibility. Improvements in the sensitivity of capillary flow high-performance LC (HPLC) technologies, for example, are enabling better separation of peptides, and ultimately, deliver more precise data. Data can be further enhanced using the latest LC columns that are designed to achieve more consistent chromatographic separation by reducing mobile phase dead volumes.

Modern high-resolution accurate mass (HRAM) technologies are also leading to improved reproducibility in biomarker verification. The latest generation of Orbitrap mass spectrometers, for example, provide increased acquisition speed and advanced peak determination to expand the number of peptides sampled, thus increasing peptide identification across varying data acquisition modes. Significant improvements in sampling depth, sequencing speed, and protein identifications provide better and more consistent data for enhanced run-to-run reproducibility and confident biomarker verification.

High-resolution verification workflows

While DDA workflows are very useful for scalable biomarker verification, achieving the required analytical sensitivity can sometimes be challenging. Data-independent acquisition (DIA) is an alternative label-free biomarker verification approach that overcomes this challenge. In a DIA analysis, a set of precursor acquisition windows are used to cover a broad mass-to-charge (m/z) range. All peptides within the defined m/z window are fragmented and a product ion spectrum for each detectable peptide is generated, providing multiplexed proteome-wide quantification of even low-level proteins.

While DIA workflows are well suited for biomarker candidate analysis in human samples, challenges with analytical selectivity and dynamic range have led to the search for method improvements. The co-isolates and co-fragments that are sampled by broad acquisition ranges can produce highly complex MS/MS spectra, making confident analysis more problematic. This can be particularly challenging when working with clinical samples such as plasma due to the natural abundance and diversity of peptides and plasma proteins.

High-resolution DIA (HR-DIA) workflows based on hybrid quadrupole-Orbitrap MS technologies are helping to obtain more confident measurements from large-scale proteomics studies. HR-DIA workflows address challenges with sample complexity by using much narrower acquisition windows, an optimization that is possible by the increased mass resolution of modern Orbitrap instruments. With a greater ability for deconvolution of complex spectra, driving improved precursor selectivity and unbiased analysis, HR-DIA workflows increase fidelity and identification range, leading to more reproducible and comprehensive protein profiling.

Validating biomarkers with sensitive and specific protein quantification

Biomarker validation requires workflows with more directed analysis, capable of sensitive and specific protein quantification. While MS approaches for biomarker validation have traditionally relied on selected-reaction monitoring (SRM) techniques performed using triple quadrupole mass spectrometers, variation in the intensities of the product ions generated from the precursor ions can result in sensitivity issues. Parallel-reaction monitoring (PRM) is an alternative approach that uses hybrid triple quadrupole-Orbitrap technologies to achieve more sensitive protein quantitation by identifying the most intense product ions to analyze. PRM offers higher selectivity and high-throughput protein quantitation, ensuring confident peptide quantification.

Once biomarker selection is narrowed to a small number of target peptides, PRM for targeted MS quantification allows the full MS/MS spectra to be acquired for each precursor. This enables higher analyte selectivity to be achieved than with SRM, facilitating better discrimination of target peptides from co-eluting interferences present in complex biological matrices. High-resolution MS can also support PRM analysis, enabling detection of low abundance peptides common in biological samples and outperforming alternative methods in terms of absolute quantification.

Despite these advantages, standard PRM methods can be limited by inconsistent retention times. Temperature fluctuations, inefficient mobile phase mixing, flow rate instability, or column contamination issues can all influence analyte retention times and ultimately affect method reliability. Direct retention time PRM (dRT-PRM) is an improvement to PRM workflows that can help to correct for these issues by monitoring and adjusting retention time windows in real-time using internal standards. In addition, dRT-PRM offers further benefits in terms of the quality and precision of peptide measurements to improve analytical reproducibility.

Accelerating biomarker development with the Cancer Moonshot

Many of the greatest challenges associated with translational proteomics workflows relate to lab-to-lab reproducibility, method standardization, and scalability. These issues are well-recognized, and large-scale collaborative programs such as the Cancer Moonshot initiative are

leading the way when it comes to overcoming them using the most advanced MS methods.

An international multi-site study, conducted as part of the Cancer Moonshot initiative, recently applied many of the next-generation MS proteomics workflows highlighted earlier to determine whether they could accelerate biomarker development. Using TMT multiplexing in discovery workflows for the large-scale analysis of human, yeast, and *E. coli* proteomes, each research group involved in the study analyzed a set of known proteins and compared their results to determine inter-lab and day-to-day measurement reproducibility. Label-free DDA-plus and HR-DIA workflows with precursor-level quantitation were subsequently used for verification and validation studies, delivering comprehensive and accurate analysis that ensured remarkable reproducibility over large patient cohorts.

These MS-based workflows were used to enhance measurement reproducibility across sites, ultimately providing greater confidence in the experimental data generated and accelerating the translation of biomarkers for detecting, monitoring, and treating cancer. Eleven international labs, including six Cancer Moonshot initiative labs, tested the protocols across biomarker identification, verification, and validation stages. In total, over 80 percent of the individual proteins analyzed were identified and quantified in common across different days at the same site, while 80 percent of protein groups were quantified in common across different days and across different labs.

The study confirmed the new MS methods could be incorporated into standardized and high-throughput proteomics workflows to offer exceptional measurement robustness and enhanced scalability from discovery to validation. By implementing the latest MS-based approaches across the biomarker pipeline, the study demonstrated how these robust methods could help to accelerate the development of potential biomarkers into the clinic.

Conclusion

To realize the full potential of protein biomarkers, the existing challenges around reproducibility and scalability encountered with traditional proteomics workflows must be overcome. The latest MS-based proteomics workflows are addressing these bottlenecks in the translational pipeline, helping to drive the development of protein biomarkers for cancer diagnosis, monitoring, and precision treatment.

Please visit mlo-online.com for references.

Yue Xuan, PhD, serves as a Senior Product Marketing Manager, Precision Medicine at **Thermo Fisher Scientific**. She is specialized in multi-omics research including proteome profiling workflow development and is the project lead for the international Cancer Moonshot multi-site study. She has a MSc in chemistry from Free University Berlin and a PhD in chemistry from Technical University of Dortmund, Germany.

Limits of detection—is not detected always synonymous with not present?

By John Brunstein, PhD

Let's start this month's episode with a quick reminder of the target audience for this series—that is, the *non-specialist* interacting with molecular testing methods. If you're an expert in MDx none of the following is going to be news to you. However, judging by questions I repeatedly encounter, for your colleagues who don't specialize in the arcane depths of clinical nucleic acid testing, the following may clarify what some of the underlying caveats are any time a molecular assay returns a negative result. With this in mind, let's consider a situation where a reliable, properly validated, and properly performed molecular test such as a PCR for the presence of a particular infectious organism, yields a negative result. What does that actually mean?

Poisson is not your friend (unless you're running digital PCR)

Well, here's a name that keeps popping up over the life of this series—Siméon Denis Poisson, French mathematician. Among other things, he examined the statistics around sampling. If you have a number of discrete items randomly distributed within a container, and you have a way of counting these items and count the whole container, you will get an accurate measurement of the number of items. If however you take a sub-portion sample of the container and count items in that, you may not get an accurate count. If your container has one countable item and your sample is 1/10 of the container, your most likely result would be not counting the item (your conclusion—container doesn't have any of the item, which is clearly wrong). Of course, your other possible result—that you got lucky and your sample happened to capture the one item—is also misleading from a quantitative standpoint, as you'd assume the whole sample likely has ~10 items. These sorts of misleading results occur when the target analyte is at low real numbers (low concentrations) and become increasingly less of an issue either theoretically or practically, as numbers increase such that the sample is more likely to have a representative number of items. Note that this could be due to increasing analyte concentration, or to increasing sample size; we'll come back to this later.

What does this mean from a practical standpoint? Well, it turns out this has been considered in depth in various validation strategies and guidance documents. You may have run across types of assays which include what are called both a "low positive" and a "high positive" control. By the usually accepted definition, a low positive control is one which gives a positive assay result 19 times out of 20 (95 percent). That's right, you read that correctly. We call it a positive control and if everything is working perfectly, about 5 percent of the time it should be negative. In fact, if you're not seeing that, you're doing something wrong and probably getting excessive false positives! (Note, however, if you have such an assay with a formal "low positive," this doesn't mean you should be overly worried if you run 20 consecutive tests on it and don't get a negative. If, however you can go to 3x the 5 percent frequency level—that is, if you can do 60 sequential tests and still not get a single negative, Poisson says in a nutshell that you've likely got a problem. Over very large numbers of tests you should see 5 percent negative rate for this type of control but for any given series of 20 it would not be unusual to see either no negatives, or perhaps two negatives. Neither is cause for alarm.)

If you have true positive samples at analyte concentrations near that of a low positive, the simple fact is that you're going to report false negatives roughly 5 percent of the time.

Take cheer though that Poisson wasn't all bad news for MDx; if you want to know how his work underpins the magic of digital PCR and allows us to quantitate targets without need for standard curves, have a look back at this space from the December 2013 issue.

A little inhibition goes a long way

Our next culprit in obscuring whether a test negative is a true negative is assay inhibition. "Nonsense!" is the response. "I have an internal control which warns me of this!" Well, actually, the interpretation is a little more complicated than that. While qualitative and quantitative internal controls (IC) work a bit differently and we'll consider each case in turn, failure of IC in either context leaves you with a non-meaningful result. It will stop you from calling a false negative, true, but you're left unable to say whether the sample in question is either positive or negative.

Internal controls are least informative in qualitative assay context. We don't want the IC signal to be sporadically failing for no reason, so it's generally at a level several times (at least 3-4x) that of a formal low positive (assuming equal detection efficiencies between IC and real analyte). Thus, when IC fails, we can be sure there's at least enough assay inhibition going on to supress detection of true targets at 3-4x a low positive level. If there's just slightly less inhibition though, we get into a zone where the qualitative IC can still be positive but the actual functional limit of detection (LOD) is no longer what we expect it to be. Of course if the IC levels are even higher, then this zone of partial inhibition where true analytes can drop out while we are blithely unaware, becomes even larger.

Quantitative contexts such as real-time PCR are a bit clearer, if we assume that the degree of inhibition observed for the IC is the same as that for target analyte. Unless we have evidence to the contrary, that seems reasonable enough. A 1 C_T (or C_P, crossing threshold or crossing point depending on your platform and terminology of preference) increase in IC corresponds to a 2-fold loss in sensitivity; put another way, your analyte LOD

has just gone up by a factor of two, say from 200 U/ml to 400 U/ml. Usually with a qualitative IC, there will be some accepted rules or guidelines as to what sort of a shift in IC C_T (C_P) is allowed before all analyte results are called into question or discarded as not reportable.

For the mathematically inclined, it's interesting to consider how a drop in per-cycle PCR efficiency relates to loss of overall sensitivity. Recall that an ideal PCR is a doubling (x2) per cycle, the theoretical yield of PCR product for N thermocycles is 2^N. Inhibition acts to reduce 2 to a smaller number, say 1.8. That's only a 10 percent loss in efficiency, but the exponential nature of the process amplifies that error. Using some hard numbers, say 35 cycles, a perfect PCR would yield 2.44e10 products, while the 10 percent inhibited assay only yields 1.27e9 products—or about a 19 fold loss. If this were our above example with an ideal LOD of 200 U/ml, it's now 3843 U/ml.

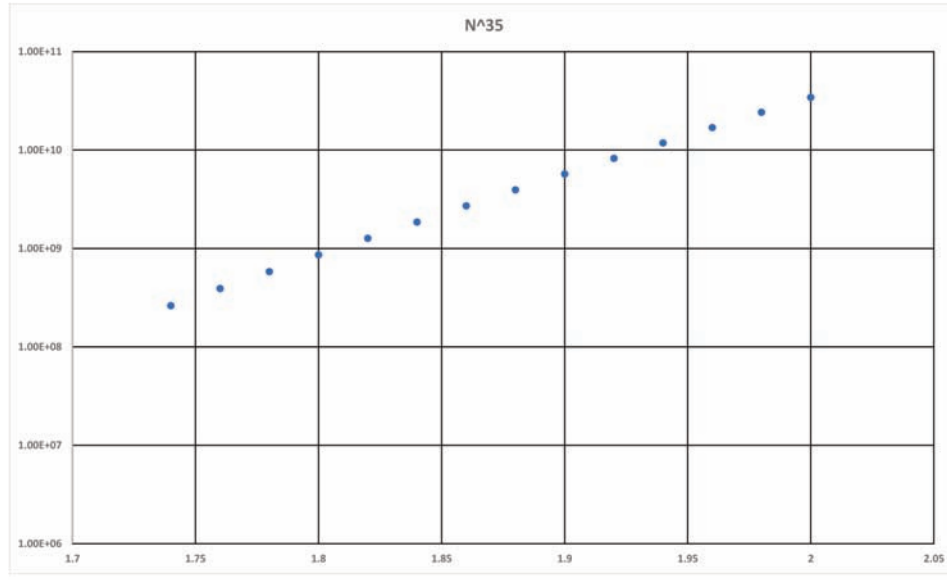


Figure 1. Theoretical PCR yield vs per-cycle efficiency

Legend. Theoretical amplicon yields at 35 cyles vs per-cycle PCR efficiency, at 35 cycles.

In either context, the bottom line is that there's potential for there to be some degradation of assay performance before it's going to fully supress internal control signals, and this is a window of opportunity for false negative results.

Reaction volumes—size matters

There was a promise above that we'd return to the issue of sample size. In this context we mean "amount of template/extract volume put in the reaction," as opposed to the size of the original specimen. I was recently approached by the sales representative for an unnamed company, who proceeded to wax lyrical about their new PCR platform with 1.2 µl reaction volumes; not nearly as tiny as digital PCR range, but certainly smaller than reactions volumes on most common platforms. If we take that to be around 25 µl—make it 24 µl for simplicity—it's 20 times smaller.

Of course, there are some real advantages to this. Per reaction reagents cost is lowered, and thermal mass is smaller, meaning shorter dwell times needed in thermocycling, and concurrent faster whole reaction times. However, all other things being equal—including ratio of template to PCR reagents per reaction—then using this platform one can only put 1/20 as much extract in the reaction as you could in a 24 µl reaction and simplistically, we've just raised our LOD by 20x as compared to running the larger volume reaction. In the early days of real-time PCR, there were even such things as 100 µl reactions which would allow for sampling ~80x more input material per reaction.

This particular line of logic is mostly pertinent to the LOD value observed in the assay validation, and where the balance between reagent cost savings and required LOD lies. For what are expected to be high copy number analytes, small reaction volumes can be great—but applying them if low range sensitivity is required may be counterproductive. Like most fields, different tools are better suited for different jobs.

Sequence variation

Finally, what about target genetic variability? MDx assay developers go to great lengths to try to find ideal, well conserved/consensus primer binding sites. These help ensure that biological pressure on the target analyte/organism limits variation off from these sequences but it's not an absolute guarantee. Especially if the analyte is an emerging organism, one for which there are necessarily limited example sequences to base primer design on, it's within the realm of possibility that you could encounter an organism with critical sequence variations under primer and/or probe binding sites. Depending on where and what these nucleotide changes are, they may cause very significant losses in assay sensitivity and lead to false negative results.

Absence of proof is not proof of absence—*traditional aphorism*

Fortunately, the single most likely reason for a well designed, well validated, and properly run MDx assay to return a negative result is that the sample doesn't contain the analyte in question. All of the above however should serve to remind the end user of any assay that while rare, false negatives can and do occur. In the MDx context we considered there are a number of factors which can contribute to this. All of this goes to underline the importance of interpreting lab results in real context and being ready to question them if they really don't seem to fit. In such cases retesting or use of an alternate secondary assay may be wise.

John Brunstein, PhD, serves as an Editorial Advisory Board member for MLO. John is also President and CEO for British Columbia-based **PathoID, Inc.**, which provides consulting for development and validation of molecular assays.

AI and interpretive algorithms

Obtaining accurate and efficient results in clinical microbiology

By Susan Sharp, PhD

An innovative and collaborative approach to pre-analytics has resulted in original devices that have made microbiology collection processes simple and easy. Many of these collection and transport systems have been proven to advance the quality of traditional and contemporary microbiology assays. Flocked swabs and other liquid-based microbiology collection devices together with full laboratory automation (FLA) for microbiology, allow clinical laboratories to fully automate their culture testing. FLA includes specimen processing, smart incubation, digital imaging, and effective algorithms for automatic segregation of bacterial cultures, followed by automated colony selection and setting up of identification and susceptibility testing.

Collections devices and full laboratory automation

Automatic specimen processor units are a solution for preanalytical microbiology. These are open platforms, modular instruments, and can address all aspects of automated microbiology specimen processing: planting and streaking, Gram slide preparation and enrichment broth inoculation, and more. These systems can automate the workflow of the laboratory and allow the freedom to walk away from specimen set up and focus on higher level tasks. Most importantly, automated specimen processing is what microbiologists have asked for in their ideal laboratory.

Testing efficiencies, quality, and safety

FLA allows samples to be evaluated faster and without the need for additional staffing. The system allows for earlier growth detection as culture plates are in a continuous incubation situation at the correct temperature and atmosphere for optimal growth. There is no constant opening of the incubator doors to retrieve plates subjecting the cultures to suboptimal conditions, and plates are not left on the bench top for hours without proper incubation and atmospheric requirements. These efficiencies will allow for a new paradigm for what we think we know about incubation times. For example, traditionally urine cultures need to be incubated for 16-18 hours prior to the selection of colonies for further identification and susceptibility testing. With FLA and continuous incubation these cultures can be read as early as 10-12 hours. This new shift will occur with other types of specimens as we see improved bacterial growth of all cultures through defined, uninterrupted incubations. FLA allows for safe work up by laboratory staff without the need to be exposed to plates possibly growing highly infectious agents, and efficiencies will be gained by never needing to touch a negative plate again. The system also offers increased traceability using a bi-directional connection with the laboratory information system (LIS).

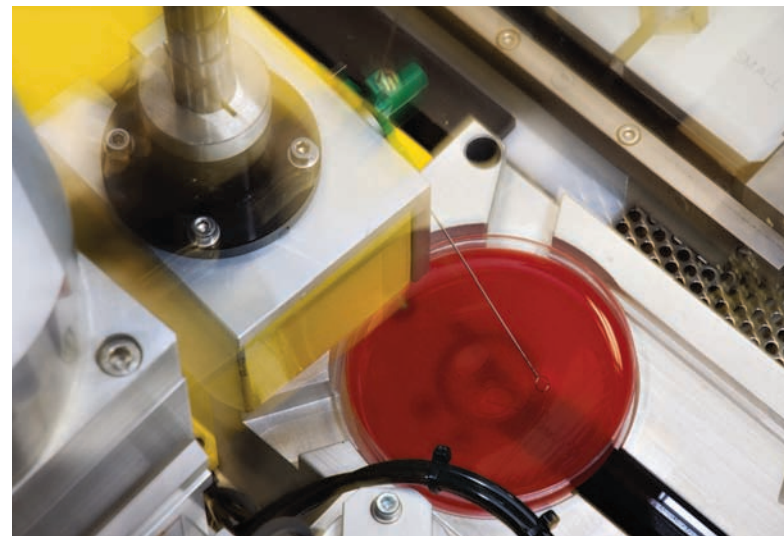
Artificial intelligence

Automated specimen processing and reading systems can be used to optimize laboratory resources for increased productivity. New AI/IA software uses artificial intelligence (AI) and interpretive algorithms (IA) to aid laboratory personnel with culture reading to allow for further optimization in the laboratory freeing up staff to concentrate on more difficult tasks.

AI/IA systems use a selection of highly sophisticated algorithms that will pre-assess, and pre-sort culture plates allowing microbiology laboratories to then read, interpret, and segregate bacterial cultures with the click of a button. As examples, algorithms that are currently on the market include:

1. Segregation of chromogenic media for the detection of methicillin-resistant Staphylococcus aureus (MRSA);
2. Digital analysis of chromogenic media for vancomycin-resistant *Enterococcus* (VRE) screens; and
3. Pre-sorted digital segregation of urine culture quantitation.

Several currently available algorithms have been submitted to the Food and Drug Administration to allow for auto-verification and automatic release of



WASP loop; image courtesy of COPAN Diagnostics.

WASPLab Studio; image courtesy of COPAN Diagnostics.

results with no technologist intervention. Laboratories can also use the software to gather and analyze specimen results together with pertinent clinical patient information to optimize their algorithms. For example, algorithms can combine culture results with the sex and age of the patient to determine if small numbers of organisms detected in urine cultures need to be screened for group B streptococci.

In general terms, here's how the software works: First a 'time zero' image is taken of the culture plate, then at user-defined incubation times additional images are taken and compared to the time zero image. Specifically, for chromogenic agars, the first question that is then asked is, "Is there something present now that was not present at time zero?" If the answer is yes, then the next question is, "What is the color of what is now present?" The final question that is asked is, "What hue is the color that is now present?" If the chromogenic media has growth, that growth is green, and the green colonies are the 'right' color (lime green for this particular media), then the AI tells you that the culture is presumptively positive. Conversely, if there is no growth or if the growth present is not the color and hue needed to be considered positive, then the AI will pre-sort that the culture as most likely negative. In addition, the software can determine colony counts of urine cultures and pre-sort these cultures into categories of:

1. No growth;
2. 100-1000 CFU/mL;
3. 1000-10,000 CFU/mL;
4. 10,000-100,000 CFU/mL; and
5. > 100,000 CFU/mL with great accuracy.

Laboratory staff will also gain efficiencies as they will be able to focus on plates that AI/IA cannot yet deal with. In addition, using these algorithms there is not the variability that we see with human interpretation, i.e., the algorithms always make the same decision each time and never deviate from standard operating procedure.

Training and quality assurance

An extension of the above discussed advances of FLA, include an added advantage of utilizing the system for efficient training and quality assurance (QA) activities. Such activities would include utilizing images of known organisms and cultures for more efficient training of new staff members. Training technologists to recognize normal organism morphology could be expedited using the plethora of stored images of previous cultures. Technologists would be able to visualize multiple images taken over time on previous cultures along with the progression of culture results to learn how clinical microbiology decisions are made in the work up of various culture types. It could take months or longer for an isolate of *Listeria monocytogenes*, for example, to come into the laboratory, but with stored images along with Gram stain images, new staff can be trained to recognize these and other less commonly isolated organisms the first time they see it in a real time culture.

Laboratory QA is designed to detect, reduce and correct deficiencies and errors in laboratory practices to release quality patient results and involves all parts of testing: pre-analytical, analytical, and post-analytical processes. CLIA regulations (Subpart P) address specific quality assurance requirements and The Code of Federal Regulations (42 CFR 493) states laboratories "must establish and follow written policies and procedures for a comprehensive quality assurance program that is designed to monitor and evaluate the ongoing and overall quality of the total testing process." Further it states that the QA program must:

1. Assess the effectiveness of the laboratory's policies and procedures;
2. Identify and correct problems;
3. Assure the accurate, reliable, and prompt reporting of test results; and
4. Assure the adequacy and competency of the staff.[4]

WASPLab Incubator; image courtesy of COPAN Diagnostics.

Liquid based-microbiology (LBM) collection and transportation devices together with FLA can assist in

a quality management system to consistently focus on meeting healthcare provider and patient requirements to enhance their satisfaction with the laboratory. LBM collection devices are manufactured to collect the best patient sample possible and maintain specimen integrity and organism viability until the specimen is processed in the laboratory resulting in superior patient results.

As just a few examples, automated specimen processing is a barcode-driven system that will reduces errors, improves accuracy of specimen processing, and eliminates transcription and transposition errors. Intuitive software and touch screen commands make all operations fast and simple, minimizing hands on time by the staff. FLA systems are flexible and can be designed to be modular and scalable to meet the unique needs of each unique laboratory regardless of space restrictions. Utilizing smart incubators and digital microbiology, users find that they are able to read plates more efficiently and accurately, detecting clinically relevant growth earlier than with traditional incubators and manual reading. This allows the laboratory to report more actionable results to clinicians faster to optimize patient care. In addition, images captured with digital microbiology can be used for blinded proficiency testing of laboratory personnel as part of a comprehensive competency assessment program. Lastly, new software AI/IA can accurately pre-assess growth on any manufacturer's chromogenic agar for faster more accurate results, segregating presumptive positive cultures that may be missed on manual reading.[2-4]

In summary, today's complete line of automated microbiology products leads the way, and will continue to do so with future innovations, to assist the laboratory with QA measures, staff training needs, and efficiencies for result reporting to improve patient outcomes.

REFERENCES

1. American Academy of Family Physicians. CLIA and Quality Assurance. Quality Assurance, CLIA and Your Lab. https://www.aafp.org/practice-management/regulatory/clia/quality-assurance.html. Accessed Jan. 28, 2019.
2. Faron ML, Buchan BW, Coon C, Liebregts T, et al. 2016. Automatic Digital Analysis of Chromogenic Media for Vancomycin-Resistant-Enterococcus Screens Using Copan WASPLab. *Journal of Clinical* Microbiology, 54(10), 2464-2469. doi:10.1128/jcm.01040-16.
3. Faron ML, Buchan BW, Vismara C, Lacchini C, et al. 2016. Automated scoring of chromogenic media for detection of methicillin-resistant Staphylococcus aureus by use of WASPLab image analysis software. *J Clin Microbiol* 54:620–624. doi:10.1128/JCM.02778-15.
4. Kirn TJ. 2016. Automatic digital plate reading for surveillance cultures. *J Clin Microbiol* 54:2424-2426. doi:10.1128/JCM.01279-16.

Susan E. Sharp, PhD, (D)ABMM, (F)AAM, MS, MT(ASCP), serves as Scientific Director for **Copan Diagnostics, Inc., U.S.** Dr. Sharp's most prominent area of interest has centered on cost-effective, clinically-relevant, diagnostic microbiology. Sharp has served as a director for microbiology laboratory services for over 30 years.

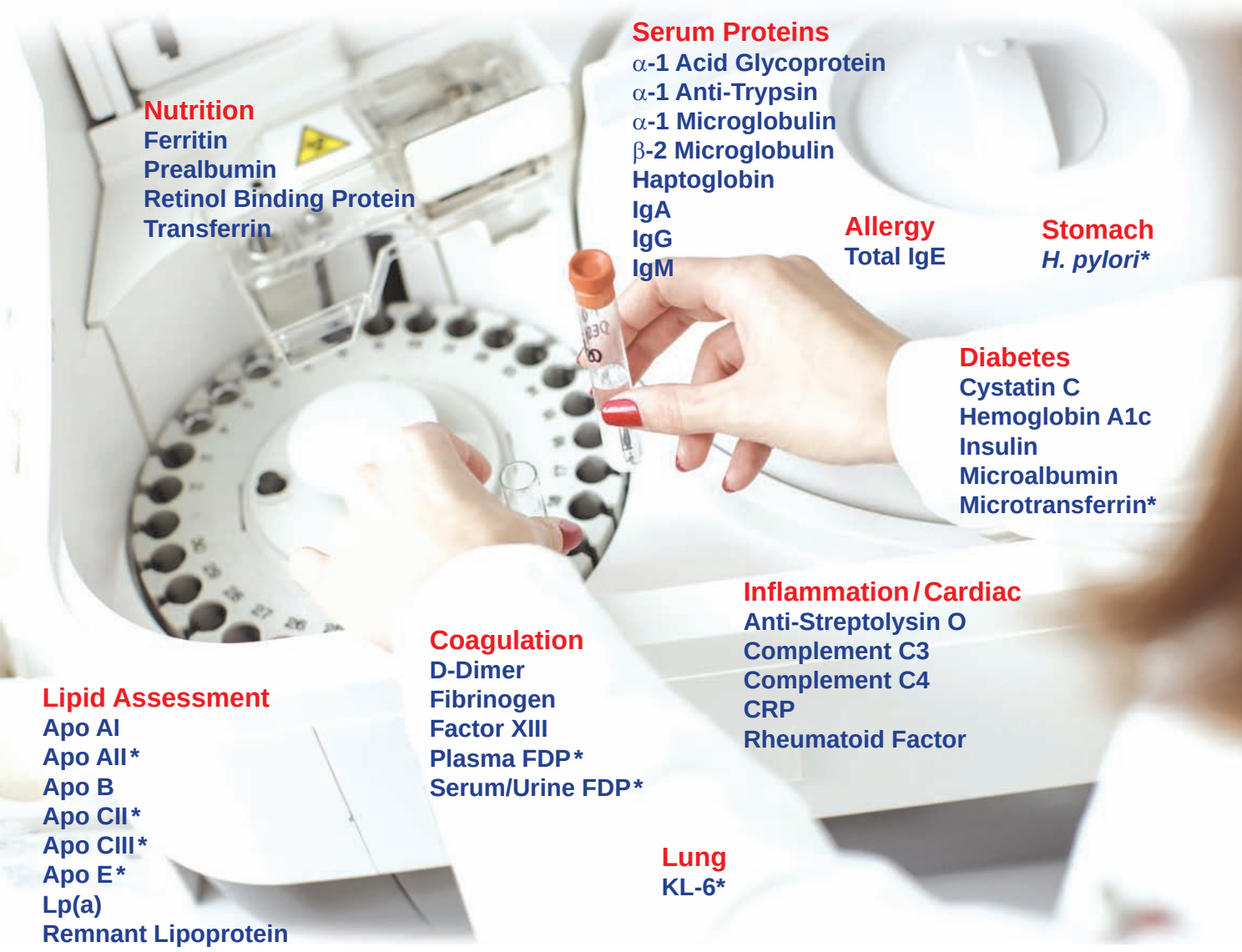
INDEX OF ADVERTISERS

ADVERTISER	WEB	PAGE
ALCOR Scientific	www.alcorscientific.com	IBC
Audit MicroControls	www.auditmicro.com	21
Beckman Coulter	www.beckmancoulter.com/dxh900-MLO	31
Binding Site	www.bindingsite.com	33
BioFire	www.biofiredx.com	3
Bio-Rad Laboratories	qcnet.com/InteliQ	23
Bio-Rad Laboratories, Clinical Diag. Group	info.bio-rad.com/bioplex-syphilis	15
CLSI/Clinical Laboratory Standards Institute	clsi.org/ast2019	37
ELLKAY	www.ellkay.com	BC
Fujirebio US	www.fujirebio-us.com	13
Hologic - Panther Fusion	www.pantherfusion.com	17
Instrumentation Laboratory.	www.instrumentationlaboratory.com	29
Kamiya Biomedical Company	www.k-assay.com/MLO.php	43
Michigan State University	bld.natsci.msu.edu	34-35
Polymedco	www.polymedco.com	5,30
Puritan Medical Products Company.	www.puritanmedicalproducts.com	18-19
Randox Laboratories	randoxonlinestore.com	11
Sysmex	www.sysmex.com/UA	IFC-1,27

K-ASSAY®. . . *High-Quality, Low-Cost Reagents*

Immunoassay Reagents for chemistry analyzers™

Over 37 different assays available



Nutrition
Ferritin
Prealbumin
Retinol Binding Protein
Transferrin

Serum Proteins
α-1 Acid Glycoprotein
α-1 Anti-Trypsin
α-1 Microglobulin
β-2 Microglobulin
Haptoglobin
IgA
IgG
IgM

Allergy
Total IgE

Stomach
*H. pylori**

Diabetes
Cystatin C
Hemoglobin A1c
Insulin
Microalbumin
Microtransferrin*

Inflammation / Cardiac
Anti-Streptolysin O
Complement C3
Complement C4
CRP
Rheumatoid Factor

Coagulation
D-Dimer
Fibrinogen
Factor XIII
Plasma FDP*
Serum/Urine FDP*

Lipid Assessment
Apo AI
Apo AII*
Apo B
Apo CII*
Apo CIII*
Apo E*
Lp(a)
Remnant Lipoprotein
Cholesterol*

Lung
KL-6*

New Products Now Available!!

- β-2 Microglobulin reagent for chemistry analyzers
- *H. pylori* Test Reagent* for chemistry analyzers
- KL-6 (Krebs von den Lungen-6)* reagent for chemistry analyzers
- Microtransferrin* reagent for chemistry analyzers
- Remnant Lipoprotein Cholesterol* reagent for chemistry analyzers
- Retinol Binding Protein reagent for chemistry analyzers

* Research Use Only

KAMIYA BIOMEDICAL COMPANY
diagnostics@k-assay.com | 800-KAMIYA-5
www.k-assay.com/MLO.php

A conversation with Kristine Russell on the ongoing history of *MLO*

Congratulations on *MLO* reaching its 50th anniversary! How long have you been publisher/executive editor? Thank you! I've been involved as the publisher of *MLO* for the past 20 years. I had a short two- to three-year break where I was not directly involved but returned to *MLO* as its new owner in 2010. It's been an exciting experience to watch and report on the increasing depth of laboratory capabilities and the professionals that accomplish the tasks that help with patient care.

Please share with us how you became publisher of *MLO*. Nelson Publishing was in expansion mode in the 90s. This was the company I worked for before I started my own two companies, NP Communications and KSR Publishing. The Nelson publications focused on manufacturing and electronic engineering. In my role as VP of Operations and Acquisitions, I was tasked with growing the company, which included looking at publications that would expand our focus in other technology areas.

I first identified *Health Management Technology,* recently rebranded as *Healthcare Innovation*—which focused on bringing technology to healthcare-based solutions.

Then I discovered *Medical Laboratory Observer* and its sister publication, *Healthcare Purchasing News*. *HPN* covers supply chain, surgical services, sterilization, and infection control—everything bought and supplied in a hospital and a lab. Both were purchased at the same time and became part of our expanded healthcare publishing group.

My family was involved in publishing so I've been around it since I was a kid. I wasn't planning on staying involved but it was a great opportunity to apply my programming and operational skills. I helped develop the IT platform that allowed us to manage not only content, but our audience development, sales, and distribution across 13 unique print publications.

How has *MLO* evolved since you've been in the driver's seat? I saw the opportunity to share information across all three of our healthcare publications (*MLO*, *HPN*, and *HI*), and focused on educating practitioners in topics like infection prevention in hospitals. And we cover how informatics solutions can bring better processes to the clinical lab. We also include a continuing education feature in *MLO* every month, working with Northern Illinois University (NIU), School of Nursing, to certify the continuing education credits. NIU is my undergrad alma mater.

I've always wanted *MLO* to elevate the value of laboratory professionals in the healthcare community. One of those ways is with our annual *MLO* Lab of the Year. The submissions tell the stories of overcoming challenges and ultimate successes that offer inspiration to the lab community.

You're very committed to the blood bank. Why is donating blood so important to you? I was asked to be on the board of directors of the local blood bank in Sarasota—Suncoast Blood Bank. Blood is the *gift of life*. Its collection and processing are difficult and time-consuming processes that give life and health back to patients who need it. We strive to make blood donors comfortable and to show how important they are when they donate.

How do you measure success? When I hear from someone that a story we published enhanced the quality of healthcare they were delivering or solved a problem.

The laboratory is challenged attracting youth into the profession. How do you think this problem can be solved? This is a universal problem in healthcare that includes laboratorians, physicians, nurses, and other important support professionals. Healthcare is a tough profession. It's rewarding and necessary, but it's full of a lot of regulations and documentation that are time consuming and not necessarily part of the discipline they were educated for—the actual care delivery. If a magic wand tool could be developed that would connect all the disparate information systems and make information capture and reporting easier, that would help!

Tell us about *MLO*'s new relationship with Endeavor Business Media (EBM). I met Chris Ferrell (EBM CEO), three years ago. I respected his enthusiasm surrounding publishing and particularly his interest in business-to-business publications. We kept in touch and he offered to purchase my publishing companies. We joined Endeavor in May 2018.

I recognized the capabilities and opportunities of joining a larger organization to grow our technology products on our websites, events, and custom projects like webinars and whitepapers. I continue to serve as VP and Group Publisher of the Healthcare Group and as an EVP with the core Endeavor Business Media management team.

What's the most important achievement you hope to accomplish in your current role? To provide accurate and cutting-edge information to enable our healthcare professional subscribers to excel at their jobs—and to enhance quality patient care—at the best possible cost.

What's the biggest change you've seen in the laboratory over the course of your career with *MLO*? Information transfer and the evolution of tools now available for laboratorians to enable them to do testing faster, more accurately, and with much more in-depth results.

Any advice for those looking to enter healthcare publishing? It's a passion of mine to watch developments in healthcare—I truly enjoy it. If you have the interest and the desire to spend 42 weeks a year on the road—immersed in all kinds of conferences—trying in your head to connect the pieces—you'll be perfect!

You're a self-proclaimed workaholic. What do you like to do to relax? I read books at 3 a.m. when I can't sleep in random hotel rooms. I'm particularly fond of Liane Moriarty novels.

Primary EDTA tube.
100µL sample.
17 second results.

Enough *"SED"*

miniSED™

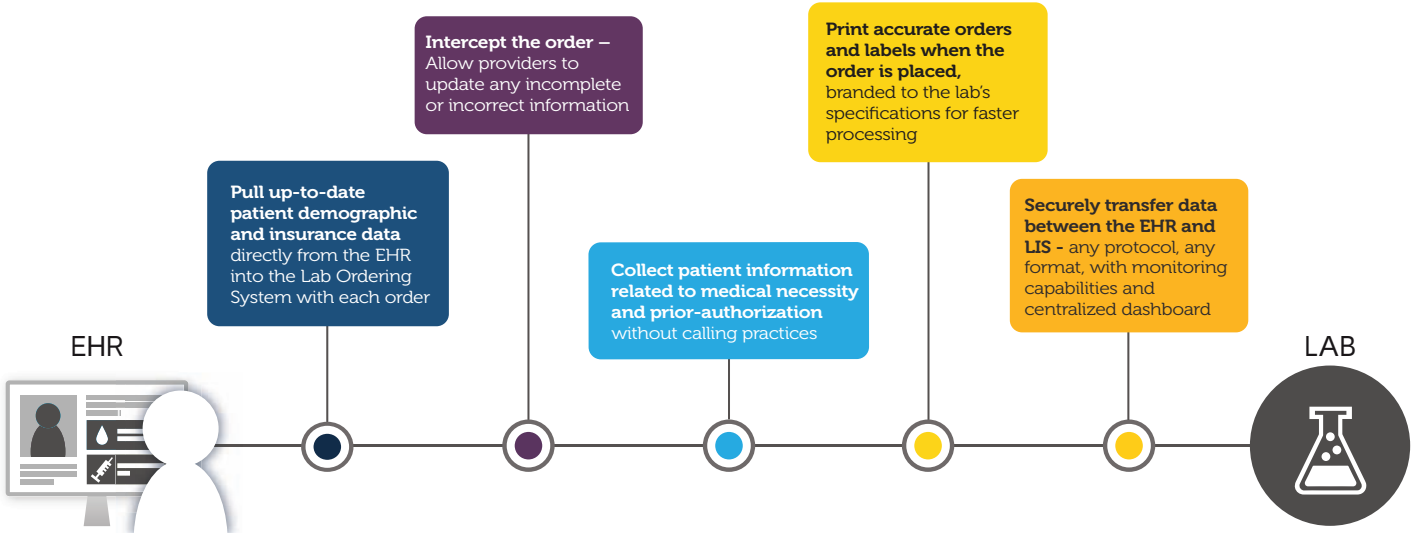
THE IDEAL ESR ANALYZER FOR EMERGENCY ROOMS, POLs, AND AS A BACKUP ANALYZER IN ANY HOSPITAL LABORATORY.

ALCOR Scientific Inc.
20 Thurber Boulevard
Smithfield, Rhode Island 02917
WWW.ALCORSCIENTIFIC.COM
TELEPHONE 800.495.5270 | FACSIMILE 401.737.4519

ALCOR SCIENTIFIC

100% Complete, Clean Orders from the EHR

Maximize laboratory reimbursements with accurate data in every order



200+ EHRs / 700+ PM systems | 48,000 practices / 200 hospitals | 250+ laboratories connected

Over 90% of claims denials are preventable. Clean laboratory orders improve the quality of coordinated care, help labs avoid denied claims, maximize reimbursements, and decrease operational costs.

ELLKAY is at the center of the electronic ordering workflow, with a suite of laboratory solutions that deliver end-to-end clean laboratory orders from connectivity to EHRs to data into the LIS, resulting in maximized reimbursements.

ENSURING LABORATORIES RECEIVE THE DATA THEY NEED

- ✔ Updated patient demographics
- ✔ Patient insurance information
- ✔ Insurance eligibility
- ✔ Provider information
- ✔ Rules-based AOE questions
- ✔ ABN checks
- ✔ Diagnosis codes
- ✔ Information related to medical necessity checks and prior-authorization

Labsales@ellkay.com | (201)-791-0606 | www.ELLKAY.com

ELLKAY
Healthcare Data Plumbers