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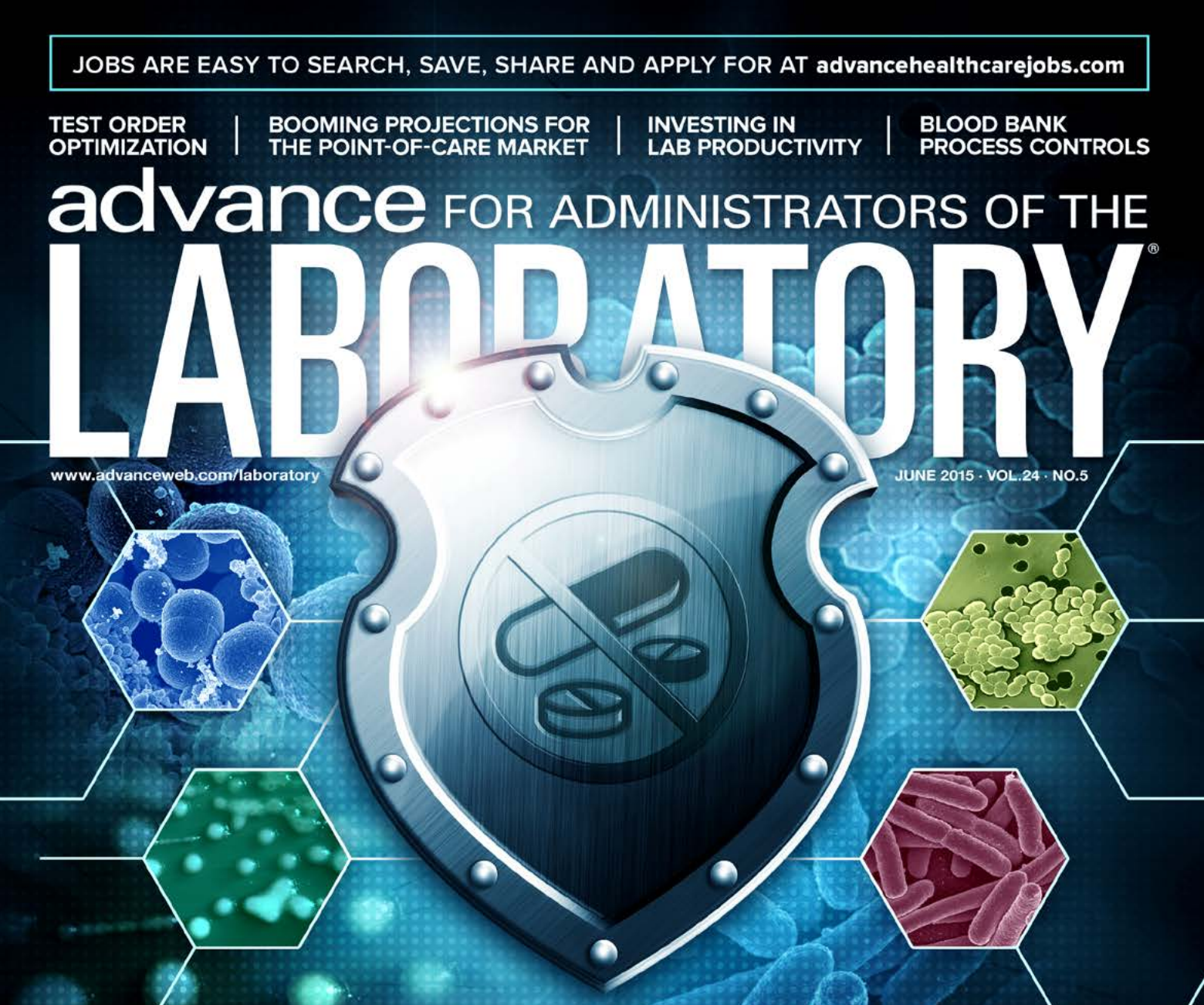

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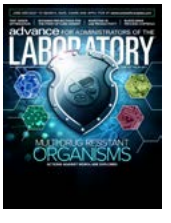

ABOUT THE COVER

Antibotic resistance is a worldwide problem that can easily cross international boundaries.

Illustration by Matthew Taraborrelli

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The Vaccination Argument

Recent events – specifically the measles outbreak at Disneyland – have led to something of a national controversy regarding vaccinations. In this article, *ADVANCE* clears the air on the subject of immunizations. Bill Miller discusses the potential consequences of the anti-vaccination movement and the need for better education concerning the rumors and realities of vaccines.

EXCLUSIVE ARTICLES

Biorepositories and Personalized Medicine

Author Nancy Alers offers insight on the role of biorepositories as the healthcare industry shifts towards personalized medicine.

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Population Health

What does it mean for the industry?

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EDITORIAL

ON RECORD

Concern Of MDROs

As members of the healthcare community, you're well aware that the use of antibiotics is the single most important factor leading to antibiotic resistance around the world. It's somewhat ironic that using antibiotics creates resistance; bacteria always seem to find ways to resist antibiotics.

In 2013, CDC published a report outlining the top 18 drug-resistant threats to the United States. These threats were categorized based on urgent, serious and concerning levels.

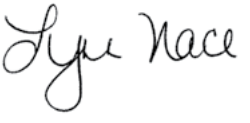
Notes the CDC website, "Antibiotic-resistant bacteria threaten to return us to the time when simple infections were often fatal. Today, antibiotic-resistant bacteria annually cause at least 2 million illnesses and 23,000 deaths in the United States."

Detecting, preventing and controlling antibiotic resistance requires coordinated efforts; CDC is working to address the threat in four areas:

1. Slow the development of resistant bacteria and prevent the spread of resistant infections.
2. Strengthen national one-health surveillance efforts to combat resistance.
3. Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria.
4. Improve international collaboration and capacities for antibiotic resistance prevention, surveillance, control and antibiotic research and development.

The timeliness of this topic is highlighted in this issue's cover story. Author Martha J. Roberts, PharmD, writes, "It's not uncommon to hear warnings of outbreaks of resistant organisms causing serious infections. During the last few weeks, for example, a strain of Shigella resistant to ciprofloxacin, one of the standard antibiotics used to treat this organism, has been reported. This Shigella development was preceded by a report in January of an outbreak of carbapenem-resistant Enterobacteriaceae (CRE)."

What do we know about MDROs? A review of a few key ones is provided, along with action items as recommended by CDC. As always, we welcome and encourage your feedback. ■



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[1] Van Der Pol B, Liesenfeld O, Williams JA, et al. Performance of the cobas CT/NG Test Compared to the Aptima AC2 and Viper CTQ/GCQ Assays for Detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. *Journ Clin Micro*. 2012;50(7):2244–2249.

[2] Van Der Pol B. Cobas® 4800: a fully automated system for the detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. *Expert Rev Mol Diagn*. 2013;13(2):131–140.

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QUEST FOR QUALITY

IQCP for ACOs

By Irwin Z. Rothenberg, MS, MBA, CLS(ASCP)

There is now little disagreement that the U.S. healthcare system is in the midst of a transformation away from reactive and acute care to proactive, integrated clinical care. The healthcare model of choice to manage this change is the Accountable Care Organization (ACO).

The success of the ACO model in fostering clinical excellence while simultaneously controlling costs depends on its ability to "incentivize hospitals, physicians, post-acute care facilities and other providers involved to form linkages and facilitate coordination of care delivery." By increasing care coordination, ACOs can help reduce unnecessary medical care and improve health outcomes, leading to a decrease in utilization of acute care services.[2]

Although the ACO model had already been adopted in the private sector, a key driver since 2012 has been the implementation of ACOs for the Medicare Program under the Affordable Care Act. By the end of 2013, there were a total of 606 ACOs of all types, 366 of which were MSSP (Medicare Shared Savings Program) ACOs. They are now in every state and Washington, DC.[3]

The Role of IQCP in ACOs

As far back as 2010, the effect of (the then proposed) ACOs on clinical laboratories was already being discussed. As reported in Dark Daily at that time, "The Affordable Care Act includes incentives linked to ACOs for providers who better manage specific groups of patients. Since better patient management often means close monitoring of chronic diseases through lab testing, medical laboratories may see an increase in demand for such tests. Clinical labs [should] be ready to accommodate more lab testing that is driven by evidence-based medicine (EBM) algorithms. They should also be ready to provide more direct information to patients."[4]

The same concerns that have been driving healthcare delivery models toward the value-added propositions of quality care, cost effectiveness and efficient utilization of resources have also been important issues for clinical laboratories, since laboratories play such an important role in determining the success or failure of ACOs to deliver quality patient care at lower cost. Critical to this is the laboratory's commitment to quality control.

When CLIA '88 became effective in 1992, the minimum requirement for quality control (QC) was established as testing two levels of control materials each day of patient testing. Since then, QC has continued to evolve. The CLIA Interpretive Guidelines allow an alternative to daily external QC as long as "equivalent quality testing" is assured. Since 2004, this alternative has been Equivalent Quality Control (EQC).

However, it was observed that there were a number of potential errors that could lead to inaccurate results that were not detected either by the test system's internal controls or by the EQC qualifying studies. Consequently, in 2005, CMS encouraged the Clinical Laboratory and Standards Institute to develop a new QC guideline. The resulting guideline, EP-23 Laboratory Quality Control Based on Risk Management, was published in October 2011. The CLIA Interpretive Guidelines incorporated key concepts from EP-23 to develop a new alternative QC policy.

The new guideline is called Individualized Quality Control Plan (IQCP). The key word here is "individualized." It is the new equivalent quality control option for non-waived testing that allows the laboratory to create a QC plan customized to its specific environment. It replaces EQC as the permitted QC alternative after Jan. 1, 2016.[4] QC is most effective when it takes into consideration all of the circumstances that are unique to the laboratory.

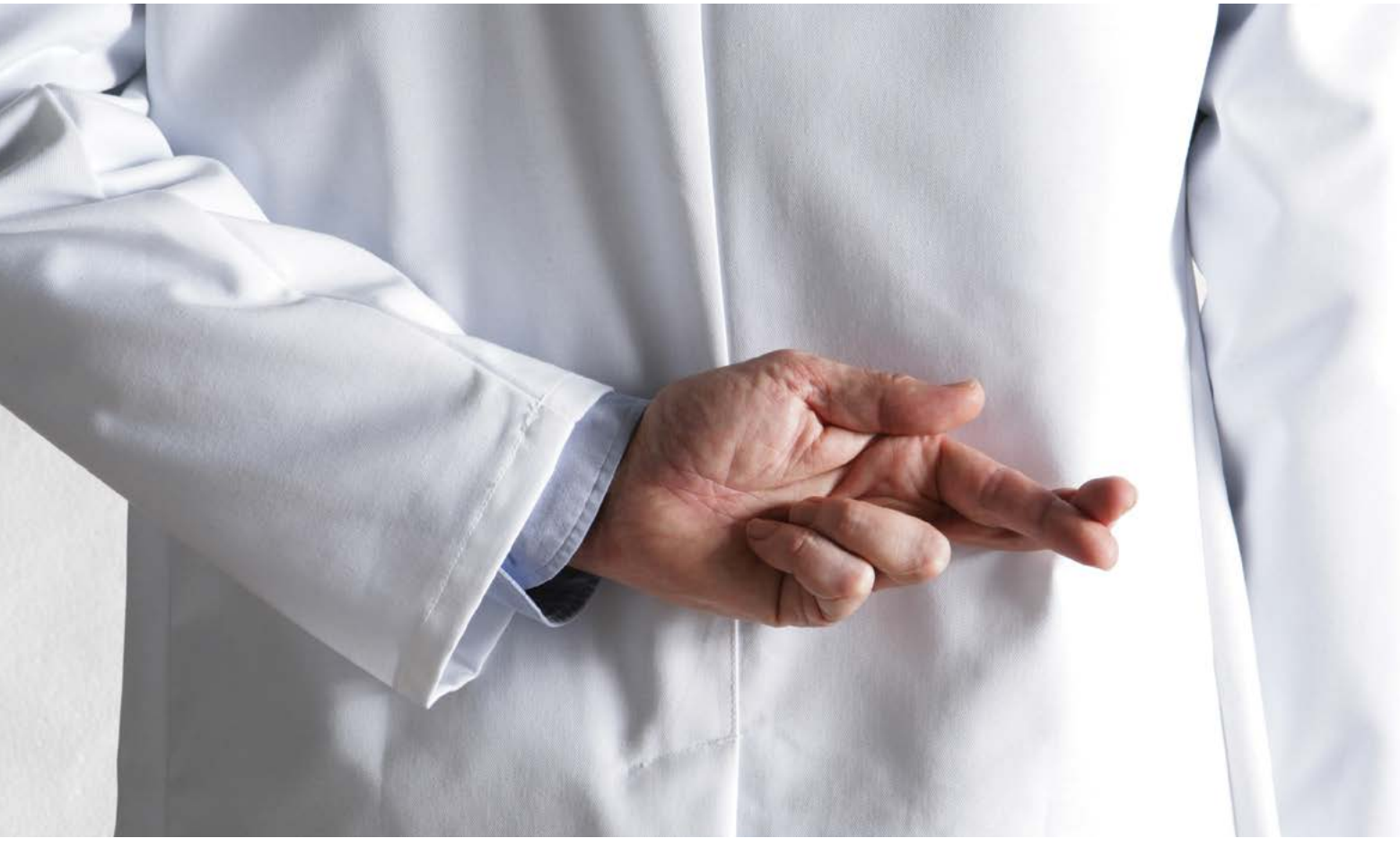
Alignment of Goals

The introduction of IQCP with its emphasis on creating QC protocols for each analyte and test system based on the uniqueness of the laboratory is a major step forward in accomplishing the level of quality patient care sought by ACOs.

The work involved in developing an IQCP, whether for one test, several or all that are performed in the laboratory, requires thorough evaluations of all aspects of the laboratory operation. It is a comprehensive analysis to uncover all potential sources of error, and includes examination of all activity during the pre-analytic, analytic and post-analytic phases. Everything from personnel training and qualifications to specimen handling and storage; from test system maintenance, calibration and operation to documentation and recordkeeping is evaluated. Once this has been accomplished for each test selected by the laboratory, a QC plan is developed to mitigate or eliminate the risks for error. ■

References can be found online at www.advanceweb.com/laboratory.

Irwin Z. Rothenberg is a quality advisor/consultant for COLA's Educational subsidiary, COLA Resources, Inc. (CRI).



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Whether a lab produces five hundred or five million results a year, the lab director bears ultimate responsibility for the accuracy and timeliness of each test result.[1] Even with sophisticated automated analyzers, an average of half the number of specimens tested between Quality Control (QC) evaluations could be affected in the event of a system failure.

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[1]Malone B. A New Approach to Quality Control. AACC. 2011;37:11. Available at: http://www.aacc.org/publications/cln/archive/2011/november/Pages/ANewApproachtoQualityControl.aspx#. Accessed June 14, 2013.

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Actions against MDROs are explored

By Martha J. Roberts, PharmD

MULTI-DRUG RESISTANT ORGANISMS

It's not uncommon to hear warnings of outbreaks of resistant organisms causing serious infections. During the last few weeks, for example, a strain of *Shigella* resistant to ciprofloxacin, one of the standard antibiotics used to treat this organism, has been reported. This *Shigella* development was preceded by a report in January of an outbreak of carbapenem-resistant Enterobacteriaceae (CRE) through a procedure called an endoscopic retrograde cholangiopancreatography (ERCP). These events add to the growing concern of the various multi-drug resistant organisms (MDROs) plaguing the country.

The Centers for Disease Control and Prevention (CDC) published "Antibiotic Resistance Threats in the United States 2013." This 114-page summary was designed to increase awareness of the threat that antibiotic resistance poses and encourage actions to address the threat. The report also discussed particular bacteria that can cause severe human infections and the antibiotics used in their treatment as well as certain fungal resistance and *Clostridium difficile (C. diff)* concerns.

A Global Concern

Antibiotic resistance is a worldwide problem that can easily cross international boundaries and continents given the multitude of travel options of the last century. In the United States, 2 million people acquire infections with bacteria that are resistant to one or more antibiotics that should have treated the bacteria. Of that, at least 23,000 people die each year as a direct result of these resistant infections. Many more of these patients die from other conditions that were complications of the antibiotic-resistant infections. In addition, *C. diff* affects 250,000 people each year. In most cases, the use of antibiotics was a major contributing factor. Approximately 14,000 people will die from a *C. diff* infection that could have been prevented.[1]

Infections resulting from these antibiotic resistant organisms result in considerable added costs from prolonged and costlier treatments, additional physician visits, increased utilization of healthcare resources and greater disabilities and deaths when compared to organisms with traditional sensitivities. The total economic costs (estimated with 2008 dollar values) has been estimated to approach $20 million in excess direct healthcare costs with additional costs as a result of lost productivity as high as $35 million per year.[1]

Now that we have considered some of the general information related to MDROs, a brief review of a few of the key ones would be beneficial.

Methicillin-resistant *Staphyloccus aureus*

MRSA is probably the most commonly known MDRO with an extensive history. Penicillin was used to treat *S. aureus* infections in the 1940s, but resistance to penicillin soon developed by the late 1940s and early 1950s, resulting in the switch to methicillin to treat skin and soft tissue infections. Then in 1960, the first case of methicillin resistance was reported and continued to occur in healthcare settings until a community-based outbreak occurred among injecting drug abusers in Detroit. The incidence of community-acquired MRSA continued to increase and, in 2008, resulted in risk factors for infection being identified among athletes, military recruits, incarcerated people, emergency room patients, HIV patients and men who had sex with men.

Of note: about one-third of the people in the world have *S. aureus* on their bodies, primarily in their nose and on their skin. About 1 percent of those people will have MRSA.[2] There are now two categories of MRSA: hospital-acquired (HA-MRSA) and community-acquired (CA-MRSA). The hospital-acquired strains are usually sensitive to vancomyin or trimethoprim-sulfamethoxazole, while the community-acquired strains are sensitive to ciprofloxacin, clindamycin, erythromycin, gentamicin, trimethoprim-sulfamethoxazole or vancomycin. The molecular mechanisms for MRSA resistance have been studied. The presence of the *mec* gene is an absolute requirement for *S. aureus* to express methicillin resistance. The CDC reports that there have been 80,461 severe MRSA infections with 11,285 deaths in 2011.

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Vancomycin-resistant *Enterococci*

VRE issues started to surface in the early 1950s, when cure rates for endocarditis caused by *enterococci* treated with penicillin were decreasing. The resistance continued when treatment changed to ampicillin or vancomycin with or without an aminoglycoside antibiotic. It was found that pheromone-responsive plasmids cause plasmid transfer between *Enterococcus faecalis* isolates. The plasmids can transfer among a broad range of species, but usually at a moderately low frequency. It was also discovered that conjugative transposition transfer of transposons occurs at low frequency, but to a very broad range of different kinds of bacteria. VRE infections now often require treatment with linezolid to eradicate the organism.

Extended-spectrum Beta-lactamases

ESBLs are enzymes that open the beta-lactam ring, resulting in the inactivation of the antibiotic classes of penicillins, cephalosporins and mono-bactam atzreonam. The first plasmid-mediated beta-lactamase was discovered in Greece in the 1960s. It was named "TEM" after the patient in which it was isolated. This was followed by the discovery of another closely related enzyme, TEM-2. These two are the most common plasmid-mediated beta-lactamases. Their resistance affects Enterobacteriaceae, *Pseudomonas aeruginosa, Haemophilus influenza* and *Neisseria gonorrhea.*

Newer resistance followed TEM-1 and TEM-2 with the development of SHV-2. This resistance was found first in France in 1984, then later in the U.S. The SHV-2 is found exclusively in gram-negative organisms, such as *Klebiella species, Escherichia coli, Acinetobacter, Citrobacter, Pseudomonas and Morganelli* to name a few. SHV-2 can be blocked by the beta-lactamase inhibitors, such as clavulante, sulbactam or tazobactam. As a result, these chemicals can be added to antibiotics to help maintain their effectiveness.

Known risk factors for ESBL-producing organisms include the length of hospital stay; length of ICU stay; presence of a central venous or arterial catheter; emergency abdominal surgery; presence of gastrostomy or jejunostomy tube; prior administration of antibiotics; prior residence in a long-term care facility; and presence of urinary catheter, ventilator assistance and hemodialysis.

Carbapenem-resistant *Enterobacteriacae*

Per the CDC, CREs were uncommon before 1992. One member of the class, *Klebsiella pneumonia* carbapenemase (KPC), was first reported in 2001. Specific strains of these organisms are found in certain regions of the country. Hospitals or long-term care facilities are the primary sites for the development for these CREs; risk factors include the use of a beta-lactam antibiotic, mechanical ventilation and diabetes. There are several reported mechanisms by which these bacteria can become carbapenem resistant. Treatment options can be limited and need to be assessed on a case-by-case basis.

Taking Action

What can we do? The CDC suggests four core actions to help prevent antibiotic resistance issues:

1. preventing infections and the spread of resistance (e.g., immunizations)
2. tracking and collecting data to develop prevention strategies
3. improving antibiotic stewardship
4. developing new drugs and diagnostic tests ■

Martha J. Roberts is lead clinical care pharmacist/critical care specialist, St. Joseph Health Services of Rhode Island, Providence.

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1. Antibiotic Resistance Threats in the United States 2013 published by the Centers for Disease Control and Prevention. Electronic access:http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf
2. National Institute of Allergy and Infectious Disease's Antimicrobial (Drug) Resistance – Section on Methicillin-Resistant Staphylococcus aureus (MRSA). Web site access: http://www.niaid.nih.gov/topics/antimicrobialResistance/Examples/mrsa/Pages/overview.aspx

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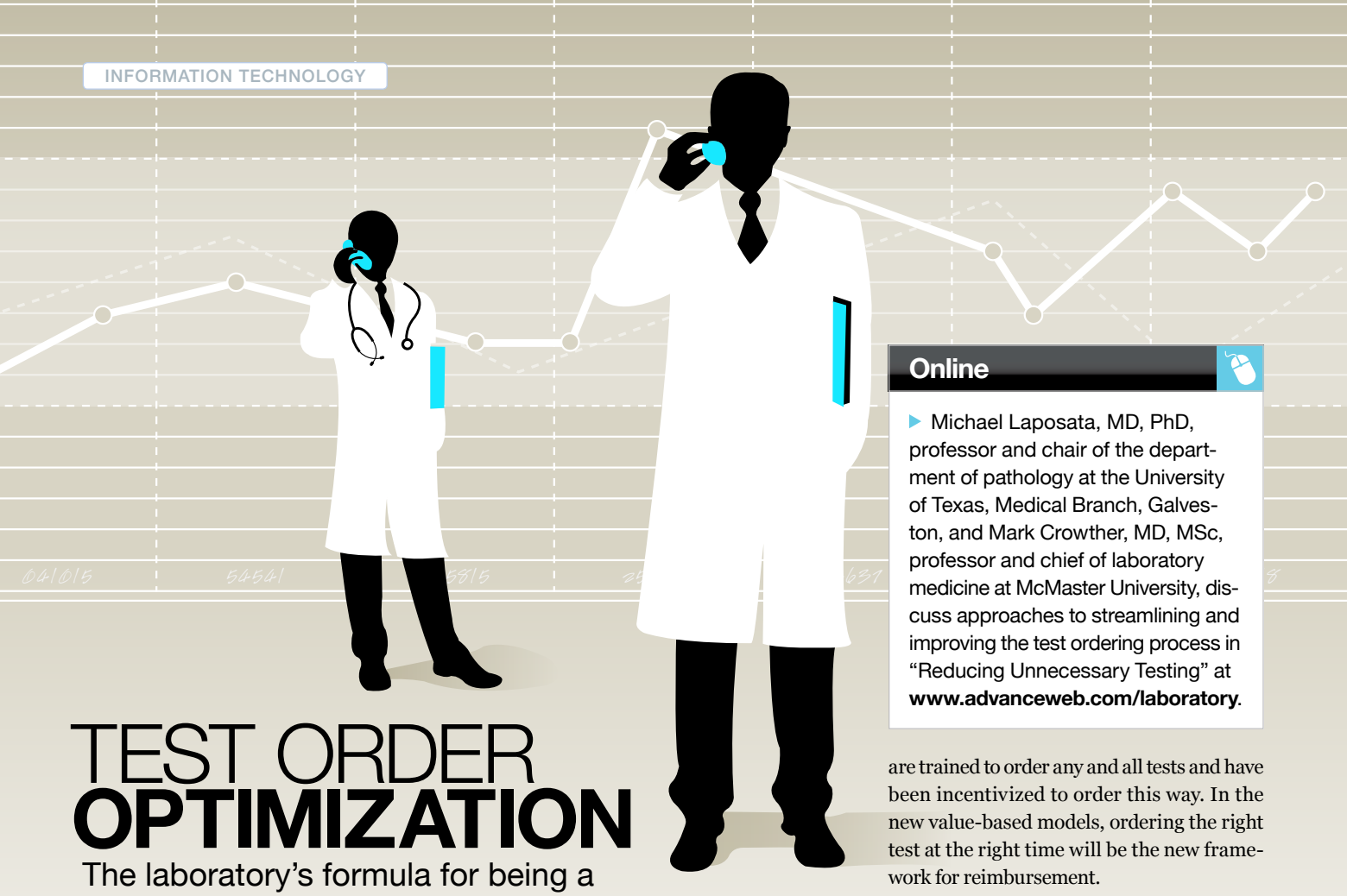

TEST ORDER OPTIMIZATION

The laboratory's formula for being a partner in a value-based or outcome-based ACO reimbursement environment

By Kim Futrell, MT(ASCP)

Going forward, healthcare organizations will be paid as a whole for keeping people healthy—for being effective in providing prompt and accurate diagnoses and for proactively monitoring and managing high-cost diseases. Rather than a focus on reimbursement per lab test, the lab's future role lies in the support of a rapid, accurate diagnosis that becomes a part of the overall cost of doing business in healthcare. Therefore, if laboratories are no longer paid per test, but are a necessary function of getting proper and effective care, they must perform as efficiently and effectively as possible. As we continue to make positive changes in our healthcare delivery system, one of the most effective ways to do this is by eliminating waste and making sure the right tests are ordered—which is the goal of test utilization programs.

3 Areas of Focus

In focusing on test utilization, there are three main areas to think about and a multitude of reasons why laboratory tests are "misordered," ranging from "that's the way it's always been done" to pressure from patients to order tests simply because they read about the test on the Internet. In a fee-for-service (FFS) environment, providers are trained to order any and all tests and have been incentivized to order this way. In the new value-based models, ordering the right test at the right time will be the new framework for reimbursement.

Because of misaligned FFS incentives, our healthcare system is riddled with overutilization and unnecessary services. In a recent study undertaken by a group of neurosurgery residents at the University of California, San Francisco Medical Center, they found that by reducing five common lab tests by approximately 50 percentr. They saved more than $2 million dollars and saw no negative effects on patient care or safety. They determined that, whether the results of these tests were normal or abnormal, it made no difference in the patients' care plan.[1]

Interestingly, according to a study performed at Beth Israel Deaconess Medical Center, they found that underutilization was just as prevalent as overutilization. In the study, 33 percent of tests were underutilized, meaning tests that would have benefited the patients should have been ordered, but were not.[2] A vital component of early chronic disease care is the increased utilization of preventive screening tests to predict chronic conditions earlier, leading to better patient outcomes and reduction of healthcare costs associated with long term chronic disease.

Online

Michael Laposata, MD, PhD, professor and chair of the department of pathology at the University of Texas, Medical Branch, Galveston, and Mark Crowther, MD, MSc, professor and chief of laboratory medicine at McMaster University, discuss approaches to streamlining and improving the test ordering process in "Reducing Unnecessary Testing" at **www.advanceweb.com/laboratory**.

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The overriding goal in regards to clinical testing is to do the right test on the right patient at the right time and do it accurately while being cognizant of costs and resources.

Influence Order Selection

There is clear evidence that the way in which test options are presented can have an influence on which tests are selected. With the push toward Meaningful Use of certified EHRs, most facilities now have computerized provider order entry (CPOE) in place. By far, the best time to intervene and offer guidance toward best test orders is at the time the order is placed. Many EHRs have capabilities that support CPOE enhancement.

It Takes a Committee

Most facilities with in-depth test utilization efforts involve the use of laboratory utilization committees that include staff from various members of the healthcare team. The team shares the collective goal of promoting the highest quality, most cost-effective testing patterns. Any successful test utilization program will require input from multiple departments and effective collaboration with ordering clinicians. With committee support, the lab should be comfortable questioning test orders, suggesting more appropriate test choices and canceling inappropriate tests. Laboratorians have the knowledge and skill set to be instrumental in promoting better test utilization.

Unnecessary Test Combinations

Discuss with your ordering clinicians or test utilization committee scenarios where it does not make clinical sense to order two specific tests together. For example, it may not be necessary to order a particular test until you know the results of the initial test, creating an opportunity to offer a reflex testing option (e.g., TSH reflexing to FT4, GGT reflexing to ALKP). For certain diagnoses, there are tests that offer greater diagnostic accuracy, such as the CRP instead of the ESR for inflammation or the Troponin instead of the CK-MB for myocardial infarction. Or, testing may only be recommended for specific diagnoses (e.g., 1,25-Dihydroxy vitamin D for renal failure patients).[3]

Testing Algorithms

Laboratory-driven algorithms, where clinicians order a testing cascade and initial laboratory results drive subsequent test selection, allow the laboratory to handle the entire cascade process with no further input from the provider. Proper implementation of testing algorithms that proceed through a logical testing sequence based on initial results can eliminate providers having to choose from an overwhelming menu of hundreds of available tests and can be instrumental in making sure that only the appropriate tests are ordered.[4] Take, for example, a thyroid cascade that starts with a TSH. If the TSH is abnormal, a FT4 is ordered, then based on the FT4 result, a reflex FT3 or anti-TPO is ordered, ensuring that only necessary tests are being performed.

Variation Analysis

One data tool that can benefit a test utilization plan is an internal ordering variation analysis, in which provider ordering patterns by diagnosis are reviewed in comparison to recommended testing, with an eye on associated costs and outcomes. It is not meant to point out that any specific provider is ordering incorrectly, but simply to reveal outliers that can be looked at as an area for improvement. For example, review your individual physician ordering patterns for diabetes, comparing ordering patterns among the group and with recommendations for diabetic monitoring from the American Diabetes Association. Once the analysis is performed and shared, providers and laboratorians can use published, recommended guidelines to establish and promote their internal best laboratory practice order sets for specific diagnoses and incorporate these into their CPOE process to make the recommendations clear to providers at the time of order.

Testing Formularies

A testing formulary, in the simplest definition, is a list of tests available for a physician to order. Formularies are often implemented in an effort to control inappropriate ordering of expensive, esoteric lab tests. With a formulary in place, the laboratory, in association with the test utilization committee, can eliminate obsolete tests (e.g., bleeding times), set frequency recommendations on certain tests (such as genetic tests that should be ordered only once per patient), and/or implement ordering tiers in which certain tests require pathologist or medical director approval.

If good medical practice is the focus, then efforts to monitor and perfect test utilization will have longevity and will be successful in our changing healthcare environment. The overriding goal in regards to clinical testing is to do the right test on the right patient at the right time and do it accurately while being cognizant of costs and resources. In today's healthcare environment, this concept not only speaks to the importance of having a well-thought-out test utilization process, but is a laboratory's formula for being a partner in a value-based or outcome-based ACO-type reimbursement environment.[4] ■

Kim Futrell is products marketing manager, Orchard Software Corporation.

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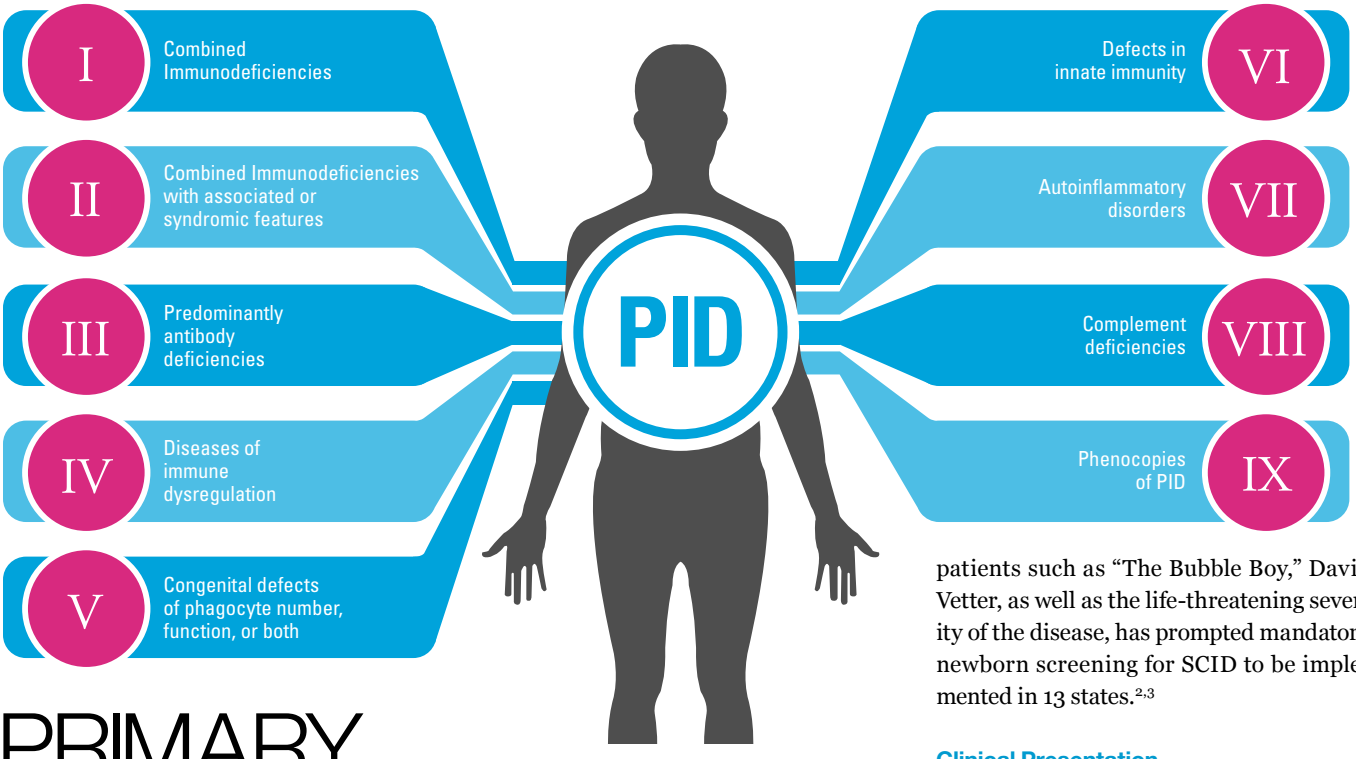

PRIMARY IMMUNODEFICIENCY DISEASES

Lack of awareness for PID leads to under-diagnosis with serious health, social and economic implications

By Debbie Boldt-Houle, PhD

Immunodeficiency is a state in which the immune system's ability to fight pathogens is compromised or absent. Immunodeficiencies can be categorized into two major types of disorders — those that are inborn and caused by a genetic mutation, called Primary Immunodeficiencies (PID), and those in patients born with normal immune systems where immunodeficiency develops later, due to factors such as malnutrition, chemotherapy, HIV, etc.

Many types of PID affect the immune system's function or development with more than 185 diseases states associated with PID.[1] In 2014, the International Union of Immunological Sciences classified PIDs into 9 different categories.[1] Predominantly Antibody Deficiencies (PADs) are the most common conditions, representing greater than 50 percent of PIDs. A rare, but more well-known category, Combined Immunodeficiences (CID), includes the most severe diseases. CID includes SCID (severe combined immunodeficiency), which is caused by combined lack of functional T lymphocytes and B lymphocytes. SCID occurs in every 1:100,000 births, and X-SCID is the most common type, found in boys. Media attention to SCID patients such as "The Bubble Boy," David Vetter, as well as the life-threatening severity of the disease, has prompted mandatory newborn screening for SCID to be implemented in 13 states.[2,3]

Clinical Presentation

Because PID causes an ineffective or reduced immune response to pathogens, symptoms of immunodeficiency often include repeated or unusual infections. Typical clinical presentation can be described as "SPUR:" severe, persistent, unusual and/or recurrent infections. Warning signs include family history due to genetic components, ineffective antibiotic treatments and failure to thrive in infants. Ten stated warning signs for PID were published over 20 years ago to help identify patients with PID.[4] With recent expansion of the clinical spectrum to include more than 180 different conditions, reconsideration of the warning signs will be necessary to ensure all patients are diagnosed efficiently.[5]

Although PID is traditionally thought of as a childhood disease, immunodeficiency can also have adult onset. More than 25 percent of PID patients are children (less than 18 years old); however, greater than 60 percent of current cases of PID are adults.[6] A national survey of PID incidence also found that more than 40 percent of PID patients were not diagnosed until adulthood, despite almost 90 percent of patients presenting with a history of serious or chronic health conditions, including repeated or unusual infections.[6]

MATTHEW TARABORRELLI

Is there something you can't see?

Severe, recurrent or persistent infections may be due to an underlying cause and the correct diagnosis of Primary Immunodeficiency can be difficult to recognize.

A deficiency in one or more of the four IgG Subclasses may result in clinical immunodeficiency despite the presence of normal, or even elevated, total IgG levels. Testing of the IgG Subclasses aids in the diagnosis of Primary Immunodeficiency.

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▶ References for this article can be found under the "Magazine" tab at **www.advanceweb.com/laboratory.**

Laboratory Testing

Laboratory testing for Primary Immunodeficiency occurs in stages with more general tests performed initially such as complete blood cell counts with differentials and total quantitative immunoglobulin assays (IgG, IgA, IgM and IgE), followed by more specialized testing such as IgG subclass assays, vaccine response and complement assays, progressing to more specific or genetic testing.

Unfortunately, the algorithm of tests performed varies greatly depending on the experience and specialty of the clinician, which can contribute to a delay in diagnosis. For example, in 2007, the average span from onset to diagnosis for SCID was 3.1 years; however, Common Variable Immunodeficiency took an average of 14 years to diagnose.[6]

If a patient presents with recurrent bacterial infections such as sinusitis, otitis or pneumonia, a clinician should consider antibody deficiencies. Determining total immunoglobulin levels compared to age matched controls is a very important step in PID testing. Dysgammaglobinemia is a hallmark of a PAD and results in low levels of a single or multiple antibody classes. Selective IgA deficiency is one of the most common PADs. Studies show that 1 in 500 Caucasians have this immunodeficiency.[7,8]

In addition to total immunoglobulin testing, IgG can be subdivided into four different subclasses: IgG1, 2, 3 and 4. PAD may occur even with normal IgG levels, as a result of a specific IgG subclass deficiency.

Another standard test for diagnosing PAD is vaccine response assays. These assays measure antibody titers pre-and post- challenge with routine vaccines, including Tetanus toxoid, Varicella Zoster, Hemophilus influenzae type B and Salmonella typhi Vi. A poor vaccine response indicates immunodeficiency, and deficiencies can occur with normal IgG and IgG subclass levels. Patients suspected of IgG subclass deficiency typically require proof of a poor antibody response to vaccine challenge before being diagnosed with a clinically significant deficiency necessitating treatment such as Ig replacement therapy.

Complement deficiencies are rare. For example, C2 deficiency incidence is estimated to be 1:10,000 to 1:20,000.[9] Patients with normal IgG and normal vaccine responses may still present with symptoms of PID, and a complement deficiency could be suspect. Some specific clinical presentations such as recurrent meningococcal disease or episodes of angioedema point to complement deficiency.

The current screen for complement deficiency includes CH50, which measures functional activity of the classical complement pathway.[10] Other tests may be required based on the clinical presentation. These include AH50, followed by specific complement protein tests, such as C2, C3c, C4 or C1 esterase inhibitor.

Incidence

The incidence of PID is estimated to range from 1:500 to 1:1,200 persons in the United States[11] or nearly 250,000 cases in America with many undiagnosed.[12,13] This incidence has great health, social and economic consequences, especially for those without a diagnosis. Negative health outcomes result from repeated serious or unusual infections, prolonged use of antibiotics and loss of tissue function due to frequent pneumonia episodes or ear infections. In addition, there are social and economic consequences that stem from continued absence from school or work due to illnesses, plus the numerous visits to the doctor or hospital.

Economic Analysis

An economic study done by the Jeffrey Modell Foundation in 2011 examined the quality of life data per year before and after diagnosis of PID.[13] After diagnosis, the number of severe infections, days in hospital, visits to doctor and missed days from school or work were drastically reduced compared to before diagnosis. The same study included a cost analysis pre- and post-diagnosis per year for the variables studied. Cost estimation of the doctor's visits, hospital stays, missed work, medication, etc., yielded a yearly expense over $100,000 for an undiagnosed patient, versus $22,000 per year after diagnosis. That is an extra cost of almost $80,000 per undiagnosed patient per year. Projecting further, consideration of the differential increase in costs for an undiagnosed PID patient to the potential 150,000 to 500,000 cases of undiagnosed PID patients implicates an economic impact on the U.S. healthcare system of up to $40 billion annually.[13] ■

Debbie Boldt-Houle, PhD, is senior director of Scientific Affairs, The Binding Site, Inc.

Transitioning from Culture to Molecular

Implementation and Integration of BD MAX™ Enteric Bacterial Panel at Cincinnati Children's Hospital

By Mavis Bauman, Medical Freelance Writer

"We are on the cusp of the biggest change in microbiology since Louis Pasteur declared that life does not arise spontaneously," says Dr. Joel E. Mortensen, Ph.D., Director, Diagnostic Infectious Disease Testing Laboratory, Cincinnati Children's Hospital, Cincinnati, Ohio. "Molecular testing is a huge paradigm shift in microbiology; therefore, a carefully considered strategy is required to move your laboratory into the molecular world. We were interested in a single platform with multiple analytes and multiple assays. We chose the BD MAX™ Enteric Bacterial Panel on the BD MAX™ System because of its syndromic and operational advantages for regional stool pathogen detection."

Millions of cases of acute diarrhea occur around the world each year. As every laboratorian knows, diarrhea leads to stool cultures but, in most circumstances, the positivity rate for cultures is only ~2-6%. Although culture may yield good specificity, the sensitivity of this labor intensive effort can be variable. In addition, the time it takes to get culture results into the hands of the clinical staff ranges from 48 to 96 hours or more. Recent revolutions in the molecular detection of pathogens in stool can offer significantly better sensitivity, specificity, and time to results, and may double the positivity rate over conventional methods.

From left: Barb Deburger, Cindi Ventrola, Dr. Joel Mortensen, Sarah Hanna

Molecular Testing Considerations

Dr. Mortensen emphasizes the importance of examining the needs and opportunities related to testing stool for bacterial pathogens, and to connect those needs and opportunities to the implementation and integration into a specific laboratory setting. In a recent series of webinars, he discussed a number of important general points when one is considering a molecular-based answer to these diagnostic questions:

- What pathogens need to be tested for your specific patient population (syndromic or broad-based testing)?
- Are you sure that results will influence patient outcome?
- Are there specific clinical scenarios that require advanced or different molecular methods?

"With any new instrument or methodology, start by looking at new technologies and what is a feasible fit for your institution and targeted patient population," says Cindi Ventrola, Manager of the Diagnostic Disease Testing Laboratory. "For us, it's not just children who are affected. Most of our stool cultures come from children, so the family is affected, as well. If a child proves positive with an enteric pathogen in the stool, that child cannot go to school or daycare, which means a parent cannot go to work. Therefore, a negative culture within 24 hours vs. 3 days has great value."

Key Analytes to Test

Given the most common gastrointestinal pathogens in its particular patient population, Cincinnati Children's evaluated which analytes should be on its ideal test panel, following IDSA Clinical Testing Guidelines (see Figure 1).

When deciding on the best platform to use for molecular testing, peer reviewed, published studies are the place to start. At that time, the BD MAX™ Enteric Bacterial Panel (BD MAX™ EBP) was too new for that type of information to be available. So, Cincinnati Children's decided to participate in a multicenter trial, comparing the BD MAX™ EBP to conventional culture methods. The net result of the trial showed very high positive and negative percent agreement (between 97.3% and 100%) and, importantly, that the BD MAX™ EBP detected a significant number of additional pathogens not found by culture. (The full results of this trial have been published in the *Journal of Clinical Microbiology*, March 4, 2015.)

BD MAX™ Enteric Bacterial Panel

The BD MAX™ Enteric Bacterial Panel detects these bacteria, which cover 95% of the causes of bacterial gastroenteritis in the U.S.:

- *Salmonella* spp.
- *Campylobacter* spp. (*jejuni / coli*)
- *Shigella* spp.
- Enteroinvasive *E. coli*, as well as Shiga-toxin producing *E. coli*

The BD MAX™ System is a fully-automated, closed system. Its batch mode allows for simultaneous processing of up to 24 individual tests.

Operational Impact On the Laboratory

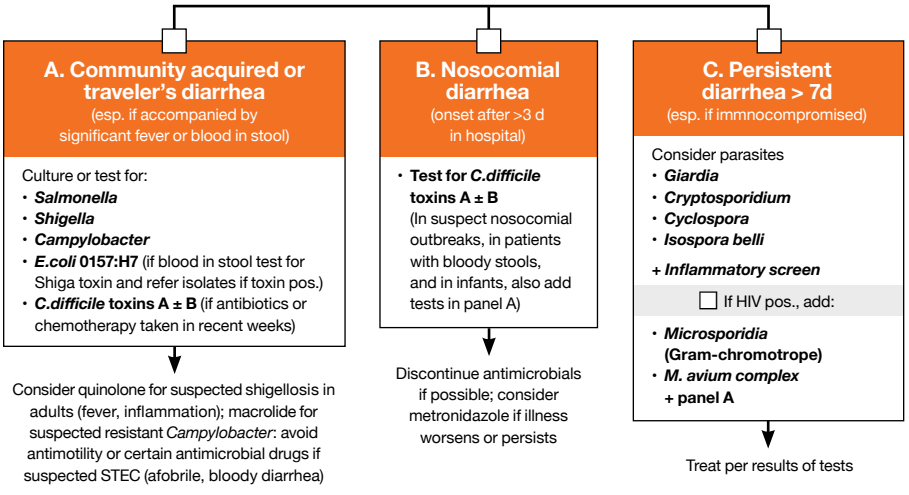
Workflow

To better understand the impact of this technology, Cincinnati Children's put together a team to do time motion studies and examine numerous measurable parameters within the laboratory.

On average, routine cultures at Cincinnati Children's required 141 decisions (i.e., the number of times the technologist needs to interact with the culture) for each and every stool culture. The BD MAX™ EBP required 25 decisions per sample – an 82% reduction of processing steps.

Figure 1: IDSA Clinical Testing Guidelines

Evaluate severity and duration | Obtain history and physical examination
Treat dehydration | Report suspected outbreaks | Check all that apply:



The BD MAX™ System also supports these additional FDA-approved assays:

- *S. aureus*
  - MRSA XT
  - StaphSR
- Group B Strep
- *C. difficile*

Further, the BD MAX™ Enteric Parasitic Panel (*E. histolytica*, *G. lamblia*, *Cryptosporidium hominis & parvum*) will soon have FDA approval. Also, in development are:

- Extended Enteric Bacterial Panel
- Enteric Viral Panel
- Vaginitis Panel
- CT/GC/TV

82% reduction in decisions/steps

85% average reduction in time to results

Further, the average time to results for cultures was 44 hours, 37 minutes. (Some of the cultures took up to 96 hours due to additional workup required.) Average time to results for the BD MAX™ EBP was 7 hours, 6 minutes – an 85% average reduction in time to results. Note that, in this initial study, Cincinnati Children's ran the BD MAX™ EBP in batch mode twice a day, once during first shift and once during second shift. Although the assay itself yields a rapid time to result, the cost savings occur when samples are batched. (The full results of this study have been accepted for publication in *BMC Clinical Pathology*.)

Another challenge to workflow that the BD MAX™ System answers is the number of additional assays available for this platform, with more on the way.

"We can't support a bunch of different platforms with one assay on each one of them," says Ms. Ventrola.

Costs

Understanding exactly how the cost of molecular testing compares with conventional cultures is crucial. Cincinnati Children's did a detailed, direct cost comparison, and a number of important factors were uncovered. For example, labor costs represent a significant variable because up to 20% of cultures require additional workup (see Table 1).

Table 1: Cost Comparison - Negative test

	Conventional Culture $ (min)	BD MAX™ System
Basic Test		
Labor (minutes)	$6.75 - 7.65 (15-17)	$0.67 (1.4 min)
Supplies	17.31	33.62**
Workup*		
Labor	15.75 - 18.00 (35-40)	N/A
Supplies	6.84 - 19.34	N/A
Total Cost in $	$26.00 - 64.00	$32.00 - 37.00**

*10-20% require significant work up of suspected pathogens **Cost dependent on contract pricing

Education

Early introduction and preparation is key when transitioning from conventional culture to molecular testing. Then, overlapping detailed training on how to use the technology allows for integration at a comfortable pace.

Dr. Mortensen and Ms. Ventrola began with general education of their staff about molecular testing of enteric bacteria. They discussed the concepts during their laboratory rounds and held more formal "Lunch & Learn" sessions for the staff.

"Our staff is very interested in new technology and new ways of doing things," says Ms. Ventrola. "The more educated our technologists are about the technology available, what our institution is considering and how it applies to what we do here, the more exciting it is for them, the easier it is for us to implement, and the better it is for our patients."

Dr. Mortensen and Ms. Ventrola continued education outside the laboratory for key user groups, such as infectious diseases and gastrointestinal physicians, some outpatient clinicians, nurses, and nurse practitioners. These individuals help support the integration process.

Training

Initially, core users were trained to serve as experts. Following that initial phase, a detailed training checklist was developed and the core users began to train additional technologists. In addition to internal facility training, BD provided several days of on-site support to train operators.

BD MAX™ System Training Checklist

- ☐ System overview
- ☐ Reagents and consumables
- ☐ Specimen collection and transport
- ☐ Software navigation
- ☐ System workflow
- ☐ Hands-on setup
- ☐ Results review
- ☐ Troubleshooting
- ☐ Quizzes to document understanding

Even laboratory staff that does not perform testing must understand the basic molecular testing methodology so they can answer questions.

A number of other tools have proved to be helpful in this transition:

- Technical service and other resources after training are also important.
- Online resources and training or paper manuals can supplement training.
- An instrument problem log can be valuable for sharing experience between technologists and to follow trends.

- Reaching out to colleagues through user groups and Listservs has become an important way to exchange information.

Implementing the BD MAX™ EBP

Ordering and Resulting

Cincinnati Children's is inserting the BD MAX™ EBP results into its traditional reporting format, as if it is a biochemical test. Moving into the era of molecular testing for stool pathogens has involved a phase-in process. For now, clinicians follow the same syndromic-based ordering procedures that have been in place for decades. The new results look and feel much the same, except that results of tests using the BD MAX™ EBP are clearly noted.

When an extended bacterial panel becomes available on the BD MAX™ System, one order will cover all tests that were previously done using culture. As Cincinnati Children's moves into the next phase, when all testing will be molecular, stool screen orders will be syndromic for bacteria, viruses, or parasites.

"Make sure clinicians understand how fast results are returned and what is included," says Dr. Mortensen. "Communicate with outside clinics and offices through newsletters and other mechanisms to ensure they have reasonable expectations."

Information Technology Interfaces

A Laboratory Information System (LIS) interface is ideal in order to limit the likelihood of errors. In this and many other settings, a bi-directional interface between the LIS and the analyzer is best. BD supplies one side of the LIS interface for the BD MAX™ System, and various vendors can supply the other.

New BD MAX™ System users like Cincinnati Children's can begin with no interface and add as they progress. As Cincinnati Children's validates the BD MAX™ System and uncovers its interfacing needs, the laboratory will examine the costs of upgrading.

Verification

An necessary step in implementing the BD MAX™ System is the verification studies. Verification is a one-time process that is completed before an assay or a system is used for patient testing in the laboratory. Verification studies should be performed by the technologists who will run the patient tests and, whenever possible, should be done on samples from your institution to make sure all possible variables at your institution are taken into account (see Table 2).

Cincinnati Children's conducts its verification studies based on ASM Cumitech 31A. Cincinnati Children's recommends starting with a challenge set of 20 known positives and 40 known negatives for each analyte from a variety of sources. ATCC strains can be used, and additional challenge samples may be obtained from the vendor or other institutions. Also, Cincinnati Children's recommends including known negatives outside of your targets, such as *E. coli, P. mirabilis,* and *Citrobacter spp.*, to rule out cross-reactions.

Table 2: Assay Verification Checklist

Task
1. Create plan for verification with dept. leadership team
a. Design study with approval of director and manager
b. Write up study design
c. Study design reviewed and approved by director and manager
2. Electrical check & KN# issued for new equipment/ instrument by CE
3. Create verification claim sheet
4. Perform verification testing including repeat on discrepant samples
5. Write up QA of verification including statistical analysis of data:
a. Precision
b. Accuracy
c. Reportable range
d. Sensitivity & Interferences
6. Submit QA of verification for review by manager and director
7. Write procedures
a. Testing
b. Preventive Maintenence (PM)
8. Create following logs
a. QC sheet
b. Calibration log, if applicable
c. PM log
d. Inventory Sheet
e. Training checklist
f. Verified Results Review sheet, if applicable
9. Clinical Lab Index; submit medication on Issue Tracking
10. LIS: Interface with Instrumentation, if applicable
11. Order CAP proficiency or establish alternative if not applicable
12. Complete Chemical Inventory Product Form for new or deleted products
13. Communicate changes to clinicians, if applicable
14. Communicate changes to other lab departments, if applicable
15. Complete cost analysis with manager
16. Submit billing information (CPT code and cost) for compendium
17. Submit information to LIS vendor

Validation

Once an instrument or system has been verified, validation demonstrates that it repeatedly gives the expected results over time and meets the manufacturer's claims. A number of tools already in the laboratory can be used for this ongoing process.

- Quality Control tracking over time
- Proficiency testing results
- Maintenance and calibration records
- Correlation with clinical findings
- Reproducibility testing

For reproducibility testing, Cincinnati Children's recommends testing 20 replicates and multiple users on multiple days, in order to account for day-to-day variances and variabilities in technologists.

CPT and Billing

During its transition, Cincinnati Children's is using the codes listed below.

Test	CPT Code
Phase 1 stool (combined with culture)	
Campylobacter, *Salmonella*, *Shigella*, Shiga Toxin (BD MAX™)	87505 x 1 (3-5 targets by a molecular method
Aeromonas, *Plesiomonas*, *Vibrio*, *Yersinia* (culture)	87046 x 2 (BAP & MAC)
Phase 2 stool (all molecular)	
Includes all of the above, when FDA approves remaining enteric bacterial pathogens	87506 x 1 (6-11 targets)
C. difficile toxin testing	87150
Staph/MRSA screen (Molecular MRSA & MSSA assay)	87640 and 87641

In the BD MAX™ EBP, Cincinnati Children's has found a cost effective way to meet the testing needs of its clinicians with syndromic-focused molecular solutions on a single platform.

Cincinnati Children's Hospital Diagnostic Infectious Diseases Testing Laboratory is closely monitoring the impact of molecular testing on patient care, as it continues to adapt and integrate this new technology into its microbiology laboratory. ■

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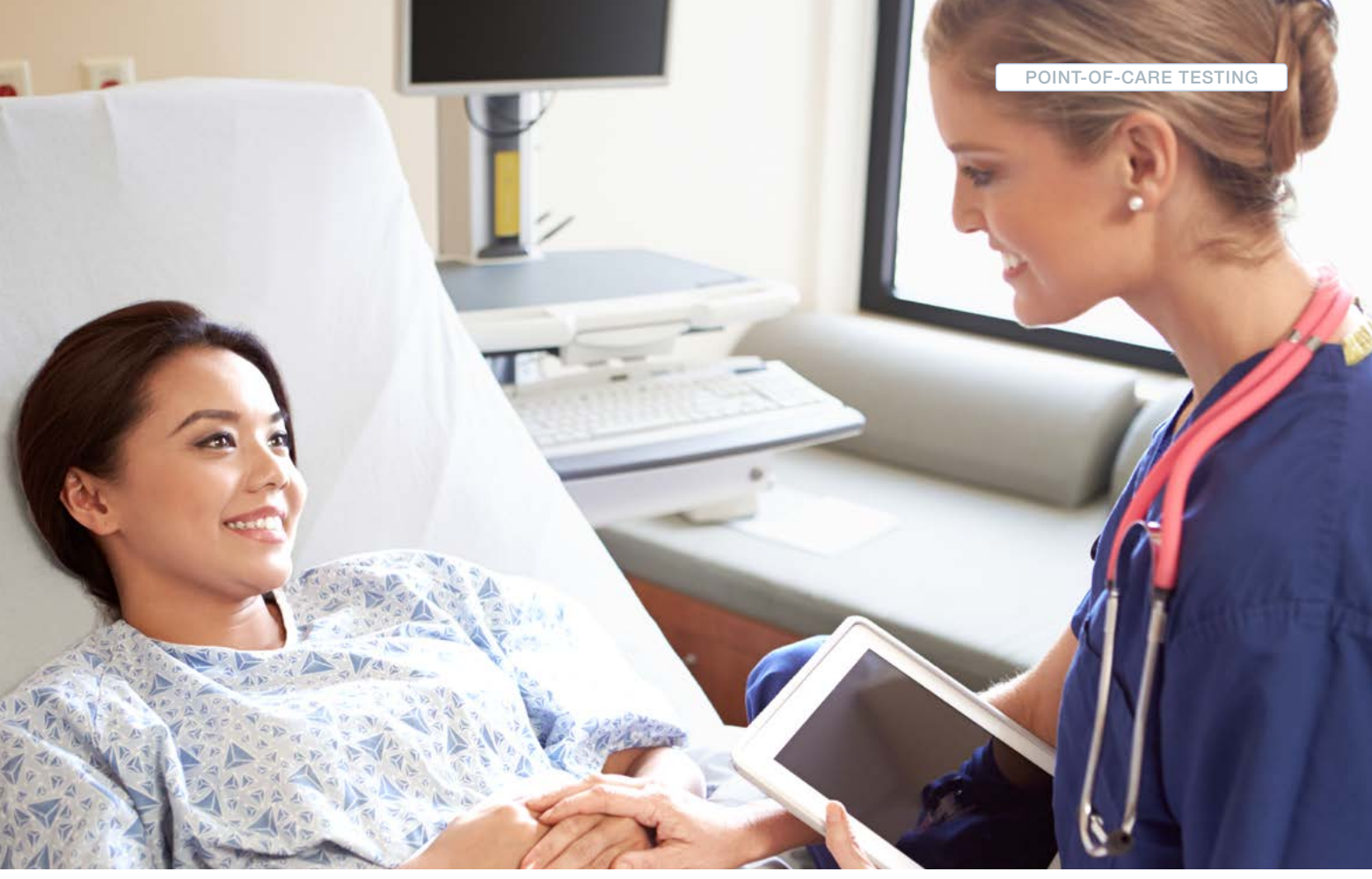

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BOOMING PROJECTIONS FOR THE POINT-OF-CARE MARKET

Rising incidences of infectious disease and chronic conditions spell gold mine for the global point-of-care market

By Robin Hocevar

While tea leaves suggest another slow year for the American economy in 2015, the global point-of-care market is another story altogether.

According to Ryan Schmidt, vice president of infectious disease marketing at Alere, projections of the global POC diagnostics market over the forecast period of 2013 to 2018 say it's poised to grow at a CAGR of 9.3% percent from 2013 to 2018, to reach $27.5 billion by 2018.

Schmidt said North America holds the largest market share, but Asia and Latin America should also experience high growth.

"This large share is primarily attributed to the huge and increasing addressable patient population base. Moreover, the development of accurate and rapid testing kits is further fueling the growth of the POC diagnostics market in North America," he noted.

Specifically, the global POC diagnostics market is categorized into several segments, such as infectious diseases testing kits, glucose monitoring kits, coagulation monitoring kits, urinalysis testing kits, hematology testing kits, cholesterol test strips, drugs of abuse testing kits, cardiac markers, blood gas/electrolytes testing kits, tumor/cancer markers, pregnancy and fertility testing kits, fecal occult testing kits, food pathogens testing kits and others. In addition, based on the type of end users, the global POC diagnostics market has been segmented into patient professional monitoring kits and patient self-monitoring kits. Furthermore, based on the prescription mode, the global POC diagnostics market has been segmented into OTC and prescription-based POC diagnostics market.

Developing Countries

The Asia-Pacific POC diagnostics market is expected to witness the highest growth

Online

▶ An aging population, longer life expectancy and a demand for more affordable healthcare are three potent reasons why portable, wearable and insertable healthcare technology is galloping forward. Read, "POC Leaps Forward" at **www.advanceweb.com/laboratory**.

in the forecast period. A number of factors, such as rising and huge incidences of infectious and lifestyle diseases, increasing funding and investment toward the development of POC products, growing focus of both international and domestic players on the Asia-Pacific POC diagnostics market and large number of R&D activities, are propelling the demand for POC testing products in the Asia-Pacific region, said Schmidt.

According to Schmidt, Alere's focusing intently on African, Asian and Latin American markets. The company's newest HIV detect assays for molecular diagnosis at the point-of-care that identifies HIV-1 and HIV-2 in less than an hour is focused initially on sub-Sahara African nations with commercialization in Europe, Asia and Latin America to follow later this year. The company also launched a rapid point-of-care 4th generation HIV test, detecting HIV- ½ antibodies and the HIV-1 p24 antigen to detect all known HIV subtypes and recombinants of the virus sooner in Africa, Asia, Europe and Latin America. Other products targeting the same countries will utilize molecular testing of HIV nucleic acids for accurate detection as well as Early Infant Diagnosis (EID). Currently, Schmidt explained, antibody POC tests cannot discriminate between a mother's and an infant's antibodies to learn if a newborn is infected with the HIV virus. Alere's also expanding their CD4 monitoring platform for HIV management designed for developing countries.

"We are working with global funders to bring innovative diagnostics in the field of malaria and neglected tropical diseases, specifically targeted for developing countries," Schmidt said.

Lifestyle Factors in the U.S.

One force driving point-of-care products in the U.S. is the increase in cardiac diseases and diabetes. An analysis by the market research firm Frost & Sullivan revealed that the market for self-monitoring blood glucose products earned $4.04 billion in revenue in 2014 and could reach $4.18 billion in 2016. The strips market contributed to over 90 percent of the revenues.

"The rising incidences of these critical lifestyle diseases, (cardiac disease and diabetes), combined with the rising usage of POC devices and technological advancements with regard to development of advanced, faster and easy-to-use devices, will continue to stimulate the market globally," Schmidt remarked.

According to a study by the International Diabetes Foundation, the number of patients diagnosed with diabetes will double by 2035. Early diabetes diagnosis and even self-diagnosis will drive the diabetes point-of-care market. The necessary constant detection of sugar levels in the blood will likely ensure growth the hospital glucose testing market for decades to come.

While the pundits debate the direction of the global economy, there's almost unanimous certainty about the profitable future of the point-of-care market.

"We believe that there will be strong growth in the diagnostic point-of-care marketing in the coming years," stated Paul Brown, head of Roche Molecular Diagnostics. "This belief was a key driver in our acquisition of IQuum, which brings PCR technology and assays to the POC marketplace. As POC testing becomes more mature and our PCR tests and platform are CLIA waived, we will be able to provide fast, lab like quality results within the physician's office. We believe this will help to improve treatment decisions and, ultimately, patient outcomes." ■

Robin Hocevar is on staff at ADVANCE.

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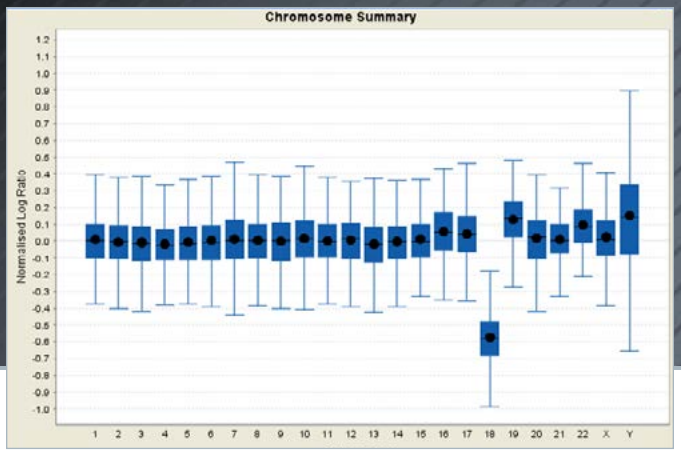

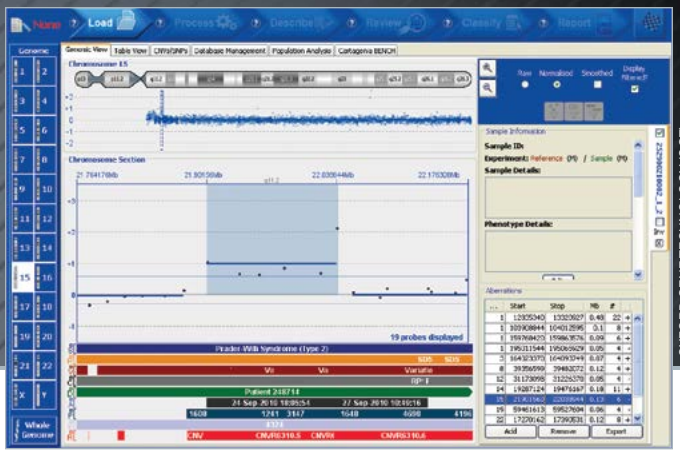

▲ **Figure** Data analysis software is a vital factor when choosing a microarray platform. LEFT: Rapid identification of whole chromosome gains and losses is key to microarray performance, as shown in this aneuploidy summary plot. RIGHT: Accurate and reliable aberration detection with extensive annotation tracks provides context to results. CytoSure™ Interpret Software, Oxford Gene Technology.

ADVANCES IN CLINICAL GENETICS

The role of the microarray in the evolving genetic landscape and what to look for in your next platform are identified

By Stephen Archibald, PhD, MCIM

A popular tool in the clinical research laboratory, the microarray is well established for the genetic analysis of a wide variety of inherited and acquired genetic disorders. Performance of both the microarray and accompanying data analysis software is rapidly evolving, especially with the latest genomic discoveries guiding new content. Modern arrays deliver standardized, evidence-based designs, and utilizing new developments in this field improves efficiency and generates more insightful data in the most cost-effective manner possible.

Moreover, with the speed of technological advances in the field of genetics, clinical researchers can gain a host of benefits by implementing the microarray alongside other high-resolution technologies such as next-generation sequencing (NGS), providing a more comprehensive analysis of the full mutation spectrum. With insights from Consultant Clinical Scientist at Sheffield Children's NHS Foundation Trust (UK), Kath Smith, who recently switched microarray platforms, we discuss the role of the microarray in the evolving genetic landscape, and the key aspects involved when considering switching array supplier.

The Microarray in Genetics Research

The field of clinical genetics research has undergone significant transformation over the last few years with the emergence and evolution of new high-resolution molecular technologies. As such, we are now witnessing a trend toward merging the areas of cytogenetics and molecular genetics. Sitting across these two disciplines, the microarray is a prime example of this – and Smith has also found this to be the case. Three years ago the Molecular Genetics and Cytogenetics Services at Sheffield were merged into a single department, and Smith is now head of the Constitutional Genetics Service

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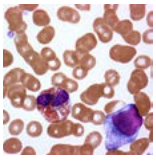

▶ The myeloproliferative neoplasms (MPNs) are a group of clonal stem cell disorders characterized by increased proliferation of one or more cell lines. In recent years, with solid research, better laboratory test offerings and the utilization of molecular markers have been paving the way for a better understanding of the MPNs for pathophysiology, classification, prognosis and treatment. Read "Molecular Genetics of Myeloproliferative Neoplasms" **at www.advanceweb.com/laboratory**.

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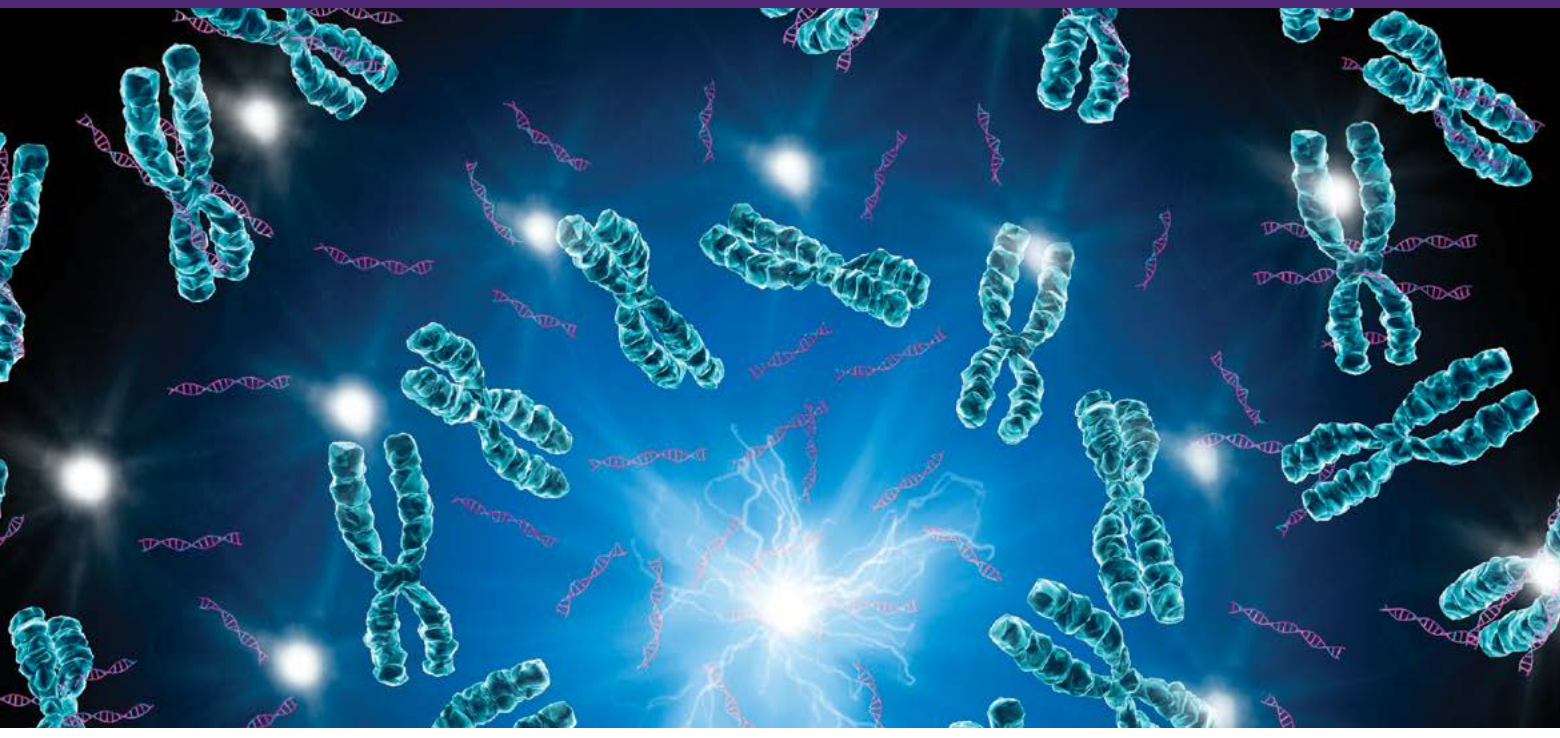

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that covers both cytogenetics and molecular genetics disciplines.

Interestingly, with the application of NGS becoming more widespread, laboratories such as Smith's are also shifting toward an integrated molecular approach, employing microarrays for robust and insightful copy number variation (CNV) analysis alongside NGS, to investigate a more comprehensive mutation spectrum. Despite the rise in NGS, at the moment there are issues in getting information on CNVs. A number of research groups claim to have robust CNV calling with NGS, and while this may one day have an impact on arrays, at the moment the general consensus is that it is far from demonstrating the necessary capabilities to replace the microarray. A particular focus of the Sheffield lab lies in the area of developmental delay disorders, for which the microarray is a particularly powerful analytical tool. As well, in all areas of clinical genetics research, the microarray is still a core technology, with array platforms on the market improving all the time. For this reason, the Sheffield laboratory participated in an objective comparison of multiple microarray platforms and found many factors were involved in the selection process.

What to Look for in a Microarray Platform

In light of the increasing pressures faced by the modern clinical research laboratory, the initiator for changing array platforms may well be improving on the quality of results and ease of use, while also maintaining cost efficiency. Accuracy and precision are key for the correct identification of aberrations and aneuploidy (Figure), while the quality of an array platform is reflected with clean, clear and correct results. In addition to the array itself, this is highly dependent on the software capabilities and user interface. In terms of software, it also helps to look for versatile features that allow a choice of standardized or customized, user-defined data analysis, in addition to fully integrated, automatic analysis of array image files.

> **Getting to grips with new software can present another area of concern when switching to a new system, with operators sometimes getting attached to the software they use.**

Another highly important factor when considering switching array platforms is maintaining laboratory productivity during the changeover period.

Ensuring a Seamless Transfer

The process of switching array platforms raises a number of potential concerns in terms of maintaining the laboratory's productivity. Facilitating a seamless transfer is vital, and while there are several factors to consider, the availability of expert technical support from the vendor is invaluable in this process.

Retaining the library of local legacy data with the new system was a major priority for Smith. Since microarray interpretation benefits greatly from a higher level of information, such legacy data is important, with every lab building up their own local database determined by local factors — both technically and genetically. In particular, the ability of microarray software to hold a robust database is important, allowing sophisticated data querying and filtering to pull out the most relevant data when required.

Getting to grips with new software can present another area of concern when switching to a new system, with operators sometimes getting attached to the software they use. Intuitive, easy-to-use software facilitates the transition, while vendors often offer full software training to help operators in quickly getting up to speed. With the principle and interpretation of arrays remaining the same, this is often simply a case of familiarity.

A modern day genetics lab experiences frequent change in terms of technology. In light of evolving microarray content, utilizing such array technology can lead to numerous benefits if staff are open to adopting the latest high-performance systems as they emerge. This important decision is based on a range of factors, and when discussing those that led to the selection of the new microarray platform at Sheffield, Smith summarizes these as:

- data quality (clean, clear and correct results);
- correct identification of every aberration tested;
- accurate and intuitive aneuploidy calling; and
- cost efficiency. ■

Dr. Archibald is director of communications at Oxford Gene Technology.

INVESTING IN LAB PRODUCTIVITY

One study's results on measuring the ROI for automated specimen processing in the clinical laboratory are revealed

By Rebecca Mayer Knutsen

Clinical laboratories outfitted with automated specimen processing capabilities can reap the benefits of measureable savings in time, resources and money. A recent study that looks at the economic impact of automated specimen processing could be a helpful model for hospitals and medical centers interested in taking the plunge.

The study, funded by Thermo Fisher Scientific, Inc., was conducted at the Medical College of Wisconsin in Milwaukee by Christopher S. Hollenbeak, PhD; Katie M. Merrill, BS; and Nathan A. Ledeboer, PhD. Hollenbeak is a professor of surgery and public health sciences at Penn State College of Medicine, and a health economist interested in resource utilization research to benefit hospitals and healthcare in general.

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ROI Stats

Today's laboratories face issues of speed and efficiency. Automation systems can help laboratories integrate workstations and enable improvements in turnaround time, employment and patient care.

The study looked at the resource utilization that goes into the specimen preparation process and estimated the ROI on automated systems over five years. The framework of the model is such that other labs may use it to calculate their own hypothetical ROI, as long as factors such as resource utilization and costs of inputs are considered.

Hospital administrators will be focused on weighing the ROI of automated systems against labor costs and workload. Specifically, labs will want to determine, "If it will work, how much will it cost and how long it will take to get an ROI," Hollenbeak said.

Based on the parameters used in the study, the investigators established an ROI of 16.7 percent over 5 years with a break-even point of just around 3 years. "The benefits you get are about 17 percent better than what it costs you to get there," Hollenbeak restated.

Results for Your Lab

Hollenbeak stresses that results may vary based on the individual lab. The study's mathematical model is useful for labs that meet a certain mix of criteria. First, the model is best applied to a lab that does not currently rely on walkaway specimen processing, but is thinking about implementing a system.

Second, the size of the lab needs to be taken into consideration. The findings in the study are based on the lab at Medical College of Wisconsin, which is a large, ▶▶

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academic center lab. "A small lab would need to put its own parameters into the model," Hollenbeak stated.

Third, a lab would need to evaluate its labor mix. Is the lab using technologists or assistants to perform the preparation tasks? Hollenbeak's model assumed the work was being done by lab assistants, which incurs less cost for the facility than using lab technologists. "A lab using technologists to perform prep tasks will get a faster ROI if they replace them with assistants," Hollenbeak explained.

Labs with limiting parameters might have a small ROI, in turn taking a longer length of time to reach an ROI.

A fourth consideration is how many days per week the lab processes specimens. If the lab does not process specimens on weekends, it would need to change that parameter because it will affect ROI, Hollenbeak told *ADVANCE*. The study is based on a lab processing specimens seven days a week.

The last consideration is the distribution of specimens processed during a typical day. Does your lab process more urine, stools or stain swabs? "There are different costs associated with each of these tasks that would impact the ROI," Hollenbeak shared.

Acknowledge Limitations

Labs with limiting parameters might have a small ROI, in turn, taking a longer length of time to reach an ROI. Hollenbeak also cautioned labs to consider the impact of its expenses, from specimen processing and equipment contracts to supplies and labor.

Hollenbeak did acknowledge a limitation to the model—the number of tasks available to employees. "We are making a big assumption that, if you adopt walkaway specimen processing, you'll have other activities for your labor," he explained. "Automated systems are not intended to replace labor, but rather, the less productive labor activity."

Automated systems allow labs to use an employee in a more valuable way—for example, to read slides and make diagnoses, instead of processing slides. "Our model is aimed at facilities interested in making their employees more useful, not letting people go," he said.

ROI aside, automated systems produce better results and provide an additional benefit to the economic profile. Additionally, the model helps take productive employees and make them more productive, using their skills beyond streaking and plating.

"The quality of the preparation is more consistent when employing an automated system, which is important when making a good diagnosis," Hollenbeak observed. "You get the same streak every time, and don't have to worry about the machine getting anxious about going to lunch." ■

Rebecca Mayer Knutsen is on staff at ADVANCE.

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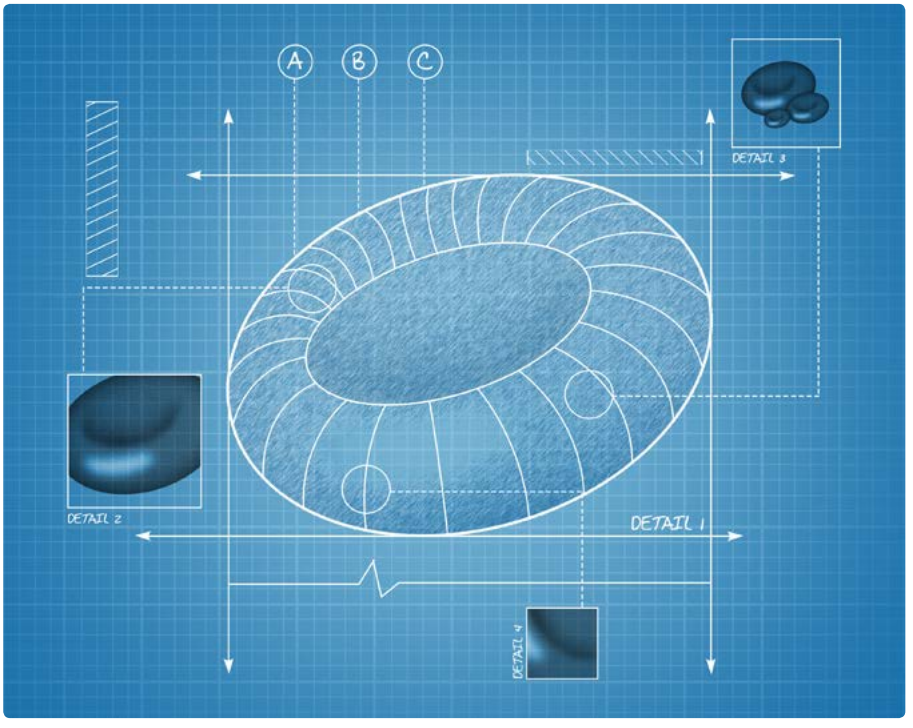
RETICULATED PLATELETS

Detection, measurement and limitations are reviewed



By Fernando P. Chaves, MD

In recent years, new hematological parameters claiming to enhance the detection of various platelet abnormalities have been proposed. Among these are reticulated platelets, named after their appearance upon microscopic review and containing remnants of RNA in their cytoplasm.

Reticulated platelets are a normal stage of the thrombopoietic process starting at the bone marrow pluripotent stem cell level, which differentiates into megakaryoblasts and later into megakaryocytes with more abundant cytoplasm and convoluted nuclei. Platelets are released into the peripheral blood as fragments of the megakaryocytic cytoplasm and, at these young stages, are very large and still contain RNA remnants. Analogous to red blood cell reticulocytes, the amount of reticulated platelets in the peripheral blood can be an indicator of the rate of thrombopoiesis.

These young platelets can be identified by different technologies—such as flow cytometry—using antibodies to RNA. Automated hematological analyzers can recognize them based on non-specific staining of their cytoplasmic material or, alternatively, simply because younger platelets have comparatively larger cell volumes if compared to mature platelets.

Proposed Clinical Utilizations

As indicators of the rate of thrombopoiesis, the main clinical utilization of reticulated platelets is the discrimination between thrombocytopenias caused by peripheral destruction of platelets and those caused by bone marrow pathology with decreased platelet production. This discrimination will guide other confirmatory testing. For example, patients with destructive thrombocytopenias will likely be tested for immune conditions such as idiopathic thrombocytopenic purpura (ITP) or for mechanical destruction of platelets seen in microangiopathic anemias or splenomegaly. Patients with suspected decreased platelet production will be evaluated for bone marrow diseases such as myelodysplasia (MDS) or acute leukemias.

More recently, some authors have proposed the utilization of reticulated platelets as an indicator of upcoming recovery of the platelet counts in patients with severe thrombocytopenia with the objective of reducing the costs and risks associated with platelet transfusion.

Pitfalls, Concerns

In general, the proposed clinical utilizations of reticulated platelets are valid;

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however, some dangerous pitfalls must be considered. Increased platelet reticulation, while typically a marker of immaturity, can be present due to various platelet pathologies. In these scenarios, increases in reticulated platelets do not mean higher rates of thrombopoiesis. For example, Saigo et al[1] performed a study to evaluate the value of the immature platelet fraction (IPF), a hematological parameter derived from reticulated platelets, in determining prognosis for MDS patients. They observed a significant proportion of MDS patients with elevated reticulated platelets — the exact opposite of what is expected in a bone marrow disease where thrombopoiesis is significantly suppressed. In their study, 12 out of 31 MDS patients had IPF values above 10 percent. The most difficult challenge for clinicians in MDS care is the initial diagnosis of this disease, which usually presents itself with thrombocytopenia. Therefore, if clinicians relied on the reticulated platelet findings, they would be misled into searching for a destructive cause of thrombocytopenia and the correct diagnosis would be delayed.

The fact that increased platelet reticulation is not only a marker of immaturity, but also of platelet disease poses serious concerns with their utilization for predicting an upcoming recovery of platelet counts. This is particularly dangerous if clinicians use this information to withhold platelet transfusion because in a significant proportion of cases the platelet count may not rebound as predicted, exposing the patient to increased risk of life-threatening bleeding. Hennel et al[2] followed 17 pediatric patients after stem cell transplantation, and the time between the peak in reticulated platelet values and platelet count recovery varied between 1 and 16 days. During this time, four patients did not show platelet recovery at all after elevation of the reticulated platelet values.

Moving to more common diseases, Cannavo et al[3] studied the value of reticulated platelets in the differential diagnosis of thrombocytopenia. Acute leukemia patients had elevated reticulated platelets to levels undistinguishable from ITP patients. As discussed above for MDS, acute leukemia is a bone marrow disease with suppressed thrombopoiesis, and if clinicians assume that the presence of reticulated platelets is solely due to immaturity, they may be led into a diagnostic mistake.

The use of reticulated platelets also poses practical workflow challenges. Traditionally, destructive and low production thrombocytopenias have been discriminated against based on the mean platelet volume (MPV) due to the larger volume of immature platelets. Unlike the MPV, reticulated platelets are not reported routinely as part of the CBC diff. Therefore, if a laboratory is facing challenges reporting the MPV, an attempt to bypass this challenge by reporting the reticulated platelet parameters will lead to increased reagent costs and increased turnaround time due to repeat and reflex testing.

There are also technical challenges due to variation in reticulated platelets during sample storage. This is concerning because this measurement is not readily available as part of the routine CBC-diff, so typically testing will occur at a later stage after the thrombocytopenia is recognized. Osei-Bimpong et al[4] recognized this challenge and proposed a correction factor. Laboratories wishing to report reticulated platelets should develop algorithms to apply this correction factor and must carefully track sample storage time for it to be effective.

Since the initial description of reticulated platelets and their proposed clinical utilizations, important pitfalls and practical limitations have been recognized. Laboratorians must be aware of these before implementing this new parameter in their test menu. ■

Dr. Fernando P. Chaves is director, Global Scientific Affairs, Beckman Coulter Diagnostics.

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BLOOD BANK PROCESS CONTROLS

By applying a few concepts of engineering process controls, your manual procedures can be written to ensure consistency, reduce workarounds and provide better patient care

By Scott Warner

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Online

▶ For an interesting snapshot of trends and how one independent blood center is keeping up with the times, read "The Changing Landscape of Blood Banking" at **www.advanceweb.com/laboratory**.

Quality is engineered into laboratory medicine through process controls. Discrete analyzers monitor temperature, sample position and dozens of other variables to carry out instructions in sequence and generate output within specific ranges. Manual procedures have a greater potential for error because they lack engineered process controls. This article describes how to apply these concepts to improve quality in blood bank tube testing.

Process Control

Process control includes activities that ensure a process is stable, predictable and produces output with a minimum amount of variation.[1] It's commonly used in manufacturing to control complex variables with automated changes that correct out-of-control situations monitored by a process engineer. Control loops of various kinds measure variables and change the process in real time.

One example is your home furnace thermostat. A temperature sensor turns the heat on if the temperature falls below a set point and off when the set point is reached. There is no error correction (no feedback loop). Your furnace is either on or off. Another example is your automobile's cruise control, in which you define the set point as the desired speed and a controller continuously adjusts the fuel valve as grade, wind speed and other variables affect vehicle drag. The controller also corrects for variation, such as the rate of change to produce a consistent speed.[2]

Laboratory automation couldn't exist without engineered process controls. Operating parameters in a chemistry analyzer, for example, such as temperature, sample location, reagent levels, absorbance readings, etc. are monitored at key steps to control the process. Built-in redundancy, control limits and fail-safes in most cases allow the analyzer to stop at a safe point if human intervention is needed.

Engineered process controls can be complex, measuring dozens of variables in a short time, but the concept works with a manual process, too. A home example is drawing water for a bath: Water temperature is determined by two flow controllers that are adjusted manually according to feedback on how hot the temperature feels until it is at the desired temperature.

In the laboratory, some manual tasks are monitored by statistical process control such as control charts. Other variables include storage temperature of reagents, built-in procedural controls and expected reaction strength. But manual lab testing is subject to a wide variation in human behavior, ▶▶

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experience and habit. Can greater process control be applied in a high-risk area, such as blood bank tube testing?

Blood Bank Process Control

Tube testing controls vary from one lab to another — size and color of tubes, arrangement of the workstation, use of a centrifuge and/or cell washer, documentation of reactions, etc. As with all process control, a consistent output is desired. Because the output (e.g., the final reaction) is not known during the process, it is "open loop;" adjustments are made to affect the output, but there is no feedback that changes the input.[3] Change to the system is made on faith there will be a valid outcome.

These controls can be defined to anticipate and reduce variation by clearly defining the expected output at each step in the process. For example, when performing a front ABO Group typing, antisera is added to two tubes labeled "Anti-A" and "Anti-B." The expected outcome is that the first tube contains blue reagent; the second, yellow. To ensure a consistent output, your reagent rack may be arranged from left to right, enabling a technologist to grab the Anti-A reagent first. An adjustment to the process would be to rearrange these vials as necessary. Thus, a process control is checking the label and color of the reagent before dispensing.

Adding Anti-A and Anti-B reagents is second nature to experienced technologists, but writing down detailed descriptions of other expected outcomes can reveal subtle opportunities for variation that leads to error. For example, if patient serum is not added first to a three-cell antibody screen panel and is skipped, the tubes containing red cells may look as expected, resulting in a negative result.

Suggestions for Getting Started

Write down the expected outcome of each procedural step. As a group, discuss how this outcome can be affected by variables that can be observed or measured. Since blood bank tube testing is primarily a visual process, describe observable variables such as reagent color, amount of material in the tube, color of material in the tube, strength of reaction, etc.

If an outcome variation is not observable, consider adding an additional control. For example, Rh antisera is clear, creating a possibility of a false negative reaction if LISS is added by mistake. Adding a step to confirm a negative Rh type with known positive cells is a control.

While tube testing is largely a stepwise, discrete process, continuous variables can be monitored as well. These include reagent storage temperatures, heating block temperatures, centrifuge speed and timer operation.

As with any manual process, human factors present the greatest opportunity for variation. Technologists can be distracted, confused or biased to make simple mistakes (e.g., the technologist can be thinking of a recent ABO type and write down that interpretation incorrectly). This kind of variation is difficult to predict and even more difficult to control. Experienced technologists develop good, consistent work habits such as arranging tubes the same way each time, reading and documenting each reaction individually, etc. Including a deliberate element of direct peer observation using the procedure to your competency assessment will help reinforce good habits.

Finally, you should use your information system to control outcomes. Drop-down boxes, reflex comments and delta checking history are examples. In the case of a crossmatch, the selection of types for the donor unit can be limited to those compatible with the recipient. Entering a positive or incompatible result can force additional documentation.

While most of your laboratory may be automated, manual processes like blood bank tube testing remain a challenge to control and reduce variation. By applying a few concepts of engineering process control, your manual procedures can be written to ensure consistency, reduce workarounds and provide better patient care. ■

Scott Warner is lab manager at Penobscot Valley Hospital, Lincoln, ME.

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How does rapid molecular PCR compare?

NEW OPTIONS FOR STREP/FLU TESTING AT THE POINT OF CARE

By Kathleen Stellrecht, PhD, D(ABMM), HCLV(ABB)

Accurate diagnosis of streptococcal pharyngitis plays a critical role in patient care because untreated Group A strep (GAS) pharyngitis can lead to both suppurative (pus-producing) and nonsuppurative complications. In addition, if that testing can be performed quickly at the point of care (POC), it offers great potential to help clinicians make faster diagnoses and reduce the unnecessary use of antibiotics.

Unfortunately, current POC rapid antigen tests for GAS do not offer a high enough level of sensitivity to preclude the need for frequent confirmatory testing, thus effectively negating their turnaround time benefit in many cases. With the advent of new commercial molecular technologies that offer much faster test times than conventional thermocycler-based PCR, Albany Medical Center wanted to explore the pros and cons of various testing approaches for GAS and other infectious diseases, most notably influenza A/B, relative to their potential impact on patient care and other areas of hospital and lab operations.

Existing Standard of Care: Culture

The medical center uses traditional culture-based media for the majority of its GAS testing—which comes from outpatient services and clinics—as well as for confirmatory testing of some negative rapid antigen tests performed at our employee health clinic. The rapid antigen test provides results at the POC in about 5 minutes, but because of the need for confirmatory testing by culture, the effective turnaround time for most of our GAS testing has been about 36-40 hours.

At the same time that we were evaluating sensitivity and turnaround time issues for our rapid antigen POC tests for GAS, we wanted to explore whether we could improve the sensitivity of our culture-based lab test standard by introducing a real-time PCR assay. Our first step was to develop our own laboratory PCR test.

When we quickly began to see differential results between our culture and PCR tests, it prompted us to go a step further and conduct an official analysis that included some FDA-cleared, rapid molecular IVD tests recently introduced to the market.

Sensitivity Analysis for GAS Tests

Our GAS testing analysis included: (1) our lab-standard culture test; (2) our lab-

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The sensitivity differences between the point-of-care PCR IVD test and our LDT and culture tests were unexpected, and they suggest some potentially significant implications for patient care.

developed PCR test; (3) a commercial POC IVD real-time PCR test (cobas Strep A test on the cobas Liat PCR System1); and (4) an alternative molecular technology designed for laboratory testing but is relatively rapid (~1 hour). The alternative molecular test was later removed from the analysis at the manufacturer's request.

We targeted the streptococcal exotoxin B gene in an analysis of 200 consecutive throat swab specimens received in the laboratory for bacterial culture. Samples were considered true positive for Group A strep if positive by two PCR tests or by discrepancy analysis.

Sixteen samples were positive by culture and by both PCR tests; four samples were negative by culture but positive by both PCR tests; and four samples were positive by the PCR IVD assay only. In a discrepancy analysis, DNA from samples that were positive by only the PCR IVD assay were concentrated 10-fold through extraction and retested with the LDT. After discrepancy analysis, an additional two samples were positive by the LDT, confirming the PCR IVD assay results.

In our analysis, the point of care PCR IVD assay demonstrated 100 percent sensitivity and 99 percent specificity, while the sensitivities for our lab-developed PCR test and culture were 91 percent and 73 percent, respectively. These compared to an estimated sensitivity of our rapid antigen POC test of about 40 percent in the hands of POC providers. Furthermore, the limit of detection of the PCR IVD test was one log lower than that of our LDT, further supporting the enhanced sensitivity seen by the PCR IVD test with clinical samples.

Analysis Conclusions

The sensitivity differences between the point of care PCR IVD test and our LDT and culture tests were unexpected, and they suggest some potentially significant implications for patient care.

The PCR IVD test uses the same specimen type and can provide results in close to the same turnaround time as our rapid antigen tests (approximately 15 minutes for the strep A IVD assay versus 5 minutes for the rapid antigen test), yet in our analysis the sensitivity was superior to that of either culture or our LDT, both of which take significantly longer.

While we have not yet taken this step at Albany Medical Center, the implementation of molecular PCR testing for Group A strep at the point of care could contribute to faster, more confident diagnoses, more timely isolation of contagious patients and a reduction in the unnecessary overprescription of antibiotics. We see even greater potential to improve the quality of care if we adopt this type of rapid POC molecular PCR technology for flu testing as well, given that the signs and symptoms of influenza can be difficult to distinguish from the signs and symptoms of other illnesses.[2] ■

Stellrecht is director of microbiology, associate professor of pathology and laboratory medicine, and associate professor of the Center for Immunology and Microbial Diseases at Albany Medical Center, Albany, N.Y. *The author wishes to acknowledge Roche Diagnostics for its support of the study.*

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▶ POC tests can be used in different ways (including for diagnosis, health screening, monitoring of therapy, and outcome prediction) and the performance requirement is dependent on the use. POC use in blood glucose monitoring of critically ill patients is discussed in "Today's POCT" at **www.advanceweb.com/laboratory**.

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FOCUS ON: DRUGS OF ABUSE TESTING

Tests and standards for an unfortunate necessity

By Michael Jones

While the need for drugs of abuse (DOA) testing may be considered an unfortunate necessity in the United States, the tests, assays and applications available for screening have evolved and adapted with the rest of the laboratory industry. In a recent interview with *ADVANCE*, Courtney H. Lias, PhD, director of the division of chemistry and toxicology devices in the Office of In Vitro Diagnostics and Radiological Health at the Center for Devices and Radiological Health, and Denise Johnson-Lyles, PhD, branch chief of the toxicology branch in the division of chemistry and toxicology devices at the Food and Drug Administration (FDA), discussed some of the issues facing DOA testing. These include options for both preliminary and confirmatory testing.

"The first method is often an immunoassay or something like that, but the second method is typically a more technical, very much more accurate, more quantitative method like liquid chromatography-mass spectrometry [LC-MS] or gas chromatography-mass spectrometry [GC-MS]," said Lias.

There are several areas in which DOA testing is utilized in the U.S., including screening for things like employment or clinical screening to determine whether a drug has been ingested. Immunoassays are a common preliminary DOA test because these are often high-throughput tests and can be done quickly and in mass quantities.

Laboratory-based testing is a commonly utilized method for DOA testing, but there are other options such as over the counter (OTC) tests and Physician's office testing. In order to receive 510K clearance from the FDA, one of the most important aspects of each testing option simply depends on how well it can be utilized in its intended environment. Before they can be marketed by the manufacturers, OTC tests must be evaluated by untrained patients at home as OTC tests are usually administered. Similarly, physician's office testing options have to be evaluated by the staff who would traditionally conduct the test.

While technology like LC-MS or GC-MS is generally seen in larger facilities, it is not always affordable or even available in smaller laboratories or other healthcare facilities.

In their interview, Lias and Johnson-Lyles also noted the emergence of a movement towards non-immunoassay technologies for screening. While technology like LC-MS or GC-MS is generally seen in larger facilities, it is not always affordable or even available in smaller laboratories or other healthcare facilities. In order to make these tests more readily available as screening options, there would have to be automated, simplified and less costly options on the market.

"At the moment, I think it's difficult and there aren't that many systems that would be able to do it," said Lias. "The larger labs that have a lot of resources might be able to do screening by using their tandem Mass Specs, but it's resource-intensive and expensive at the moment."

Lias and Johnson-Lyles also mentioned the introduction of new substances, pointing out the new drug "Spice" as an example. Although the current methods of DOA testing have now become standardized, the laboratory testing industry has consistently shown the ability to adapt to new circumstances with updated tests and assays. ■

Michael Jones is on staff at ADVANCE.

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