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MEDICAL LABORATORY OBSERVER

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CE

Effective antimicrobial resistance stewardship in the lab

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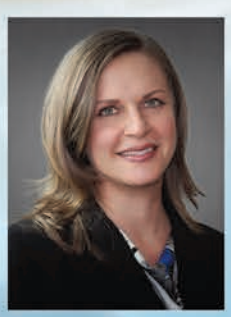
What's lurking in your lab?

A clinical future for WGS

EXECUTIVE SNAPSHOT

Carmen L. Wiley
PhD, DABCC, FAACC
AACC President



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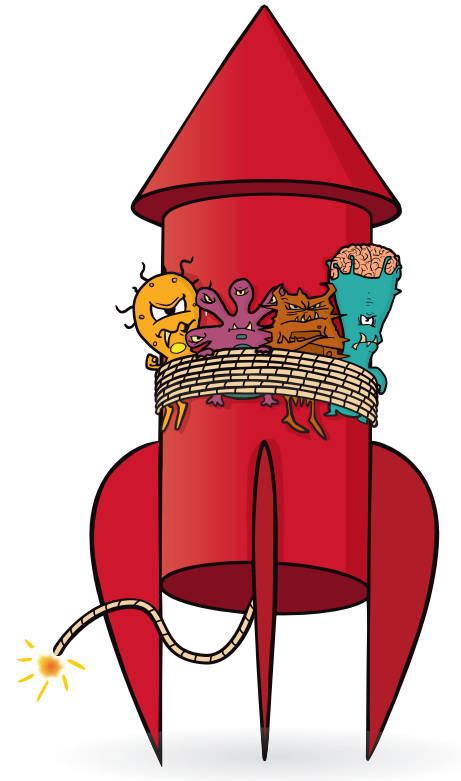

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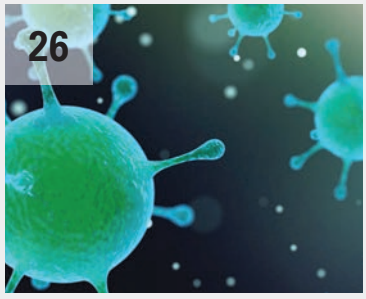

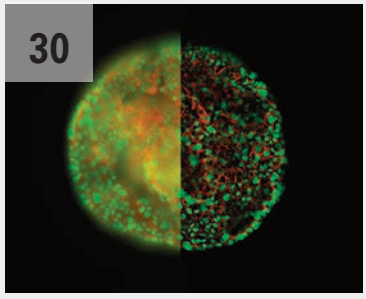

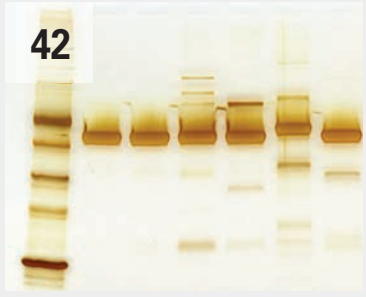

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ADM311000EN00 (06/19)

Mandatory immunization health history forms

By Lisa Moynihan
Editor

My stepdaughter is transferring from a small, private university in Florida to the very public University of Florida (UF) this Fall. When she told me the news, I was a bit apprehensive. As a Florida State University (FSU) graduate myself, you may assume my disappointment lies in football rivalry. However, this is false. My anxiety stems from identifying her immunizations in a timely fashion as students will not be cleared to register for classes until all immunization requirements are met.

Her previous university had a student body of 4,200 students and did not require immunization certifications. The new university, topping 52,000 students, sent along paperwork that read like this:

Section A: Required immunizations: (1) MMR/Measles, Mumps, Rubella Vaccine, (2) Hepatitis B Vaccine, (3) MCV4 (Menactra/Menveo)/Meningococcal Meningitis Vaccine, and (4) Tuberculosis Screening (only required for international students).

Section B: Optional immunizations: (1) TD (Tetanus/Diphtheria) and/or Tdap (Tetanus/Diphtheria/Pertussis), (2) Varicella (Chickenpox), (3) Hepatitis A, HPV, Polio, and (4) Meningitis B.

In an article in the *Gainesville Sun* from March 30, 2019, the UF Student Health Care Center (SHCC) confirmed an increase in mumps cases. While UF requires all incoming students have the MMR vaccine, some students have the option to decline due to health, religious, or personal reasons, thus increasing the risk of contracting mumps.[1]

Most people receive the MMR vaccine as a toddler. However, after 20 years, the vaccine reduces to 88 percent effective.[2] As a result, UF is encouraging students to receive the third MMR vaccine to provide them with even greater immunity. Ironically, the SHCC cannot administer the third vaccination without a doctor's order since it is not a routinely recommended vaccination.

Although state health officials are working with the SHCC and other providers in Alachua County to find the reason behind the rise of mumps cases, questions remain. In fact, the university diagnosed and recorded 24 people have tested positive for mumps while at UF as recently as May 3.

Although not required for matriculation, my bigger concern was the lack of information on her immunization history chart regarding the varicella-zoster virus. Oral history states she (may or may not have) contracted chickenpox as an infant and (may or may not have) ended up receiving the vaccine. She was told that since she is (likely) no longer producing the antibodies, she should get the two recommended vaccines as an adult.

I found this interesting as the majority of literature I've read states children who recover from chickenpox do not suffer complications and are left with lifelong immunity to the disease.[3]

So, was she given the correct information?

I suppose receiving the vaccine won't hurt (figuratively, anyway). Another advantage is that the chickenpox vaccine prevents shingles in 50 percent of those vaccinated and reduces the incidence of postherpetic neuralgia by 66 percent.[4] Considering shingles are on the rise in young people, I guess that's a good thing, too.

Visit mlo-online.com for references.

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TAGRISSO is approved as a first-line treatment for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test[1]

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- Used with either tissue or plasma samples

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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend osimertinib (TAGRISSO®) as a preferred first-line treatment option for patients with sensitizing EGFR mutations and metastatic NSCLC.[5] According to the NCCN Guidelines®, biomarker testing is recommended for all appropriate patients with mNSCLC, including testing for sensitizing EGFR mutations, before selecting first-line therapy if clinically feasible.[5,*]

*The NCCN Guidelines for NSCLC provide recommendations for individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays.

Learn more about treatment with TAGRISSO at **TAGRISSOhcp.com**

IMPORTANT SAFETY INFORMATION

- There are no contraindications for TAGRISSO
- Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 TAGRISSO-treated patients; 0.4% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed
- Heart rate-corrected QT (QTc) interval prolongation occurred in TAGRISSO-treated patients. Of the 1142 TAGRISSO-treated patients in clinical trials, 0.9% were found to have a QTc > 500 msec, and 3.6% of patients had an increase from baseline QTc > 60 msec. No QTc-related arrhythmias were reported. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia
- Cardiomyopathy occurred in 2.6% of the 1142 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) 10% from baseline and to <50% LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO
- Keratitis was reported in 0.7% of 1142 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist
- Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose
- Most common adverse reactions (20%) were diarrhea, rash, dry skin, nail toxicity, stomatitis, fatigue and decreased appetite

Please see Brief Summary of Prescribing Information on adjacent pages.

EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; mNSCLC, metastatic non–small cell lung cancer; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitor.

References: 1. TAGRISSO® (osimertinib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2018. **2.** US Food and Drug Administration. List of cleared or approved companion diagnostic devices (in vitro and imaging tools). https://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm301431.htm. Updated October 24, 2018. Accessed November 30, 2018. **3.** cobas® EGFR Mutation Test v2 [package insert]. Branchburg, NJ: Roche Molecular Systems, Inc.; 2018. **4.** FoundationOne®CDx [technical specifications]. Cambridge, MA: Foundation Medicine, Inc.; 2019. **5.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V5.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed June 7, 2019. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. To view the most recent and complete version of the guideline, go online to NCCN.org.

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TAGRISSO® osimertinib

FAST FACTS

Ovarian cancer

Ovarian cancer is a group of diseases that originates in the ovaries, or in the related areas of the fallopian tubes and the peritoneum.

21,000
is the approximate number of women in the U.S. who get ovarian cancer each year.

13,980
is the approximate number of women who will die from ovarian cancer each year.

1 in 78
is the approximate risk of a woman developing ovarian cancer in her lifetime.

8th
is the rank of ovarian cancer among the most common cancers.

5th
is the rank of ovarian cancer among cancer deaths.

90 percent
of women who develop ovarian cancer are 40 years of age or older.

60 years
of age or older is when the greatest number of women develop ovarian cancer.

70 percent
of ovarian cancers are caused by the tumor type high-grade serous carcinoma.

• **Sources:** https://www.cancer.org/cancer/ovarian-cancer/about/key-statistics.html, https://www.cdc.gov/cancer/ovarian/index.htm

Antimicrobial resistance

Antimicrobial stewardship requirements for ambulatory healthcare organizations introduced. Effective January 1, 2020, new antimicrobial stewardship requirements will be applicable to Joint Commission-accredited ambulatory healthcare organizations that routinely prescribe antimicrobial medications. The rationale, references, and requirements behind the updated standards are detailed in a new R3 Report: *Antimicrobial Stewardship in Ambulatory Health Care from The Joint Commission.*

This project is a continuation of The Joint Commission's ongoing initiative to promote the appropriate use of antimicrobial medications in the hospital, critical access hospital, and nursing care center programs.

With improving patient safety as its goal, The Joint Commission developed new requirements to help decrease misuse of antimicrobial medications, which contributes to antibiotic resistance and adverse drug events.

The new Medication Management standard includes five elements of performance (EPs) to address antimicrobial stewardship in the ambulatory setting.

The new EPs align with current recommendations from scientific and professional organizations and address the following concepts:

(1) Identifying an antimicrobial stewardship leader;

(2) establishing an annual antimicrobial stewardship goal;

(3) implementing evidence-based practice guidelines related to the antimicrobial stewardship goal;

(4) providing clinical staff with educational resources related to the antimicrobial stewardship goal; and

(5) collecting, analyzing, and reporting data related to the antimicrobial stewardship goal.

In addition to an extensive literature review and public field review, The Joint Commission obtained expert guidance from a Technical Advisory Panel (TAP) and a Standards Review Panel (SRP). The prepublication version of the antimicrobial stewardship requirements will be available on the Prepublications Standards section of The Joint Commission website until the end of December 2019: https://www.jointcommission.org/assets/1/6/Prepub_AHC_ABX_Standards_20190426.pdf

Vaccine

Hepatitis B vaccine for non-responders. CyTuVax B.V. (Maastricht, The Netherlands) unveiled the results of the HBAI20 Phase 2 "BE-Responder" trial. The trial focused on "non-responders" to hepatitis B vaccination—persons who have been vaccinated with at least one complete vaccination course (three injections of a licensed hepatitis B vaccine) without achieving a protective immune response.

In this study, the HBAI20 vaccine can reduce the percentage of non-responders to eight percent compared to 21 percent in the HBVaxPro-10 group ($p = .068$ Fisher). A statistical evaluation using a generalized linear mixed model demonstrates that subjects who have received the HBAI20 vaccine are 3.5 times more likely to attain seroprotection at the end of the study compared with subjects who received the licensed HBVaxPro-10 vaccine ($p < .05$).

With the HBAI20 vaccine, seroprotection was achieved earlier than with the HBVAxPro-10 vaccine. Eighty-three percent of the non-responders attained seroprotection after two vaccinations. In contrast, with the licensed HBVaxPro-10 vaccine, after three injections only 79 percent of the non-responders achieved seroprotection.

The safety profile of HBAI20, as compared to HBVaxPro-10, showed a temporary higher number of transient mild and moderate local side effects including: Impaired arm movement, redness, and pain at injection site. This indicates that HBAI20 induces a stronger immune response. No differences regarding systemic side effects were observed in the study.

Genomics

Study of multiethnic genomes identifies 27 genetic variants associated with disease. In a study published in the journal *Nature*, researchers identified 27 new genomic variants associated with conditions such as blood pressure, type 2 diabetes, cigarette use, and chronic kidney disease in diverse populations.

The team collected data from 49,839 African American, Hispanic/Latino, Asian, Native Hawaiian, Native American, and people who identified as others and were not

defined by those ethnic groups. The study aimed to better understand how genomic variants influence the risk of forming certain diseases in people of different ethnic groups. The work was funded by the National Human Genome Research Institute (NHGRI) and the National Institute on Minority Health and Health Disparities (NIMHD), both parts of the NIH.

In this study, researchers specifically looked for genomic variants in DNA that were associated with measures of health and disease. Everyone has DNA sequences that consist of the chemical bases A, C, G, T. Genomic variants occur in DNA regions where one of those bases is replaced with another, across various individuals. The team found that some genomic variants are specifically found in certain groups. Others, such as some related to the function of hemoglobin, are found in multiple groups.

Apart from finding new genomic variants the study assessed whether known disease associations with 8,979 established genomic variants and specific diseases in European ancestry populations could be detected in African American, Hispanic/Latino, Asian, Native Hawaiian, and Native American populations.

Their findings show that the frequency of genomic variants associated with certain diseases can differ from one group to another. For example, a strong association was found between a new genomic variant and smokers and their daily cigarette usage in Native Hawaiian participants. However, this association was absent or rare in most other populations. Not finding the variant in all groups despite large numbers of participants in each group strengthens the argument that findings from one population cannot always be generalized to others.

A variant in the hemoglobin gene, a gene known for its role in sickle cell anemia, is associated with greater amount of blood glucose attached to hemoglobin in African Americans. The paper in *Nature* is the first to confirm this association within Hispanic/Latinos, who have shared ancestry that is mixed with European, African, and Native American ancestry.

Such an effort is vital because a vast majority of human genomics research use data based mostly on populations of white European ancestry. For example, a separate study showed that among 2,500 recently published human genomics papers, only 19 percent of the individuals studied were non-European participants.

Molecular diagnostics

New solution for high throughput molecular diagnostic testing. BD announced the CE-IVDD certification of the BD COR System in Europe. The high throughput solution for infectious disease diagnostics sets a new standard in automation for molecular testing.

The BD COR System integrates and automates the complete molecular laboratory workflow from pre-analytical processing to diagnostic test result. The system will be initially available with the BD Onclarity HPV Assay for the detection and extended genotyping of human papilloma virus (HPV). The system enables the processing of samples directly from liquid based cytology vials, the creation of molecular aliquot tubes and assay testing, replacing labor-intensive and error-prone manual processes with automated ones.

The company plans to continue seeking regulatory authorizations to sell the BD COR System around the world while expanding the content menu to include many other assays for infectious diseases.

The BD COR System is modular and scalable, designed to address multiple lab needs for expanding molecular testing and increasing test volumes. It has on board capacity for reagents and samples that provide six to eight hours of system processing, eliminating multiple technologist interactions per shift.

The BD Onclarity HPV assay detects and identifies 14 high-risk HPV types and provides genotyping information from specimens collected for cervical cancer screening purposes in the BD SurePath Vial and in the Hologic PreservCyt Solution (not approved in U.S.). The assay can be used in accordance with clinical guidelines and within the scope of local regulatory authorizations as part of a comprehensive approach to cervical cancer prevention. Different test configurations are CE marked and FDA approved.

Autoimmune

New clues on tissue damage identified in rheumatoid arthritis and lupus. Research supported by the Accelerating Medicines Partnership (AMP) on Rheumatoid Arthritis and Systemic Lupus Erythematosus (RA/SLE) provides new insights into tissue damage for these autoimmune conditions.

Findings include the identification of novel molecular signatures related to immune system signaling in kidney cells that may reflect their active role in disease process; molecular targets, including specific white blood cells, for potential treatment in lupus nephritis; and specific types of fibroblasts and white blood cells that are involved in rheumatoid arthritis. These discoveries set the stage for uncovering potential drug target candidates that could advance to experimental treatments. Results of the studies were published in three papers in *Nature Immunology.*

A primary goal of the AMP RA/SLE program, which is led by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), is to study tissues where the disease is active in patients, whereas most previous work studied mouse models or only human blood samples.

AMP researchers looked at all the cell types in either biopsy samples from kidneys of people with SLE or the synovial tissues of joints from people with RA. The program seeks to quickly find the most promising treatment targets so less time is lost chasing unsuccessful leads.

HIV

Most Americans have never had an HIV test. According to a report published on June 27 in the CDC's *Morbidity and Mortality Weekly Report* (*MMWR*), it recommended that everyone between the ages of 13-64 years be screened at least once in their lifetime for HIV, yet less than 40 percent of people in the U.S. have ever been tested. The new data underscores the urgent need to scale up HIV testing to end America's HIV epidemic. The analysis of 2016-2017 data from a national population-based survey suggests most people are not getting the recommended screening, even in areas with a high burden of HIV.

The cornerstone of effective stewardship is in the microbiology lab

By Christine Ginocchio, PhD, MT (ASCP)

Over the past century, the number of deaths due to infectious diseases has decreased dramatically through the extensive use of antibiotics. Antibiotics have also made a number of "modern-day medical miracles" possible, such as organ transplantation, cancer chemotherapy, treatment of preterm babies, and major surgeries.

Without antimicrobials, the infections associated with these diseases and medical interventions would be extremely frequent and potentially fatal. Because antimicrobials are so effective, they have been massively overused to treat both humans and animals. The development of antimicrobial resistance (AMR) is accelerated by the selective pressure exerted by the widespread use of antimicrobials.

Cases of AMR were usually detected in hospitals, but they have now spread outside these settings to the community. Some bacteria have become resistant to multiple drugs, leading to situations where there are no treatment options left to fight the patient's infection. Until just recently, a lack of new antibiotics in the development pipeline further compounded the situation.

Antimicrobial resistance phenomenon

AMR is a phenomenon which describes the non-susceptibility of microbes (bacteria, fungi, viruses, and parasites) to antimicrobial drugs. As microbes evolve over time, whether exposed to antimicrobials or not, they can develop resistance mechanisms that allow them to survive exposure to antimicrobials. AMR is a natural anomaly which confers a survival benefit to microbes, but is increased and accelerated by their exposure to antimicrobials through their misuse or overuse in human medicine, by inadequate infection prevention and control, from poor hygiene and sanitation practices, and due to unnecessary antibiotics used in agriculture and farm animal production. In addition, as a result of globalization of populations, animals and food, these antibiotic-resistant so-called "superbugs" can spread rapidly and easily between cities, countries, and continents.

Earning CEUs

See test on page 17 or online at www.mlo-online.com under the CE Tests tab.

LEARNING OBJECTIVES

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

1. Discuss the positive and negative attributes of the use of antibiotics.
2. Define antimicrobial resistance (AMR) and the factors that have caused it.
3. Recall statistics of AMR including usage, deaths, and associated healthcare costs.
4. Discuss how effective Antibiotic Stewardship Programs (ASPs) can be accomplished and the main goals of an ASP.

The infections caused by resistant pathogens are becoming increasingly harder to treat, with many reports of patients with no antibiotic options left to treat their infection. A recent global study from a team at Johns Hopkins University showed that the problem has been fueled by an astonishing 65 percent increase in antibiotic use between 2000 and 2015.[1] The status quo is not an option, as the need has never been more urgent because of the increase in the incidence of AMR worldwide. The number of antimicrobial R&D programs has declined steadily over the past 30 years.[2] Fortunately in recent years, several new agents have achieved U.S. Food and Drug Administration (FDA) approval, and several more are under late-phase development. However, without prudent use of these new compounds, their efficacy may be short lived.

The cost of non-action is enormous and will grow, putting patients at risk "with a return to a situation where 40 percent of the population die prematurely from infections we cannot treat" and making medical practices in some patients (chemotherapy, organ transplantation, some otherwise routine surgeries) highly risky.

Annul deaths attributable to AMR now exceed 700,000 globally and are predicted to reach 10 million per year by 2050.[3] This is a conservative estimate, since that report only considered a relatively small sub-group of resistant human pathogens. Moreover, the World Bank warns about the economic consequences of AMR, in particular a decrease in annual global GDP between 1.1 percent and 3.8 percent by 2050. In low-income countries, AMR could increase extreme poverty, with an additional 28.3 million people affected by this issue by 2050.

A global emergency

Nearly all of the world's largest governmental and public health organizations have identified AMR as a global emergency, including the World Health Organization (WHO), U.S. Centers for Disease Control and Prevention (CDC), G20, United Nations General Assembly, and the European Commission. In the United States, the CDC and Centers for Medicare and Medicaid Services (CMS) highly recommend all U.S. hospitals implement antimicrobial stewardship programs (ASPs). Effective January 2017, the Joint Commission hospital accreditation body (JCAHO) required all hospitals and nursing care centers have Antibiotic Stewardship Programs (ASPs).

ASP efforts outside of the U.S. include:

- The United Kingdom's five-year national strategy (2013-2018) for tackling AMR includes optimizing antibiotic prescribing through stewardship.[4]
- The German Society for Infectious Diseases published an evidence-based guideline in December 2013 requiring successful implementation of ASPs in German hospitals.[5]
- In South Africa, antimicrobial surveillance and reporting, antimicrobial stewardship, and improved infection prevention and control form the three pillars of the national AMR strategy framework for the years 2014-2019.

Appendix 1: Goals of antimicrobial stewardship and evidence for success

The four main goals of antimicrobial stewardship are listed below with examples of evidence that stewardship programs can help achieve these goals. [McGowan et al., 2012; Davey P et al., (Cochrane Database), 2013]

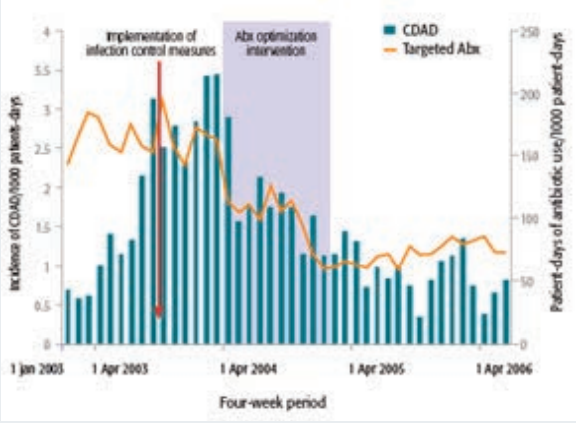
Goal 1: Improve patient outcomes (with improvement in infection cure rates, reduction of surgical infection rates, and reduction in mortality and morbidity)

CHARACTERISTIC	Inappropriate Antibiotics (n=238)	Appropriate Antibiotics (n=522)
DEMOGRAPHICS		
Age, mean ± SD (yr)	57.7 ± 15.8	59.9 ± 16.5
Male	48.7%	54.2%
CHRONIC HEALTH STATE		
Immunosuppressed	32.4%	34.3%
Chronic dialysis	14.7%	7.1%
Nursing home resident	13.4%	18.2%
Coronary artery disease	11.7%	7.9%
Chronic obstructive pulmonary disease	21.6%	17.2%
Congestive heart failure	21.6%	18.1%
Malignancy	23.1%	34.1%
Diabetes mellitus	27.5%	20,1%
Charlson score, mean ± SD	4.8 ± 3.7	4.8 ± 3.7
DISEASE SEVERITY		
Acute Physiology and Chronic Health	23.2 ± 6.6	23.9 ± 6.7
EVALUATION II, MEAN ± SD		
Need for mechanical ventilation	62.6%	51.5%
Need for vasopressors	59.9%	58.0%
Organ failures, mean ± SD	2.3 ± 1.0	2.2 ± 1.1
Treatment with drotrecogin alfa (activated)	3.8%	4.4%
INFECTION CHARACTERISTICS		
Nosocomial	69.3%	48.7%
Community-acquired	5.9%	11.1%
Healthcare-associated	24.8%	40.2%
ADDITIONAL FACTORS		
Length of stay before infection (mean ± SD)	15.3 + 20.7	7.5 + 14.9
Length of stay before infection (median)	9	1
Hospital mortality	51.7%	36.4%

Adapted from Shorr AF. et al, Crit. Care Med. 2011;39:46-51.

Goal 2: Improve patient safety

- Reduce antimicrobial consumption without increasing mortality or infection-related readmissions e.g. 22%-36% reduction in antimicrobial use [Dellit et al., 2007].
- Reduce *C. difficile* colonization or infection by controlling the use of "high-risk" antibiotics [Valiquette et al., 2007].

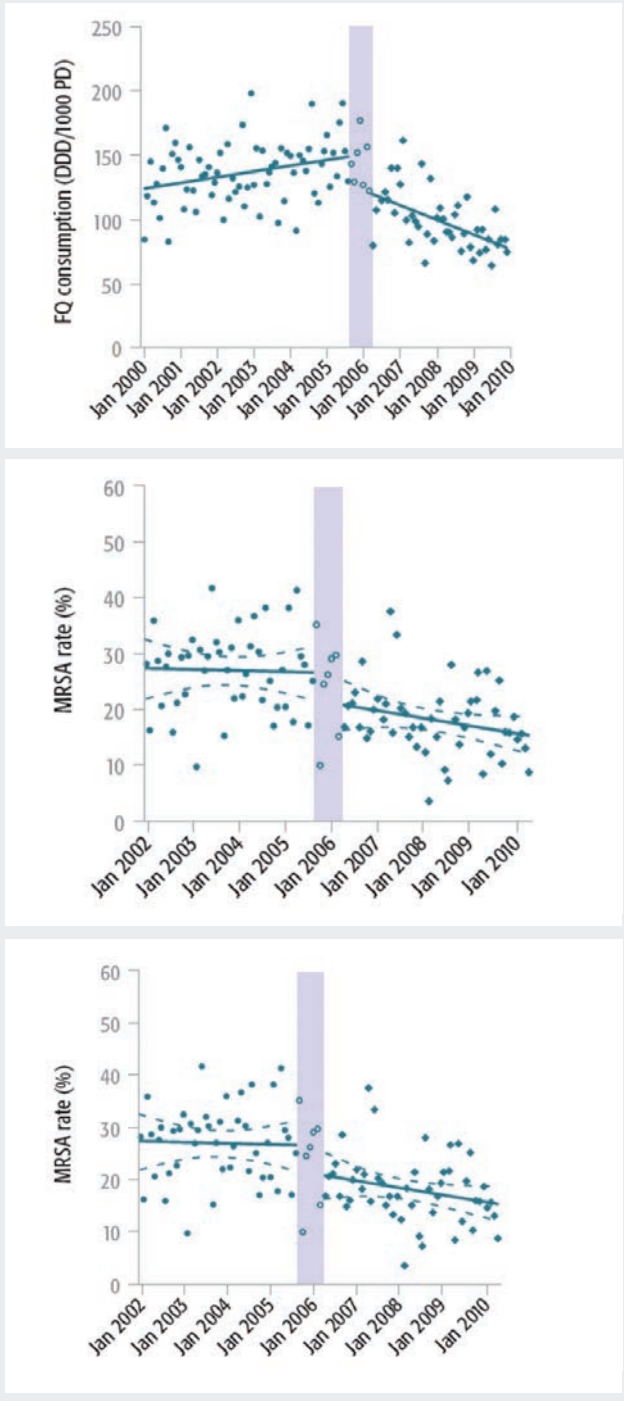


Adapted from Valiquette L et al., Clin Infect Dis 2007;45:S112-121.

Example of robust stewardship program with strict implementation of infection control measures leading to sustained reduction in *C. difficile* infection [CDI] cases during an epidemic.

Goal 3: Reduce resistance

Restricting relevant agents can reduce colonization or infection with Gram-positive or Gram-negative resistant bacteria.



Example of a reduction of fluoroquinolone use associated with decreased MRSA and fluoroquinoloneresistant *P. aeruginosa* isolation rates.

Appendix 1: Goal 4 continued on page 12

Appendix 1: Goal 4 continued from page 11

Goal 4: Reduce healthcare costs

Savings achieved by reducing antibiotic costs can be greater than the cost of the intervention or program (from $200,000 to $900,000 depending on the studies) [Dellit et al., 2007]. Such cost-effectiveness data are sparse but emerging [Stevenson et al., 2012; Davey et al., (Cochrane Database), 2013].

YEAR	METHOD A*	METHOD B**
2000[a]	158,161	229,076
2001	548,002	1,267,638
2002	806,393	1,446,883
2003	473,174	1,354,129
2004	244,160	1,555,048
2005	419,613	2,005,202
2006	983,690	2,172,756
2007	675,036	1,990,967
2008	817,503	2,557,972
2009	1,278,301	2,782,519
2010	2,175,927	3,456,373
2011[b]	1,770,827	2,406,399
Yearly average	920,070	2,064,441
Total savings	10,350,787	23,224,961

Note: data are US dollars
[a] April-December 2000
[b] January-June 2011

* Method A: Inflation rate determined using the annual US consumer price index for Medical Care Commodities.
** Method B: Inflation rate determined using an Anti-Infective Specific Index (see artide).

Adapted from Beardsley J et al. Inf. Control Hosp. Epidemiol., 2012;33:398-400.

Example of annual savings associated with the implementation of an ASP.

Image courtesy of bioMerieux.

Combatting AMR

Diagnostics play a major role in combating AMR on three different levels:

1. To achieve optimal diagnosis and therapy of the individual patient.
2. To achieve optimal cost-efficient functioning of healthcare systems.
3. To promote the public health and improve life for patients with infectious diseases worldwide.

With so much focus on the threat of AMR, we too often only focus on the need for novel antibiotics, but forget that we must also take urgent steps to sustain the efficacy of the antibiotics we already have in order to preserve these life-saving drugs for future generations. To do this we need innovative and rapid diagnostics, and we need to use them properly.[3]

In fact, diagnostics have done much to curb the spread of resistant organisms through more rapid technological advancement than new antibiotics, which take many years to research, develop, and gain regulatory approval. The common cornerstone of every effective ASP is the microbiology lab. While many U.S. hospitals have implemented mandatory ASPs to reduce the misuse and overuse of these drugs, many hospitals have yet to launch robust and effective stewardship teams and programs because the lack the expertise, funding, time—or because it simply is not a priority among hospital management.

As healthcare providers, we must continue to remind hospital administrators that diagnostics provide nearly all of the basic information used in about 70 percent of clinical decisions. Unfortunately, the microbiology laboratory does not stand among hospital stakeholders as having the biggest influence in antibiotic usage, but this must change for us to defeat AMR. It is vital that hospital administrators realign their perception of the microbiology lab as simply a cost-center and begin to see if for what it really is: The cornerstone of effective stewardship. We must rapidly advance our ASPs nationwide and to do this hospital administrators are encouraged to do the following:

- Consider in vitro diagnostics as a fundamental tool in the fight against AMR and of all ASP efforts;
- support the transformation of the microbiology lab role in ASP into a vital component; and
- develop educational programs around the importance of diagnostics in combatting AMR and their pivotal role within ASP efforts, for both clinicians and their patient populations.

While implementing effective stewardship takes effort and resources, stewardship provides rapid cost savings, in addition to improving patient care. For example, ASPs can dramatically reduce pharmacy expenditures on overuse and misused antibiotics. **(Appendix 1)**

With the microbiology laboratory and the pharmacy working in close partnership, rapid therapeutic decisions can be made and personalized based on the latest diagnostic information. By identifying the most appropriate antimicrobial therapies, stewardship programs are essential to improving patient outcomes and patient safety, preserving the efficacy of existing antimicrobials, and reducing resistance and healthcare

continued on page 16

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continued from page 12

costs. One of the cornerstones of high-performing stewardship programs is the proper use of rapid diagnostic platforms.

The founding of PACCARB

Noting that the rise of antibiotic-resistant bacteria represents a serious threat to public health and the economy, President Barack Obama created the President's Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB) in 2014 with the Executive Order for Combating Antibiotic-Resistant Bacteria.

Detecting, preventing, and controlling antibiotic resistance requires a strategic, coordinated, and sustained effort. The federal government works domestically and internationally to detect, prevent, and control illness and death related to antibiotic-resistant infections by implementing measures that reduce the emergence and spread of antibiotic-resistant bacteria and help ensure the continued availability of effective therapeutics for the treatment of bacterial infections.

The Advisory Council provides advice, information, and recommendations to the Secretary regarding programs and policies intended to support and evaluate the implementation of U.S. government activities related to combating antibiotic-resistant bacteria.

The PACCARB consists of 30 members, including 15 voting members that are special government employees, five non-voting liaison members representing their respective organizations, and 10 regular government employees representing the Department of Health and Human Services (HHS), the Department of Defense (DoD), and the United States Department of Agriculture (USDA). The members are supported by a Designated Federal Official and other staff members within HHS.

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TEST QUESTIONS

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

1. **Although antibiotics have substantially contributed to modern day health miracles, there is a large concern regarding their massive overuse in humans and animals.**
   - ○ a. True
   - ○ b. False

2. **About how many new antibiotics are currently in development to be used in treatment against cases of antimicrobial resistance (AMR)?**
   - ○ a. none
   - ○ b. two
   - ○ c. five
   - ○ d. ten

3. **AMR refers to the nonsusceptibility of _____ to drugs.**
   - ○ a. bacteria and viruses
   - ○ b. viruses and parasites
   - ○ c. bacteria, viruses, parasites, and fungi
   - ○ d. parasites, viruses, and fungi

4. **What factor(s) has/have led to the rise in AMR cases?**
   - ○ a. agriculture/animal production
   - ○ b. poor hygiene and sanitation practices
   - ○ c. inadequate infection prevention and control
   - ○ d. all of the above

5. **Antibiotic resistant superbugs cannot spread rapidly between cities, countries, and continents.**
   - ○ a. True
   - ○ b. False

6. **Studies on antibiotic use have shown an increase of _____ between 2000 and 2015.**
   - ○ a. 10 percent
   - ○ b. 35 percent
   - ○ c. 65 percent
   - ○ d. 80 percent

7. **How many AMR-related deaths are predicted by the year 2050?**
   - ○ a. 10 million
   - ○ b. 15 million
   - ○ c. 25 million
   - ○ d. 50 million

8. **Which agency requires hospitals in the U.S. to have antimicrobial stewardship programs (ASPs)?**
   - ○ a. CMS
   - ○ b. CDC
   - ○ c. WHO
   - ○ d. JCAHO

9. **Germany, South Africa, and the United Kingdom have published ASP guidelines for practice in their countries.**
   - ○ a. True
   - ○ b. False

10. **Which factor plays a major role in combating AMR cases?**
    - ○ a. effective treatment plans
    - ○ b. diagnostics
    - ○ c. pain management
    - ○ d. none of the above

11. **Which hospital department has a common foundation for effective ASPs?**
    - ○ a. blood bank lab
    - ○ b. microbiology lab
    - ○ c. emergency department
    - ○ d. sterile processing

12. **Which factors play a role in the lack of effective hospital-based ASPs?**
    - ○ a. non-priority in administrators
    - ○ b. lack of funding and expertise
    - ○ c. lack of time
    - ○ d. all of the above

13. **About what percentage of clinical decisions does diagnostics play in patient cases?**
    - ○ a. 55 percent
    - ○ b. 70 percent
    - ○ c. 80 percent
    - ○ d. 95 percent

14. **The main goal(s) for an effective ASP is/are**
    - ○ a. reducing resistance of existing antibiotics.
    - ○ b. improving patient safety/outcomes.
    - ○ c. reducing healthcare costs.
    - ○ d. all of the above

15. **Which two hospital departments have the capability to work closely together to make personalized, rapid therapeutic decisions for antibiotic therapy?**
    - ○ a. emergency department and pharmacy
    - ○ b. ICU and emergency department
    - ○ c. microbiology lab and pharmacy
    - ○ d. microbiology lab and surgery

16. **Which organization was created by Barack Obama during his presidency to control the spread of AMR organisms?**
    - ○ a. PACCARB
    - ○ b. ARB
    - ○ c. USDA
    - ○ d. CDC

17. **Barack Obama's advisory council consists of 45 voting members to implement activities that relate to combatting antibiotic-resistant bacteria.**
    - ○ a. True
    - ○ b. False

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2. **To what extent was the article well-organized and readable?**
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A practical approach to evaluating requests in testing new antimicrobials

By Catherine A. Hogan

Many new antimicrobials have recently come to market to address the rising threat of multidrug-resistant (MDR) bacteria. Clinical and public health laboratories are critical participants in the management of patients with MDR infections and must develop a plan for antimicrobial susceptibility testing (AST) of these new agents, either in-house or at a reference laboratory.

Herein, we present an example of a practical approach to this challenge. Let's consider how a laboratory might respond to the scenario of receiving the following request from the institutional antimicrobial stewardship team: *Can the lab start testing carbapenem-resistant Enterobacteriaceae (CRE) for ceftazidime-avibactam (CZA; AVYCAZ) susceptibility?*

Consider the clinical need

The antimicrobial stewardship program (ASP) chair has requested all CRE be tested for CZA susceptibility. This request seems simple, but careful consideration should be given to different testing approaches. Some key questions for the laboratory to consider are listed in **Table 1**.

Testing in-house vs send-out?

This requires consideration of:

- Expected volume of testing, based on the number of carbapenem-resistant *Enterobacteriaceae* from last year's antibiogram.
- Availability of testing options and materials.
- Capacity to perform testing in-house.
- Staffing capacity to perform verification studies, write standard operating procedures (SOPs), etc.
- Impact of testing option(s) on turnaround time to results.

A basic cost-analysis of in-house vs send-out testing should be performed, keeping in mind that the results of testing CZA are often critical to patient care.

Close collaboration with infectious diseases, critical care physicians, laboratory medicine, and administrative colleagues is essential to ensure an optimal workflow.

For the purpose of this exercise, let's assume the laboratory encounters ~100 isolates per year that meet the testing criteria defined in **Table 1**, and determines testing should be done in-house.

How to perform the verification studies

The essential components of a verification study are presented in **Table 2**; further guidance is found in references.[6-9]

How to perform QC? Should we consider an IQCP?

CLIA requires a laboratory to either perform AST QC daily or develop an individualized quality control plan (IQCP).[4] In many laboratories, CRE are relatively uncommon and CZA will be tested infrequently (i.e., less than once a week). As such, the lab may choose to not perform an IQCP, but to perform QC each time a patient isolate is tested.

What results should I expect? (i.e., how often are carbapenem-resistant isolates R to CZA?)

In vitro susceptibility rates of *Enterobacteriaceae* to CZA are very high, with > 99.5 percent susceptibility overall, and > 97 percent among class A and D carbapenemase-producing isolates.[13,14]

In contrast, as highlighted previously, little to no activity is expected against MBL-producing *Enterobacteriaceae*. If the laboratory encounters a high rate of resistance, this should be investigated to ensure it is not due to technical error.

Summary

In summary, broad-spectrum agents such as ceftazidime-avibactam have strongly enhanced the therapeutic arsenal against MDR gram-negative organisms, an important cause of morbidity and mortality in patients in hospitals and long-term care facility settings.

Implementing testing and completing a verification study for a new antimicrobial agent such as CZA carry additional workload which may seem daunting to the laboratory. However, accurate and timely microbiological testing is instrumental in identifying effective therapies that may significantly impact patient outcomes and enable effective resource allocation.

Table 1. Example of considerations when developing a CZA testing strategy in the clinical laboratory

Question 1. **Should isolates from all patient populations and/or anatomical sites be tested?**
Information review: Drug label[1] shows CZA is FDA-approved for: • Complicated urinary tract infection in adults and children ≥ 3 months old • Complicated intra-abdominal infection in combination with metronidazole in adults and children ≥ 3 months old • Hospital and ventilator-associated bacterial pneumonia in adults
Decision: ASP chair and laboratory determine that testing will be done routinely for CRE from: • Blood, urine, and intra-abdominal isolates from children/adults • Lower respiratory isolates from adults • Isolates from other sources (e.g., wounds, cerebrospinal fluid [CSF]) will not be tested routinely
Further discussion: Should all urine isolates be tested? Many CRE from urine were deemed colonizers by ASP upon review of the hospital's data, and not treated. (CRE often colonize the urinary tract, especially among nursing home residents in whom CRE are more common.) Laboratories are not restricted to only performing susceptibility testing on isolates from clinical specimen sites that are FDA approved. Such testing may provide guidance for off-label use of a drug when there is no FDA-approved alternative, as may be seen with some MDR isolates.
Question 2. **Should reflex testing be done for all *Enterobacteriaceae* with phenotypic resistance to all carbapenems on our panel (ie, ertapenem, imipenem, meropenem), or only if resistant to meropenem and/or imipenem?**
Information review: • Laboratory data on number of isolates that are R to ≥ 1 carbapenem • Laboratory data on the number of *Enterobacter* isolates that are R to ertapenem but S to imipenem and meropenem; literature review indicates these are mainly AmpC producers[2] • Literature review reveals some carbapenemase-producing CRE (CP-CRE) may be I to imipenem and/or meropenem[3] • CLSI M100 Appendix B indicates *Proteus/Providencia/Morganella* spp. may be I or R to imipenem (but not ertapenem or meropenem), via intrinsic resistance mechanisms
Decision: • Test all *Enterobacteriaceae* that are I or R to meropenem or imipenem. • Do not test *Proteus/Providencia/Morganella* that are I or R to imipenem only. • Do not test any *Enterobacteriaceae* that are R to ertapenem only.
Further discussion: • Should the laboratory test CZA on isolates that are S to one or more agents that might be appropriate for therapy (ie, CRE that are S to a fluoroquinolone or trimethoprim-sulfamethoxazole)? • Should other antimicrobial options be considered for routine testing of CRE (ie, fosfomycin for *E. coli* urinary tract infection)? • The laboratory may initially decide against these options, with the plan to reconsider as needed in the future.
Question: 3. **If phenotypic/molecular carbapenemase testing is done, should these results inform the decision to test CZA?**
Information review: • CZA is a novel beta-lactam combination agent composed of ceftazidime and avibactam with activity against class A, C, and D beta-lactamase-producing isolates, including those that express KPC, the most common CRE type in the USA.[4] • CZA has no activity against class B metallo-beta-lactamases (MBL) (ie, NDM-1, IMP, VIM). • Laboratory protocol already includes testing isolates that meet CP-CRE definition (see question 1) by the modified carbapenem inactivation method (mCIM)/EDTA modified carbapenem inactivation method (eCIM) methods for carbapenemase.
Decision: • An isolate positive for both mCIM and eCIM indicates production of an MBL and does not need to be tested since it will be CZA resistant.[4]
Further discussion: • Should the CZA testing be done in parallel with, or after, the mCIM/eCIM testing? The latter option will result in a delay of result reporting.
Question: 4. **Might testing for non-*Enterobacteriaceae* be considered if requested by clinician?**
Information: • CZA has no activity against *Acinetobacter* spp., but has activity against *P. aeruginosa.* • Drug labeling demonstrates that indications for use include *P. aeruginosa.* • FDA Susceptibility Test Interpretive Criteria (STIC) website[5] includes breakpoints for *P. aeruginosa.*
Decision: • P. *aeruginosa* will be included in verification studies or discussed with reference laboratories that will perform CZA testing.
Further discussion: • Discuss with ASP if CZA should be tested routinely for *P. aeruginosa* isolates (ie, those "R" to all other antipseudomonal beta-lactams ([aztreonam, ceftazidime, cefepime, piperacillin-tazobactam, meropenem and/or imipenem])

Table 2. The essential components of a verification study

Pre-verification activities	
Determine need for/ scope of verification study	According to CLIA (§CLIA 493.1253), any new testing introduced in your laboratory requires a verification study. The extent of the verification study is at the discretion of the laboratory director. If CZA is added to an existing FDA-approved AST system already in use in the laboratory, a limited study may be sufficient. Otherwise, a more robust study should be considered.
Selection of AST method	**Available methods:** FDA-cleared AST methods for new antimicrobials typically include disks, gradient diffusion strips (including some that may be research use only [RUO]), and manual broth microdilution. Testing for new agents on automated instruments is generally not available for several years post antimicrobial approval; contact the manufacturer for information.
	Literature review: The laboratory should consult the literature to review AST method performance data. • Example: recent data show gradient diffusion strips perform better than disk for CZA.[10,11] Note: please refer to the CLSI workaround for potentially false "R" disk diffusion results below. • When evaluating published studies, carefully review the methods section to ensure the authors followed CLSI recommendations for AST evaluations.[9]
Review breakpoints and testing considerations	**CLSI M100 and FDA STIC website:** Both sources list MIC and disk breakpoints for new antimicrobials. New antimicrobials are sometimes listed on the FDA website earlier than in M100. Either breakpoint is acceptable for use by clinical laboratories; however, manufacturers of commercial AST systems must use the breakpoints listed on the FDA website. **Example:** • M100 and FDA list CZA disk (S ≥ 21mm; R ≤ 20mm) and MIC (S≤ 8/4; R≥ 16/4) breakpoints. • There is no intermediate breakpoint for CZA. • CLSI and FDA recommend disk zones of 18-20 mm should be confirmed by an MIC method, due to the risk of overcalling resistance.[4]
Verification	
Accuracy	**Method**: Compare categorical (MIC and disk) and essential (MIC only) agreement of the AST method with a reference method. Reference/comparator methods are typically disk diffusion or broth microdilution (BMD) performed in-house or by a reference laboratory.

	Select testing isolates:
	• Minimum of 30 isolates recommended by CLSI
	• Ideally, isolates should span a range of MICs and include diverse species and resistance phenotypes (including ESBL, AmpC, KPC, OXA-48)
	• Suggest including isolates resistant to CZA, such as those harboring an MBL
	• Sources include:
	  • In-house collections
	  • Proficiency testing challenges
	  • Colleagues
	  • Antimicrobial's pharmaceutical company
	  • CDC & FDA Antibiotic Resistance (AR) Bank (contains challenge isolate panels that include BMD MICs)[12]

	Testing and data analysis:
	• Test isolates by the new AST method and the comparator in parallel.
	  • If using the CDC & FDA AR Bank isolates, only test by the new AST method; MIC results posted were generated by reference BMD testing and are acceptable to use for comparator results without additional testing.
	• A limited number of errors are acceptable. Generally acceptable error rates, with caveats, are below:
	  • Major errors (ME): < 3% of the total susceptible isolates
	  • Very major errors (VME): < 3% of the total resistant isolates
	  • If testing 30 isolates, only one ME and one VME is acceptable.[7]
	  • Given the lack of an intermediate breakpoint for CZA, all errors are MEs or VMEs; the laboratory director may accept a higher error rate and consider follow-up testing if the zone/MIC is near the breakpoint.
	  • Always address discrepancies:
	  o Repeat testing for isolates with discrepancies by both methods.
	  o If discrepancy is not resolved, send to a reference laboratory for evaluation by a third method. CDC & FDA AR Bank isolates cannot be forwarded to another laboratory.
	  • Proper documentation of the verification study design; results needs to be performed and stored for future reference.

Precision	**Method:**
	• One option is to evaluate precision through routine testing of QC strains.
	  • For CZA, *Klebsiella pneumoniae* ATCC 700603 is used.
	  • Note that ceftazidime, or another antimicrobial listed in Table 4A-2 or 5A-2 of CLSI's M100, should also be tested to ensure integrity of this QC strain.
	  • 95% of results must fall within acceptable QC ranges.
	• During the verification of CZA, daily QC should be performed by the recommended CLSI or manufacturer method.

Post-verification activities	
Activities	Ongoing QC, training and proficiency documentation for staff, maintenance of software and correlation of results with clinical findings.

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A clinical future for WGS

By Willem K.C. van Loon

The ever-decreasing cost of next generation sequencing (NGS) has allowed genetic testing to make the leap from research into routine screening applications. In the clinical setting, NGS is now commonly used for prenatal testing, HLA typing, and cancer diagnostics. Regardless of the application, current techniques are based on targeted sequencing, using DNA capture methods to look at specific genetic markers. The problem with this approach, particularly in cancer or rare disease diagnostics, is that the limited information provided can lead to erroneous or inconclusive results. Whole genome sequencing (WGS) eliminates this issue by providing comprehensive sequence coverage, then using bioinformatics approaches to identify relevant genetic markers.

NGS has revolutionized the use of genetic testing across a broad range of disciplines. Constantly decreasing costs and improved accessibility have led to rapid growth in sequencing-based applications—from medical research to agriculture—driving the development of powerful technology platforms that offer even faster and cheaper sequencing. But sequencing is only one piece of the puzzle, and both up- and downstream processing steps are just as important to the overall reliability and cost effectiveness of NGS. In particular, the efficiency and reproducibility of pre-analytical DNA isolation and library preparation have a significant impact on the overall cost and practicality of the technique.

A targeted approach

Consistent and reliable results are crucial for any technique intended for clinical use or routine screening applications, making fast, efficient, and reproducible DNA library preparation essential.

Classical NGS applications are based on target enrichment using one of two strategies:

(1) Targeted PCR amplification followed by library preparation and sequencing of the PCR products, or

(2) generation of a whole genome library followed by targeted capture of the sequences of interest.

Both approaches require a number of sequential incubation and wash steps, and careful processing is required to avoid the sequencing results being skewed by experimental bias. To mitigate this issue, standardized library preparation kits are now available for many targets of interest to clinical research, covering areas such as cancer, infectious diseases, liquid biopsies, microbiome analysis, and epigenetics. However, these kits do not address the main drawback of targeted sequencing; that capture/hybridization and enrichment steps are extremely time consuming, often requiring lengthy incubation times. This leads to turnaround times (TATs) of several days from sample to results, limiting the potential usefulness of next generation sequencing.

Comprehensive coverage

Current targeted sequencing strategies were developed as a result of the high cost of sequencing in the early days of NGS. However, as sequencing platforms have become faster, more powerful, higher capacity, and more efficient, the cost of NGS has plummeted; it is already well under $1,000 to sequence an individual human genome and is likely to reach the $100 milestone within a decade. This dramatic decrease in sequencing costs has been accompanied by similar reductions in the cost of data storage and analysis, making WGS a viable option for disease diagnostics. As the name suggests, WGS involves library generation and sequencing of all the DNA within a sample, then uses data mining and other advanced bioinformatics approaches to identify relevant genetic markers.

A major advantage of this approach is that it avoids capture/hybridization and enrichment steps associated with targeted techniques. This allows much faster library generation and eliminates the requirement for space for additional incubators within the laboratory. WGS approaches also have the potential to significantly improve diagnostics for cancers and rare diseases by removing the need to choose (potentially incorrect) genetic biomarkers for analysis. And even if initial diagnostic analyses prove inconclusive, the full genomic data is available for re-analysis, avoiding further processing of blood or biopsy samples. As with targeted sequencing methods, a number of WGS sample preparation kits are now available to ensure consistent and unbiased library generation.

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Embracing automation

Laboratory automation plays a central role in any clinical laboratory and is essential for broad uptake of genetic testing in a clinical environment. Many of the targeted sequencing kits available for both research and diagnostics have already been automated using liquid handling platforms, due to the labor-intensive nature of target enrichment techniques, which require numerous reagent addition, incubation, and wash steps.

Some suppliers have taken this approach a step further, offering complete workflow solutions combining all the necessary hardware, software, and reagents to generate sequencing-ready libraries. This type of end-to-end solution is vital for genetic testing to become more widespread in a clinical setting, providing optimized, reliable, and easy-to-use systems suited to a multi-disciplinary laboratory.

Reducing manual activities, and the associated risk of processing errors and cross-contamination, obviously helps to improve throughput and the consistency of results, as well as traceability, but cannot compensate for the long incubation times required for sample capture/

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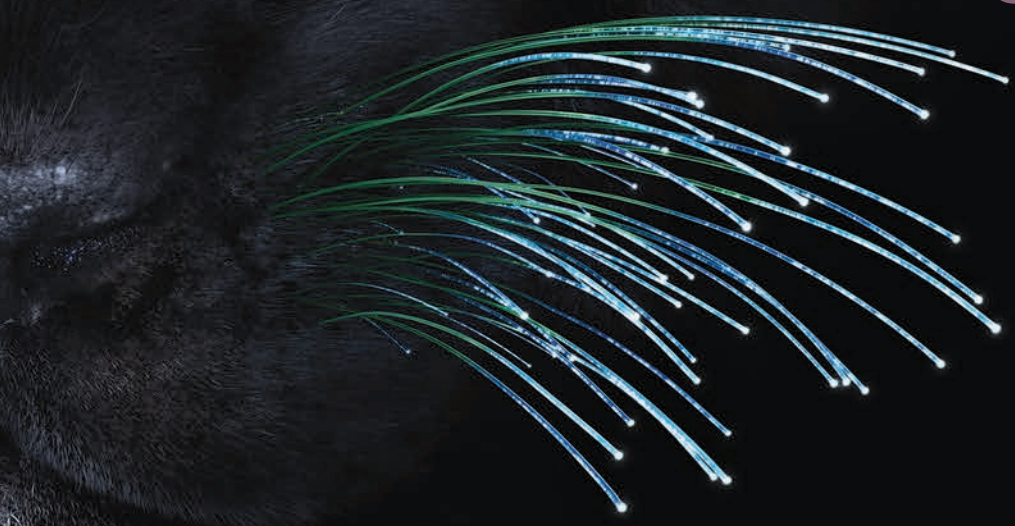

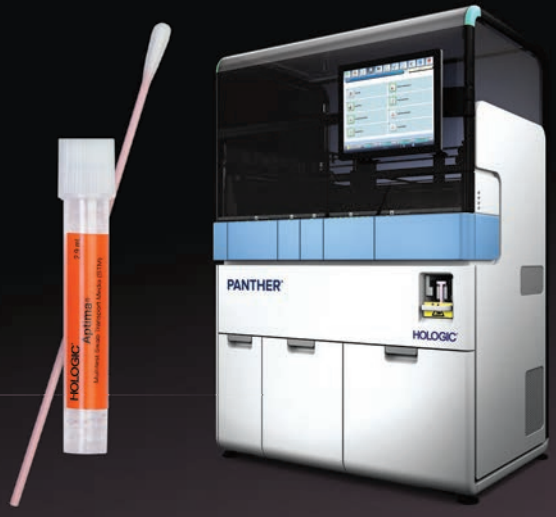

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hybridization and enrichment. Fortunately, many of these automation platforms can be easily adapted to perform untargeted library preparation for large amounts of genetic material, providing an elegant solution for WGS.

The cost of QC

Another aspect of sample preparation for NGS which can significantly impact the total cost of sequencing, is library quantification and quality control (QC) testing. Historically, this has been performed by qPCR analysis or using an automated capillary electrophoresis platform. This essential step generally requires manual set-up and, in the case of qPCR, takes several hours to perform—further impacting TATs. While electrophoresis is faster, the majority of instruments available have limited throughput, and still require significant user input. And both methods require costly reagents, driving up overall sequencing costs.

Fluorescence-based QC testing

A recently developed alternative to this approach is fluorescence-based QC testing, which is achieved by incorporating a specific number of fluorescent labels into the library molecules during preparation. This method eliminates sample loss for QC, is independent of fragment size, and can be easily automated by integrating a fluorometer or microplate reader into the library preparation workstation. This method also has the advantage of being much faster than qPCR- or electrophoresis-based analysis, taking around six minutes for QC testing of an entire 96-well plate. This has the knock-on benefit of reducing the overall library preparation workflow—to go from DNA to pooled libraries, ready to be loaded into the sequencer—from around six to eight hours to less than four hours. In a clinical setting, this technology could have a significant impact on TATs for time-critical patient results, potentially doubling throughput by allowing two library preparation runs per day.

Summary

WGS is growing in popularity as the cost of NGS falls. Automation of library preparation is essential for reproducible and reliable processing as this technique moves toward clinical applications, helping to standardize results and accelerate TATs. A more integrated approach—combining hardware, software, and reagents from a single supplier—will help to improve access to this technology and aid the translation from clinical research into routine diagnostics.

Willem K.C. van Loon serves as Director of Genomics at **Tecan**, Switzerland, and works with his team to automate a wide range of genomics applications. He holds degrees in Chemistry and Laboratory Automation from The Hague University of Applied Sciences, and has extensive experience in the automation of life sciences laboratory workflows, collaborating with major liquid handling providers, reagent suppliers, and customers around the globe.

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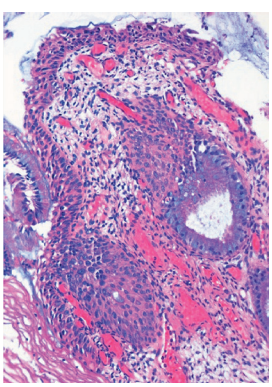

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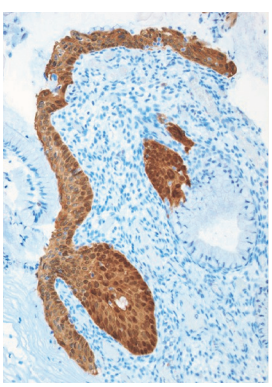

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What's lurking in your lab?

By Editors Lisa Moynihan and Janette Wider

In an ideal world, not only does your lab have an active infection prevention and control (IPC) program in place, but a dedicated IPC supervisor who regularly trains staff in emergency preparedness procedures or "spill drills." Your laboratory also conducts audits every month to identify real and perceived safety hazards and passes with flying colors every time.

But this isn't always the reality.

Although we all have room for improvement, the importance of cleaning tasks, while not the most enjoyable aspect of a laboratorian's job, is a *mandatory* aspect of lab safety and IPC. Keeping the laboratory clean *and* safe is imperative not only to your safety but the lab's ultimate success.

Below are some basic tips for cleaning the lab and keeping it safe:

Clean every day

Every lab should have a housekeeping checklist. The checklist should include basic routines like cleaning and clearing countertops and workbenches. The floors should be swept as well as doing a wet mop of the biohazardous areas at least once per day. Touchpoints like doorknobs, light switches, and telephones should also be sanitized.[1]

Be aware of your surroundings

It's good practice to ensure aisles are clear, especially if a pathway leads to an evacuation route. A haphazard wire from a computer, for example, could cause a staff member to trip and fall. Tie wires up if necessary. Be sure the floors are clean and replace anti-fatigue mats on a regular basis. If there's wax buildup in histology areas, use scrapers to remove the wax.[2]

Address messy workspaces

Cluttered workbenches can be hazardous and contain hidden dangers. Paper strewn about can easily hide sharps, infectious materials, and unknown chemical hazards. In addition, fans should not be used in the laboratory in order to cut down on dust. Dusting should be routine.[2]

Handwashing stations

All employees should wash their hands on a regular basis. Up to 90 percent of healthcare workers do not wash their hands. Make sure the sinks for handwashing are clean, disinfectant soap dispensers are full, and paper towels are easy to reach. Sink clogs can cause backup that may lead to contamination; be sure sinks are functioning properly.[1]

Gloves

A 2014 study of safety measure compliance investigated "the use of PPE and compliance to the code of conduct." Ninety-six percent of those responded that using gloves was important when dealing with human samples. Thirty-nine percent said they always wear gloves as part of their daily routine, 27 percent said often, and 33 percent said sometimes.[3]

The percentage of wearing gloves as part of a daily routine for laboratorians should be at 100 percent. There's no excuse as to why a staff member in the lab would intentionally forgo wearing gloves. Placing reminders throughout the lab helps staff remember to always wear gloves.

Using gloves is important when handling human samples.

Personal protective equipment

Personal protective equipment (PPE) is gear or clothing used to protect the wearer from specific hazards and hazardous materials. It is the final protection system to be used when administrative and engineering controls do not reduce risk to an acceptable level. PPE does not reduce or eliminate the hazard—it only protects the wearer.

Maintaining PPE is a very important part of laboratory safety. Literature or meetings about what kind of PPE, when it is necessary, how to wear it, and how to care for it can be helpful for staff to refresh their memory on proper procedures. Do you know how to properly remove gloves without contaminating yourself? It may seem like a simple question, but believe or not, not everyone in your lab knows how.

Lab coats, gloves, and safety eyewear are the basic PPE needed in a lab. Additional PPE may be needed for other hazards. Your ICP supervisor should be regularly assessing your lab's general and specific PPE needs and ensure PPE is provided and properly used in the laboratory.

Keep lab equipment clean

Lab equipment should be checked for cleanliness, often. When an employee is done using lab equipment, it should be cleaned according to established standards. All employees should keep the lab's equipment in top condition[1] to show their commitment to laboratory stewardship.

A major part of keeping laboratory equipment clean is disinfection protocols. Benches should be disinfected after every work shift and after any spills occur. The CDC recommends a 10 percent bleach solution for disinfection. Labs should choose commercially available brands that are effective at eliminating bacteria, fungi, and viruses. Don't select a brand that is only effective against more resistant organisms. The product should be left on the surface for the amount of time designated by the manufacturer.[2]

Glass, of course, is also part of lab equipment and should be cared for either by automatic washing that has a disinfector or manually cleaning beakers, flasks, droppers, and funnels.

Inventory fridge and freezer contents

Not sure if that's a sandwich or a lab specimen? You would think it would go without saying, but mixing food and specimens is unacceptable. Yet, it still happens. In addition to those friendly reminders for your fellow laboratorians, be sure to inventory the lab's fridge and freezer contents. Include important information such as origin and expiration dates. Rotate contents to ensure easier inventory maintenance and timely disposal of expired items.[1]

Inspect emergency equipment

In order to be safe, the lab's emergency equipment must be inspected. First, schedule regular inspections for the lab's fire suppression and sprinkler systems. Next, keep first aid kits in easily accessed areas. Last, regularly check fire extinguishers to make sure all units are fully charged and properly stored.[1]

Maintain emergency stations

Hand in hand with emergency equipment are the stations at which the equipment resides. Ensure emergency eyewashes, showers, and fire extinguishers are unobstructed. Ensure easy access to bloodborne pathogen and chemical spill response kits. Activate components in all stations several times a week to ensure proper operation. Arrange for regular station inspections by qualified technicians.[1]

Disposal of broken glass

For safe disposal, designate one trash bin for broken glass and materials with sharp edges. Only allow the bin to become half-full before disposing of the contents in an outside dumpster. These basic guidelines should be applied to all damaged or cracked glassware.[1]

Designate one trash bin for broken glass.

Proper waste disposal

It is important to work closely with the safety coordinator to determine the best methods for removing dangerous waste from the lab. Instruct all lab staff in strict adherence to policies applying to poisons, heavy metals, carcinogens, and other hazardous wastes.[1]

Outsource large cleaning jobs

Sometimes the task at hand is just too large or too messy to handle and you must call in the professionals. If you haven't already, establish a reliable backup of industry certified cleaning crews. A commercial cleaning contractor can tackle a variety of projects including full facility air duct cleaning, deep carpet cleaning and stain removal, post-remodel and construction cleanup, and mold removal and remediation.[1]

Conduct audits

Lab directors should conduct audits of their department's physical environment to identify safety hazards specific to their lab. Audits do not need to interfere with day-to-day activities, and they should be performed on a regular basis—at least monthly.

Changes can occur in a lab at any time and the implications of change should be recognized, including the movement of instruments, the placement of new equipment, and the movement and/or stocking of new supplies.[1]

UVC disinfection

Ultraviolet (UV) disinfection is a technology that can be a supplemental cleaning measure for laboratories that is environmentally friendly—which is especially nice for those committed to sustainability. UV light is

a form of light invisible to the human eye that exists on the electromagnetic spectrum between X-rays and visible light. We are exposed to low levels of UV light from the sun's rays every day, although much of the UV energy is absorbed by the ozone layer.[4]

The high energy from short wavelength UVC light is absorbed in the cellular RNA and DNA, damaging nucleic acids and preventing microorganisms from infecting and reproducing. This absorption of UVC energy forms new bonds between nucleotides, creating double bonds or "dimers." Dimerization of molecules, particularly thymine, is the most common type of damage incurred by UVC light in microorganisms. Formation of thymine dimers in the DNA of bacteria and viruses prevents replication and inability to infect.[4]

Create a strong lab safety culture

After all is said and done, creating and maintaining a clean, safe, and successful lab boils down to one thing: ***A strong lab safety culture.***

A few key tips to keep in mind:

- Everyone involved in laboratory operations—from the highest administrative position to each and every laboratorian—must be safety minded.
- Safety awareness can become part of everyone's habits only if senior and responsible staff demonstrates a sincere and continuing interest in safety and discusses it repeatedly.
- Over-familiarity with a particular laboratory operation may result in overlooking or underrating its hazards. This attitude can lead to a false sense of security, which frequently results in carelessness.
- Be alert to unsafe conditions and actions and call attention to them so that one can make corrections as soon as possible.
- Every laboratory worker has a basic responsibility to himself/herself and their colleagues to plan and execute laboratory operations in a safe manner.

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The next generation laboratory

How AI and automation are transforming medical science

By Dr. Constantin Kappel

Technology in the laboratory has changed a great deal in a very short time much to the benefit of those working in the environment. Just a few short years ago, a piece of laboratory equipment like a microscope was simply a tool: An extremely sophisticated device capable of providing truly remarkable images, but not in itself capable of providing an answer. Only the scientist using it could do that.

This is no longer the case. As has been seen in countless other sectors from automotive to banking, retail to aerospace, the equipment we use in medical science has evolved beyond being just the picks and shovels—it can support us in unlocking solutions that weren't possible before.

Since I left the world of research and joined Leica Microsystems in 2007, my focus has been on what I believe is now the most important part of any laboratory device: The software that sits behind it. This software can not only improve the quality of imaging, it can process volumes of information that would take a human researcher years to analyze and reveal information that might never otherwise be found.

Alongside natural language processing and generation, image processing is one of the most exciting areas in artificial intelligence (AI)—the full potential of which we are only beginning to realize. AI has the power to transform medical science: Removing some of the biggest research bottlenecks, rapidly advancing the speed at which we can analyze biological information, and expediting scientific discoveries in areas like developmental biology, cancer research, neuroscience, and immunology.

Quantitative shift

The problem scientists have always faced in microscopy is the ability to process large volumes of images quickly. It's not quite Google scale of big data, but for a single research project we could be talking about hundreds of thousands of images or more—far too many for a human to evaluate efficiently and comprehensively. As a result, microscopy has always been a very descriptive discipline, without the quantitative rigor that can be more easily found in other areas of laboratory research.

AI is empowering us to automate this process and move toward a far more quantitative approach to image analysis. There are now intelligent systems that can process huge quantities of images and use deep learning techniques to self-improve as they go. The human still needs to provide 'training' data for the neural network to learn the correct mapping. But once trained, the algorithm can analyze huge quantities of image data and detect patterns that would not have been identified otherwise. While we don't expect a move away from 'traditional' biology in the foreseeable future, elements such as human supervision may be made easier, as machines learn how to cluster information automatically or navigate a complex environment on their own.

The impact on scientific progress is going to be significant. Historically, to investigate a particular change in a cancerous cell, for example, you might need to look at 1,000 different proteins. That could potentially be 1,000 different PhD theses by 1,000 different people, with thousands of images viewed by each one. An AI could complete this analysis in less than a day. In addition, because it's working across the piece and learning as it goes, it can identify interaction patterns that the others couldn't possibly hope to have identified when looking at each protein in isolation. As a result, we can expect a dramatic productivity increase, mediated by AI, which will accelerate the pace of discovery by orders of magnitude.

Scientists driving change

Companies like Leica Microsystems are investing heavily in AI and automation technologies because we believe that this is going to be indispensable in the future. However, it's the scientists and researchers that are driving this change by pushing existing microscopy technology to the very edge of what's possible.

There is currently a major trend toward live samples, especially in areas like immunology and the study of infectious diseases. Model organisms enable you to see biological changes in real time—understanding how an organism reacts to a virus, or how multiple infections affect the organism differently when introduced simultaneously.

One of the big areas of AI development and investment has been in improving image quality for model organisms, tissue sections, and 3D cell cultures like organoids. Using techniques like computational clearing, it's now possible to use camera-based fluorescence microscopes to capture images of thick samples without the out-of-focus blur that made this method previously unviable. Coupled with AI-driven image processing, this vastly increases the information gained from images that can be captured and interpreted in a short space of time.

In the past this has raised concerns about image validation, with some in the scientific community questioning whether images that have been 'processed' in this way can be interpreted quantitatively. But we're starting to see this skepticism reducing as researchers begin to realize that slight imperfections introduced by the physics of the image acquisition itself can be reversed by AI. While the notion of software becoming an integral part of this acquisition process requires a good deal of rethinking, the upside is enormous. Being able to push microscopy over these entrenched boundaries leads to a paradigm shift away from the focus on the 'raw image,' and toward the microscope as a source of quantitative information.

Changing skill sets

It's not just mindsets but skill sets that are set to experience a shift. More and more we're starting to see those with skills you'd associate more with Google or Facebook—coding, engineering, data science—showing interest in medical science as the exciting possibilities that AI and automation bring to this sector make it increasingly attractive for those with a software engineering background.

Does this mean fewer opportunities for more traditional biologists? Actually, the opposite. The rise of AI will be liberating for scientists and researchers who often find themselves mired in tedious and time-consuming tasks in the laboratory. Technology is finally reaching the level of maturity where these tasks can be automated. Leica

continued on page 35

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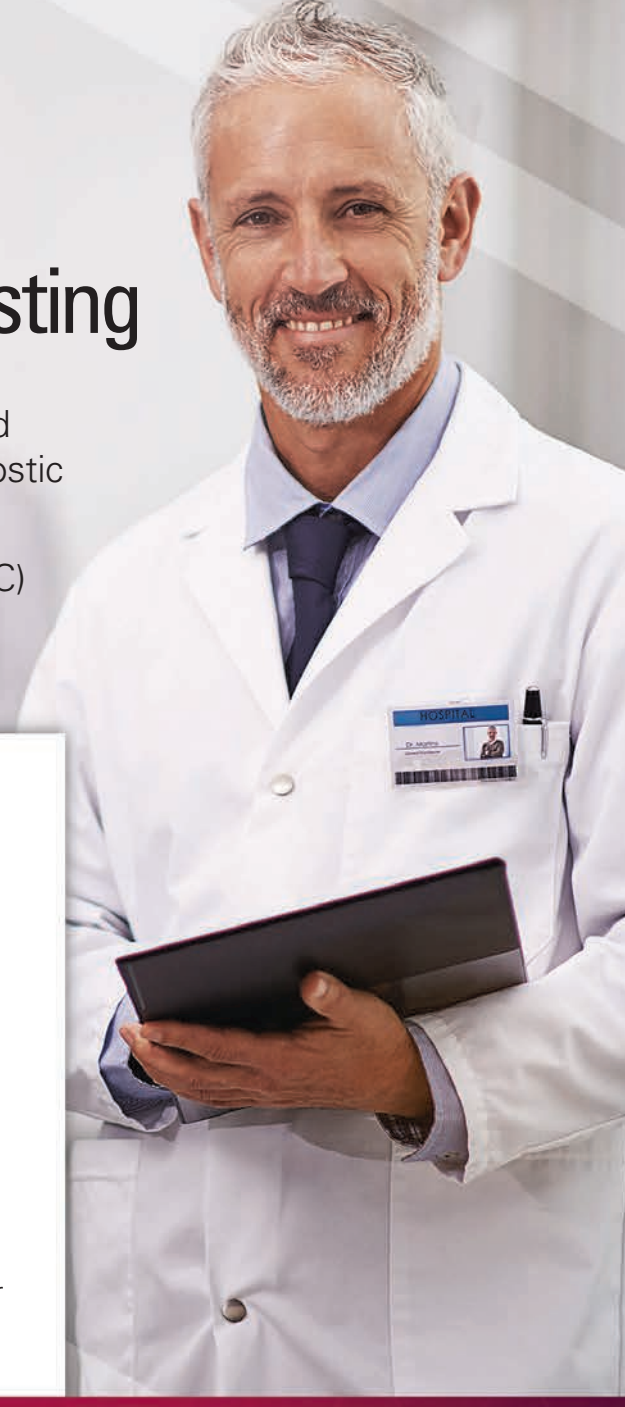

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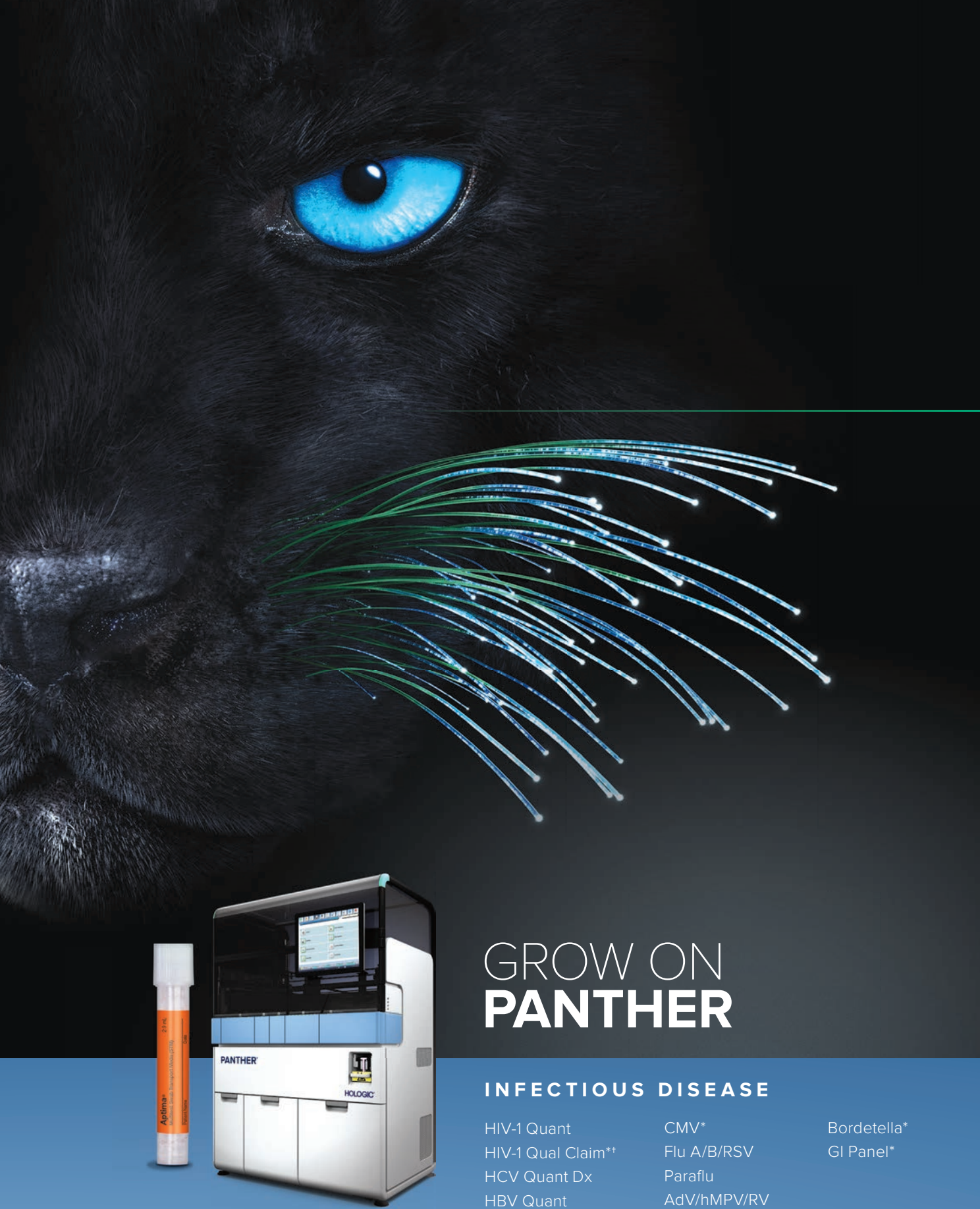

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FDA Clearance of Aptima® Vaginitis Molecular Assays Ushers in a New Era of Comprehensive and Objective Diagnostic Testing for Vaginitis

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

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

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

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

Hologic provides testing for cervical cancer and the detection of most STIs, including chlamydia, gonorrhea, *Mycoplasma genitalium*, trichomoniasis, HIV, HPV and Hepatitis B and C. All these assays run on the fully automated Panther® system. In addition, the Aptima® Multitest Swab Specimen Collection Kit, enables healthcare providers to test up to 7 disease states and infections, including BV, *Candida species*, *Candida glabrata*, trichomoniasis, chlamydia, gonorrhea and *Mycoplasma genitalium*. The Aptima "orange vial" and Aptima assays are run on the Panther system. Hologic's Panther and Panther Fusion® systems now offer 16 FDA-cleared assays that detect more than 20 pathogens.

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

Aptima® BV Assay

Aptima® CV/TV Assay

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continued from page 30

Microsystems has an automated research assistant in our Personal AUtomated Lab Assistant (PAULA) system. Now we're looking at how we can deploy this technology for microscopy, in a device that could look at an image of a sample on a regular basis and automate a response when there are changes—all without ongoing human intervention. It's not about cutting out the experts. It's about freeing up experts to do more value-adding tasks and empowering them to use AI to do what a human would never be able to do. **Figure 1** and **Figure 2** are two examples of images with computational clearing.

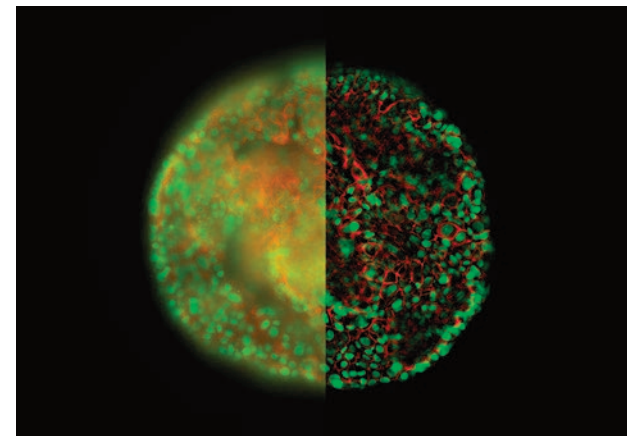


Figure 1. HeLa cell spheroid stained with Alexa Fluor 568 Phalloidin (Actin) and YOYO 1 iodide (Nucleus). Acquired with a standard wide field fluorescence microscope (left half) and an exposure of the same sample taken with a THUNDER imager (right half).

The age of AI

The Human Protein Atlas is a Swedish-based initiative aimed at mapping all human proteins in cells, tissues and organs. All the data in the knowledge resource is open access to allow anyone to pursue exploration of the human proteome. One of the finest examples of AI best practice in action is the work of Emma Lundberg's SciLifeLab on the Human Protein Atlas. A decade's worth of invaluable work, this project has specifically stained virtually every protein in vertebrate cells and imaged where they go with a microscope. Now, we have a colossal bank of images that we can begin to analyze with deep learning techniques to determine patterns in subcellular localization of proteins.

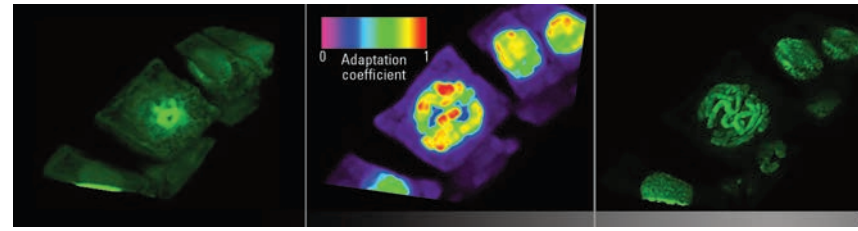
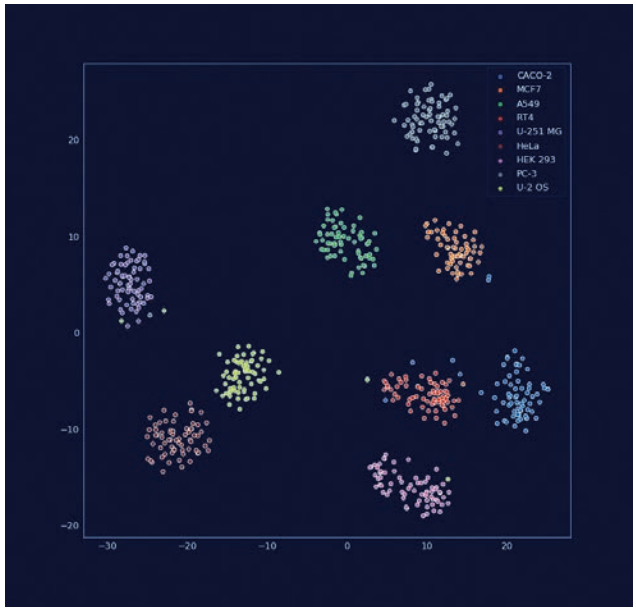


Figure 2. The LIGHTNING detection system for image information extraction ensures the clear and unobstructed view of the relevant information. LIGHTNING works with a decision mask (middle) that takes individual volume segments into account which is remarkable superior to a global processing.

Leica Microsystems recently sponsored a competition through Kaggle[1] to create an algorithm to sort images into 28 classes, each showing different organelles of the cell. Data scientists comprised of 2,172 teams worldwide took on the challenge of predicting where a protein has gone in the cell with only an image as a cue. This task is particularly tricky as some proteins go to multiple places at the same time and some of those patterns are very rare. To succeed the data scientists had to search for independent data on the web to complement the competition data, use models pre-trained on millions of photographs, and fine-tune them to recognize microscopy images or to exploit techniques borrowed from facial recognition. Endeavors like this will help us to understand the role of proteins in health and disease on the level of individual cells.



Classification of adherent cell lines in fluorescence microscopy using a neural network classifier. This figure shows clusters of image features (i.e. patterns) detected by the network superimposed with ground-truth knowledge of the nature of cell lines (cell line names shown in legend). The network was trained using a subset of data from the Human Protein Atlas.

This is where we as an industry need to be focused in this new era of technological advancement. By no means are we seeing the end to traditional biology; we are seeing biology about to be immeasurably enhanced by nascent but fast-developing techniques in AI and automation. Yes, there are still unknowns and we need continued investment in these areas to realize their full potential. But everyone needs to acknowledge that the age of AI is upon us—either we embrace it now, or we miss the chance to take advantage of a world of new possibilities.

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Dr. Constantin Kappel joined **Leica Microsystems** in 2007. His roles included technical sales and product management of confocal microscopy, before shifting his focus toward machine learning and AI in microscopy.

Automation in action in the blood bank

By Bob Stowers

For Newton Medical Center, a 103-bed, not-for-profit facility serving a rural community of about 60,000 people in and around Wichita, Kansas, the philosophy of continuous improvement applies to every facet of healthcare delivery. That vision, which was articulated by the highest level of leadership, started with a seemingly simple organizational strategic goal—reducing paper use, storage, and maximizing full-time employees' time. This vision ultimately led to automation across more laboratory functions, including the transfusion medicine department, to help drive positive change at every level.

It was a bit of an unprecedented move. Core labs have been early adopters of automation, taking advantage of the time and cost savings it offers in accelerating throughput for screenings and sample management. Clinical labs gain real benefits when workflow is automated, streamlined, and standardized using the right solutions. However, blood bankers traditionally (and rightly so) focus primarily on safety and have been more hesitant to automate.

Benefits of automation

Now, more hospital decision makers are recognizing the benefits of automation in transfusion medicine, as enhanced standardization and result reproducibility help to optimize staff time and skills.

For Newton Medical Center's lab, which conducts 1.2 million laboratory tests and 1,100 transfusions annually, the journey toward achieving meaningful improvements through automation took 10 years. Creating a paperless system using electronic health records (EHRs) and rules was just the beginning. Management looked to automation to reach all lab goals, which included:

- Improving specimen and operator workflows,
- reducing risk and random error potential,
- reducing variation and total time for test results, and
- increasing employee productivity and satisfaction.

When Newton Medical Center undertook the effort, blood bank automation was a relatively new concept. According to Aaron Hurst, a seasoned laboratory supervisor of quality systems, the shift required a significant change—not just to day-to-day tasks but to the mindset and culture of the entire staff.

"Implementing a culture change involved sharing the plan on the supervisory level, which then helped champion the cause with the nurses who would be implementing the new process," he said.

Over a six-week period, Hurst took the time to explain the advantages, showing nursing teams how the new process would make their jobs easier. He identified key goals for the blood bank operations:

- Reducing waste and the potential for errors,
- optimizing blood product utilization,
- addressing an aging and shrinking blood bank workforce,
- improving efficiency, and
- improving transfusion services on a 24/7 basis.

The administration's vision set the direction to create a paperless system in the lab, with all blood product placed into an electronic inventory and unit retypes automatically ordered. This process change drove a new culture, with provider orders following EHRs blood transfusion rules. The staff was now able to view all orders on mobile handhelds and to monitor key tasks and samples using tracking boards. The engagement with nursing administration continued, with ongoing dialogue and once-a-shift huddles focused on the advantages of implementation.

Newton Medical Center

Other changes were introduced to protect patient safety, a paramount concern for Newton Medical Center. In blood banking, patient history is critical to avoid administrative errors. Checking and answering questions about patient history is routine, with patients having no blood type history automatically added to a blood type confirmation order.

But while many blood banks still write labels, Newton Medical Center automated the process by enabling positive patient identification (PPID), with staff members printing labels for scannable wristbands at the bedside. The labels included one unique barcode for the blood bank wristband and another for the blood bank tube, with a barcoded lock combination code assigned to each specimen. The introduction of PPID increased productivity by 12 percent for the entire lab and reduced turnaround time (TAT) by nine minutes for all blood draws.

Integrating an analyzer

Effectively integrating an analyzer into the laboratory introduced significant efficiencies. Newton Medical Center wanted an analyzer that was bidirectional, offering two-way communication with the LIS for a standardized,

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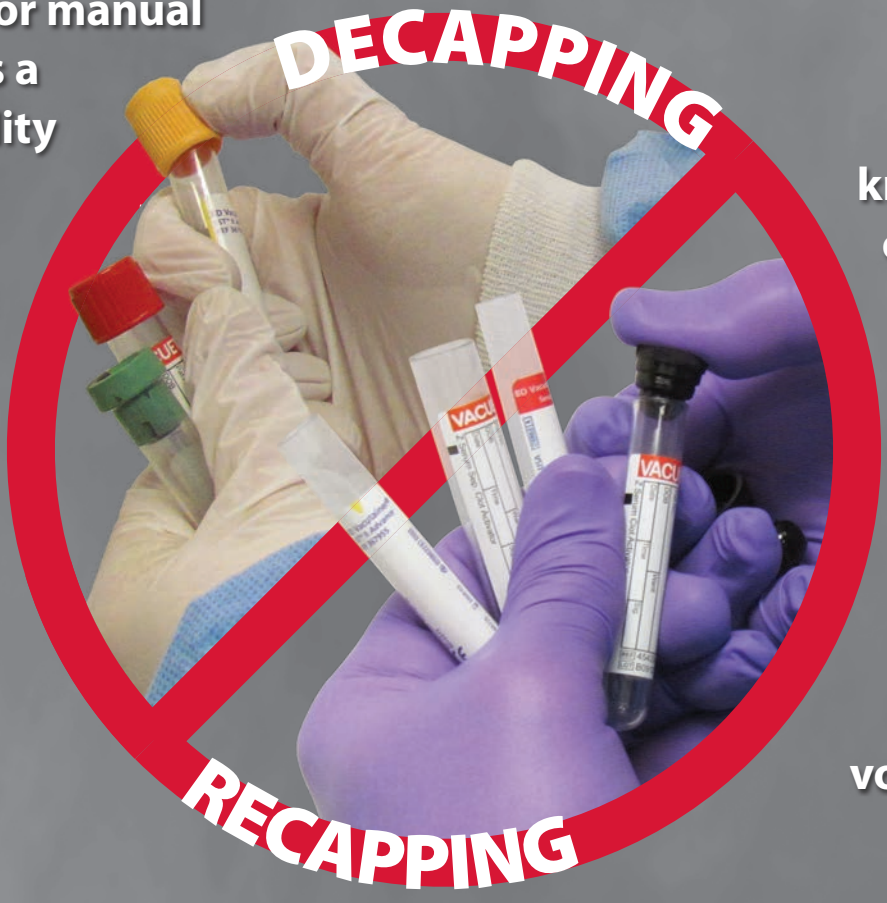

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flexible process, and a seamless flow of information. The system went beyond middleware by bridging the gap between instruments and hospital networks to operate as a powerful interface and efficiently communicate patient information to and from instruments and practitioners.

The system's predictable TAT benefitted patients, staff, and clinicians. Besides improving workflow, the analyzer offered traceability features, producing the documentation needed for accreditation and offering proof that the hospital was delivering high-quality service. Proactive and predictive monitoring afforded reliable system uptime.

Newton Medical Center recognized the value of automating more of their complex tests. The analyzer they chose utilizes advanced software to automate a large menu, allowing laboratory technicians to effectively manage both the blood bank and the specimen processing area while helping to cover automated and manual loops.

This innovative approach can serve as a model for other labs, many of which automate only basic tests and screens while assigning a highly skilled staff member to handle time-intensive complex tests manually. Effective full menu automation via the right analyzer can benefit every lab, even those that manage a small percentage of complex tests. Data management and performance metrics while automating and standardizing lab processes offers operational control. Decreased hands-on time, simpler skill level requirements, and streamlined operations optimize lab resources. Automation yields trusted results by elevating quality, increasing safety, and ensuring greater compliance.

Results

With these and many other changes, Newton Medical Center saw significant positive results. For example, risks for critical errors in processing and documentation were reduced from 164 to two, or by 99.8 percent. The two remaining risks were 1) the manual process of unit selection/assignment, and 2) nursing staff members opting to bypass the mechanical barrier.

Blood product utilization was also down by 34 percent, with a 79.8 percent reduction in units returned to the supplier. Previously, the standard process was to order two units of blood, which were not always needed. Now, orders are for a single unit followed by a reassessment, with more ordered only if necessary. The hospital's analysis shows that 38 percent of transfusions require a single unit.

The process changes lowered the cost per blood product by $151.71, saving $1.97 million from 2008 to 3Q 2015. The method changed reduced cost per blood product by $51.27, with the total cost per unit given at $202.98, representing a savings of $761,000 from 4Q 2015 to 2018.

TAT from blood draw to start time (PPID) was reduced by 12.5 minutes (58 percent), while time for routine types and screens went down 26 minutes (36 percent). The new process optimized staffing, as well, with an 85 percent reduction in transfusion services staff time. All transfusion service staff reported less stress, and competency and proficiency training time decreased by 50 percent.

Automation across tasks

Automation across tasks reduced the risk of human error, while allowing the reallocation of staff for more value-based activity, i.e., diverting cognitive thought to problem-solving, not routine testing. At the outset, the lab had 20 technologists and four dedicated blood bankers. After automation processes were put into place, there were 18 technologists and no specialists, with the lab techs doing blood banking and covering all aspects in the lab. Of the original 20 staff members, one retired and the other was reassigned.

While Newton Medical Center's initial focus was on transforming the facility's blood bank processes, it also used automation to make improvements in the core laboratory testing functions. Those improvements included incorporating a discrete testing platform and instituting bar code tracking from start to finish. The lab also automated testing and built standardization into the laboratory information system (LIS).

The staff played a crucial role, with its support optimized using a computerized rule-out assist for antibody identification, on-board analyzer prompts, and remote access. The laboratory's policy and procedures were also computerized for quick access and consistency. Altogether, these improvements resulted in a 40 percent increase in lab testing capacity.

Potential future improvements to the hospital's chemistry functions focus on layout, identification, and mitigation of hidden costs, flexibility for future expansion, and growth and resource utilization that minimizes space, staff, and capital resources for 80 percent of lab testing.

In terms of optimizing operator process flow, factors such as distance for med techs to accomplish tasks, required waste, and time spent could all be improved with the right automation solution.

Change yields big benefits

The decade-long transformation for Newton Medical Center reaped tremendous rewards. According to Hurst, the keys to successful implementation were:

- A clear vision from leadership,
- a focus on opportunities and advantages for patients, the nursing team, and the laboratory and,
- cultivating a culture of continuous improvement.

"Looking back over the past 10 years, we learned that change happens when leadership sets a clear vision," Hurst said. "Although change may be challenging at first, the focus should be on the benefits."

And a culture of continuous improvement involves embracing ongoing change.

"We make two to three changes every month in our lab to benefit patients or improve productivity," Hurst said. So, for Newton Medical Center, the automation journey continues.

Bob Stowers, serves as head of the Transfusion Medicine Product Portfolio at **Ortho Clinical Diagnostics**. Stowers joined Ortho in 2009 and has held key positions in the company's U.S. and global commercial organizations. He holds a BS in Clinical Laboratory Science from the University of Wisconsin-Madison.

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SIEMENS Healthineers

Jumping genes: Alu elements in human disease

By John Brunstein, PhD

There are probably few—if any—readers of this for whom the name Barbara McClintock doesn't ring a bell. While all Nobel Prize laurates gain widespread recognition, in her case it was compounded by the uphill battle she'd faced for acceptance of her work. A cytogeneticist working on corn as a model system, she had come to the conclusion that not all genes were static fixed loci at defined points in the genome. To say that her conclusion there were "jumping genes,"—coding DNA elements capable of moving from one chromosomal location to another—was met with generalized disbelief is a polite understatement. Time and weight of data proved her right and her 1983 Nobel in Physiology or Medicine, at the age of 81, was as much a testament to her perseverance as it was to good science.

The DNA features she discovered are properly referred to as transposable elements or transposons. Structurally, they share a number of features similar to some types of viruses (retroviruses) and can in a way be thought of as akin to a virus, in that they can replicate themselves semi-autonomously by use of host cell machinery. Unlike true viruses though, transposons don't leave the cell, and progeny simply move to a new genomic location where they take up residence. They are in effect the simplest example of what's termed "the selfish gene," a postulate that genetic elements merely seek to replicate themselves. While most have "chosen" to do this through cooperative association with other genes to create viable replicating organisms, transposons do this purely on their own behalf and more as a parasite on the host cell than as a productive component of a larger whole. Our interest in them today stems first from the fact that they're not just limited to existing in corn but are in fact found in most organisms including humans, and second with regard to this rogue, every-gene-for-itself intracellular lifestyle.

LINES and SINES

Humans don't just have one type of transposon—there's actually a number of types which are loosely grouped based on their physical size into Long Interspersed Elements (LINES) and Short Interspersed Elements (SINES). As you'd expect, the larger these are physically, the more genetic information they can code for. The one known as LINE-1 at a size of ~6000 base pairs codes for two open reading frames (regions that can be transcribed to mRNA then translated to protein). One of these proteins has RNA binding activity but an unclear biological function; the second has endonuclease (DNA cutting) and reverse transcription (generation of DNA sequences based on RNA templates). Essentially after a LINE-1 element is transcribed (driven in part by transcription factor binding sites in its 5' end), the expressed second protein makes cuts in the host DNA via its endonuclease function. It then makes a DNA copy of the LINE-1 full transcript via its reverse transcriptase function. This DNA copy gets inserted into the cut host genome and host cell DNA repair machinery ligates this into place. The host chromosome has now gained a new copy of LINE-1 and every subsequent cellular replication cycle replicates this as part of its "normal, innate" nuclear DNA. This is considered autonomous retrotransposition, as LINE-1 supplies its own key enzyme functions for the process. Although the process itself occurs rarely, it's easy to see how over long biological timescales this can lead to accumulation of multiple replicate copies of the LINE-1 element. LINE-1 is thought to be the only fully autonomous transposable element of the human genome, and it's proven an effective biological strategy with nearly 17 percent of the human genome made up of this sequence (roughly 170,000 copies per cell)!

Our focus today, however, is on a SINE, and in particular the one (really, the one family) known as Alu elements. Named after a restriction endonuclease site (*Alu I*) they characteristically contain, they're much shorter than LINE-1, at only about 280 base pairs long. This means they haven't got much coding capacity of their own beyond some transcriptional start signals and are thus not autonomous. In fact, Alu elements require both cellular factors and the second protein product of LINE-1 for their replication, being in a sense parasitic both to the host cell and to the LINE-1 elements. This parasite of a parasite approach is apparently an even more effective selfish gene strategy, as Alu elements make up about 11 percent of the human genome (about 2 million copies per cell).

Biological impacts

Not surprisingly, there are some very real impacts from having so many genetic freeloaders in our genome—and unstable ones at that. Particularly through the transcriptional and other genetic signals they carry, an Alu element may influence many aspects of proximal host gene expression including basal gene expression levels, intron splicing and polyadenylation, and RNA editing. Evolutionary pressure on the cell as a whole would generally lead to host genome adaptation to these to accommodate, compensate, or perhaps in some cases even derive a benefit from impact of a particular Alu element in context. Such host adaptations take time however, and clinical pathologies can arise when a novel Alu transposition event occurs leading to an abrupt genetic change at what's essentially a random loci—the insertion of a new Alu copy.

Some things to know about this are that since it's a transcription (RNA) initiated replication process, replication is error prone. Unlike DNA polymerases, many of which contain what's called a proofreading function whereby each

nucleotide added to the nascent template copy are subjected to a second look to confirm a true complementary match as opposed to one based on a transient tautomeric shift, RNA polymerases are biologically optimized for speed and processivity. Once a nucleotide is added to a growing transcript the polymerase rushes ahead to the next base. Since a proportion of all of the bases making up DNA and RNA can and do exist in tautomeric forms where there are brief rearrangements of hydrogens and double bonds compared to the forms we see in textbooks, RNA transcripts tend to have low but significant mis-copy rates from their DNA template.

I sense some readers suddenly panicking, why if this is so, aren't we all a mess due to errors in regular mRNA transcripts? It's because we make multiple copies of transcripts from active genes, and on average they're OK. Whether they're OK or not, they have a short life before degradation and replacement with new transcripts as needed. Rare sporadic errors in mRNAs are thus not likely to be of significance.

If, however you now take this not-quite-perfect RNA copy of a DNA, then reverse transcribe it back into DNA for long term propagation, you've now fixed that genetic change for the long term. A consequence of this is that only a small proportion of the Alu elements in our genes are actually competent to replicate and insert new copies of themselves. In all, it's estimated that there's only about one novel Alu insertion. That's a very good thing, because these insertional events are potentially problematic.

Recall that about one percent or a bit more of the human genome is coding for host proteins (roughly 21,000 genes). If we go making cuts and stuffing unrelated DNA willy-nilly in the genome, it stands to reason that about one percent of these would be in genes and the result would be an insertional inactivation of the gene. Because the Alu element carries transcriptional signals and potentially other regulatory elements, it's also quite possible for it to exert unwanted influences on gene expression of things it's merely near to. In either case the result is dysregulation of a gene or genes, almost certainly with deleterious results.

Another aside, exactly this process is used in some model organisms to identify genes relating to a phenotypic trait. Simplistically, transposons endogenous to the organism can be encouraged to activate, and progeny organisms with changes to phenotype of interest are examined for any new transposon insertion sites on the assumption they may be in or near genes related to the phenotype. It's called transposon tagging.

Besides novel retrotransposition events causing insertional inactivation, the high total number of Alu elements in and of itself can lead to other genetic problems. Specifically, these local islands of sequence similarity can be points for unequal homologous recombination events, where the chromosomal context around each Alu element isn't the same. These can occur both extrachromosomally (leading to exchange of nonhomologous chromosomal segments) and intrachromosomally (where they tend to lead to deletion or duplication of regions, depending on whether the two Alu elements are in same or inverse polarity orientations).

Real-life examples

So now that we've covered the theory that there really are mobile genetic elements in humans, they sometimes activate and insert new copies of themselves, and that can have bad consequences for the cell—what about real life examples? Do people show up in clinical settings with problems attributable to novel Alu insertions? Absolutely; as far back as 1999[1] it was estimated that novel Alu insertions were detectable in approximately one of every 200 live births, and were responsible for 0.1 percent of known genetic disorders. Particular reports from the literature include spontaneous occurrences of hemophilia;[2-4] Apert syndrome;[5] neurofibromatosis Type 1;[6] and optic atrophy.[7] Readers looking for a longer list are directed to a review from 2012 and its references, listed as reference eight below.

Clinical presentations relating to Alu-influenced recombinational events are likely harder to identify with certainty than ones from insertional events, but cases have been reported (see reference nine for an example) and are likely more frequent than we know.

From a treatment perspective, each Alu induced mutation—insertional or recombinational—is unique and treatment (if any) would likely have to relate to direct biochemical intervention in impacted pathway(s) where possible, or perhaps genetic engineering tools as envisioned in other innate genetic disorders. They therefore remain for the clinician rather a curiosity than a type of condition with a common treatment or prevention—but likely one of not insignificant frequency at the root of novel genetic presentation.

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

Does reagent quality play a role in reproducibility of experimental data?

By Joanne Gibson, PhD

Currently, there is a great deal of (necessary) attention focused on the lack of reproducibility of scientific studies, often caused by bias due to small sample size, cherry picking data, and selective reporting. Confidence in published research comes with independent replication of findings. The impact of these findings on the scientific community can be significant—particularly as downstream research undertakings can potentially lead to avenues for innovation of diagnostics, or disease treatments, for example.

The consequence of irreproducible results in the clinical setting can—at a minimum—require retesting of patients. At worst, it can yield inaccurate patient results, with potentially life-threatening consequences.

Reagent quality is key

While many variables affect the reproducibility of experimental data, reagent quality should be considered one of the most fundamental requirements.

In the field of life sciences, a high-quality reagent is one that generates reproducible results in an otherwise identical experiment. Reagent production in Good Manufacturing Practice (GMP) facilities ensures a standard that minimizes variation during assay or drug development and, ultimately, an introduction into the clinical setting. It covers all aspects of production, including the location, starting resources, equipment, and staff training.

However, manufacturers of life science reagents more often supply products for "research use only" in academic settings, contract research organizations (CROs), pharmaceutical companies, and other biotechnology companies. In these instances, reagent quality is just as critical, since reproducibility of results can underpin downstream research efforts. Research findings are often scrutinized in peer-reviewed journals, and the researcher's reputation and the lasting significance of his or her findings rests on the reproducibility of the protocols in an entirely independent setting, by an independent researcher, using independent equipment.

Thus, choosing a reagent that performs reliably, particularly in more sensitive applications, is a critical first step toward improving the reproducibility of research. Considerations such as manufacturing processes, quality control testing, sourcing of raw materials, packaging, and shipping all contribute to the development of a high-quality product.

In 1978, New England Biolabs (NEB) produced a recombinant protein for research purposes, which enables streamlined consistency of product quality. The cloning of restriction endonucleases and many other enzymes for use in recombinant DNA technologies has enabled the implementation of stringent control measures. Native bacterial strains often do not produce sufficient amounts of the enzyme-of-interest. Additionally, other enzymes may be co-purified in the final product, and there may be impurities in the native strain, such as non-specific endo- and exo-nucleases. We can address these challenges by choosing a specific expression vector and host strain for consistent expression and production of recombinant enzymes in a tightly controlled system. Not only can impurities—such as DNases, RNases, or phosphatases—be reduced, but also yields are higher, resulting in greater product consistency and less lot-to-lot variation.

Once a product is manufactured, enzyme quality is continually monitored through a set of quality controls (QCs) that address specific attributes, such as concentration, purity, functionality, and reliability. Are there contaminants (i.e., DNase or proteins in DNA products)? Does the enzyme maintain consistent activity over an extended period of time?

QCs also need to be continually reassessed and improved as technologies improve and sensitivities increase. For example, a contaminant that was previously undetectable may now be identified and measured due to the rapid technological advances of sequencing instruments.

Product application in QC

Product application is another factor to consider when developing and reassessing a set of QCs. In fact, a QC test that was developed many years ago may no longer be sensitive enough to satisfy today's molecular diagnostic applications. It is therefore important to continually refine QC practices when developing and maintaining reagents through their lifecycle. For example, residual *E.coli* DNA contamination from a host strain might not affect a targeted qPCR experiment and can be identified and ignored in many sequencing applications. But it needs to be removed entirely for a pathogenic *E.coli* test.

Quality measures sometimes require the complete rethinking of production methods—for example, in cases such as the re-engineering of clones to produce more product or eliminate targeted background contaminants (proteases) in a particular strain, or the development of different fermentation processes. Sourcing materials from outside vendors can introduce another variable in the process of reagent production. It is thus vitally important that vendors have in place a sound quality management system.

Several platform tests from NEB that cover multiple reagents have been developed or refined as part of a quality improvement effort that helps to bring about best practices. The analyses include qPCR, RNase detection, capillary electrophoresis (CE) exonuclease detection, CE phosphatase detection, CE polymerase detection, protein purity, protein concentration, and identification by mass spectrometry.

The use of mass spectrometry for the detection and monitoring of mutations caused by toxic overexpression of a recombinant product is an essential layer of information for the maintenance of a high-quality product, regardless of whether the mutation affects the activity of the end-product. Further, customers who are developing a platform for a regulated market are supplied with three independent lots to validate their test with NEB products and demonstrate reproducible results.

continued on page 44

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Linearity FLQ Thyroid for Roche Systems Total T3, Total T4, TSH, Free T3, Free T4	**Size** 10 x 2 mL **Order Number** **K926M-5** **Open Vial Stability** 7 days @ 2-8˚C

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Case study: QC practices when manufacturing T4 DNA Ligase

As an example, NEB considers all these factors when it manufactures its T4 DNA Ligase. Ligases are an important tool in molecular biology that facilitate the joining of DNA strands for the construction of recombinant DNA. NEB's ligase production methodologies incorporate extensive QCs that include testing for:

- Endonuclease activity using agarose gel electrophoresis to examine nicking of supercoiled DNA
- Exonuclease activity by assessing the release of radioactive nucleotides following incubation of ligase with radiolabeled single- and double-stranded DNA
- Non-specific DNase activity, which is evaluated by agarose gel electrophoresis following incubation with a DNA substrate
- Protein purity using SDS-PAGE to compare contaminating protein bands to the protein-of-interest
- RNase activity, which is assessed by gel electrophoresis following incubation (for two and 16 hours) with an RNA substrate
- Functional testing, which encompasses blunt- and cohesive-end ligation and subsequent transformation efficiency

The extreme purity of NEB's T4 DNA Ligase can be seen in **Figure 1**, where equivalent amounts of protein from alternate suppliers were analyzed side-by-side, and in **Figure 2**, where T4 DNA ligase samples from different suppliers were examined for contaminating nucleases.

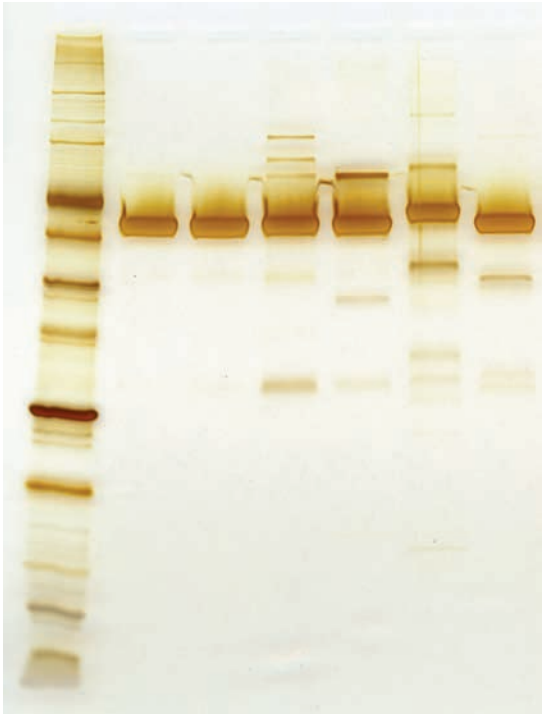

Figure 1. Extreme purity with NEB's T4 DNA Ligase. Equivalent amounts of protein were loaded, and silver stained using SilverXpress. Marker M is NEB's Broad Range Protein Marker.

continued on page 46

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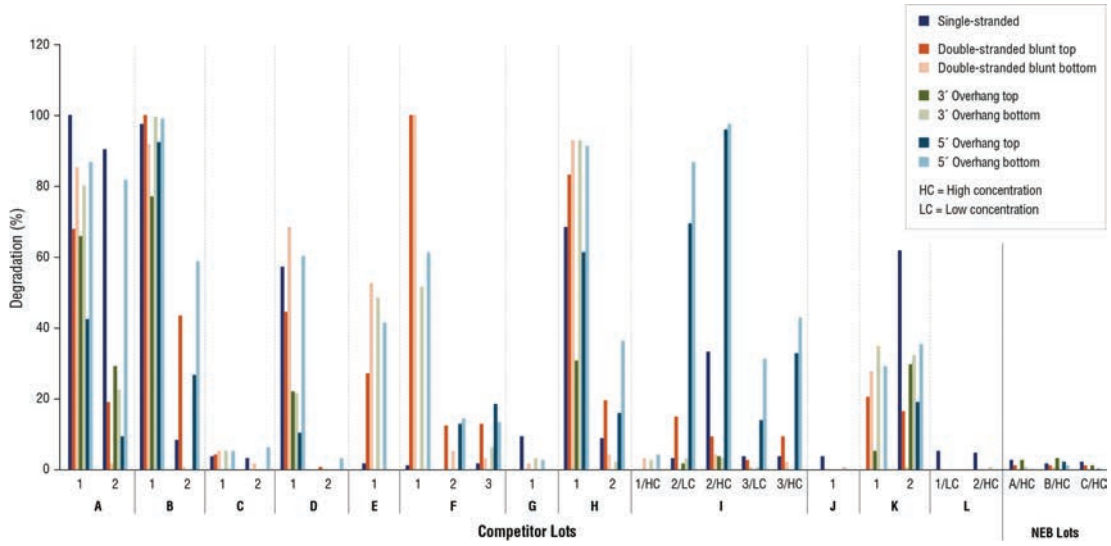


Figure 2. T4 DNA Ligase Nuclease Contamination Study. T4 DNA Ligase from multiple suppliers was tested in reactions containing a fluorescent labeled single stranded, double stranded blunt, 3′overhang or 5′ overhang containing oligonucleotides. The percent degradation by contaminating nucleases is determined by capillary electrophoresis and peak analysis. The resolution is at the single nucleotide level.

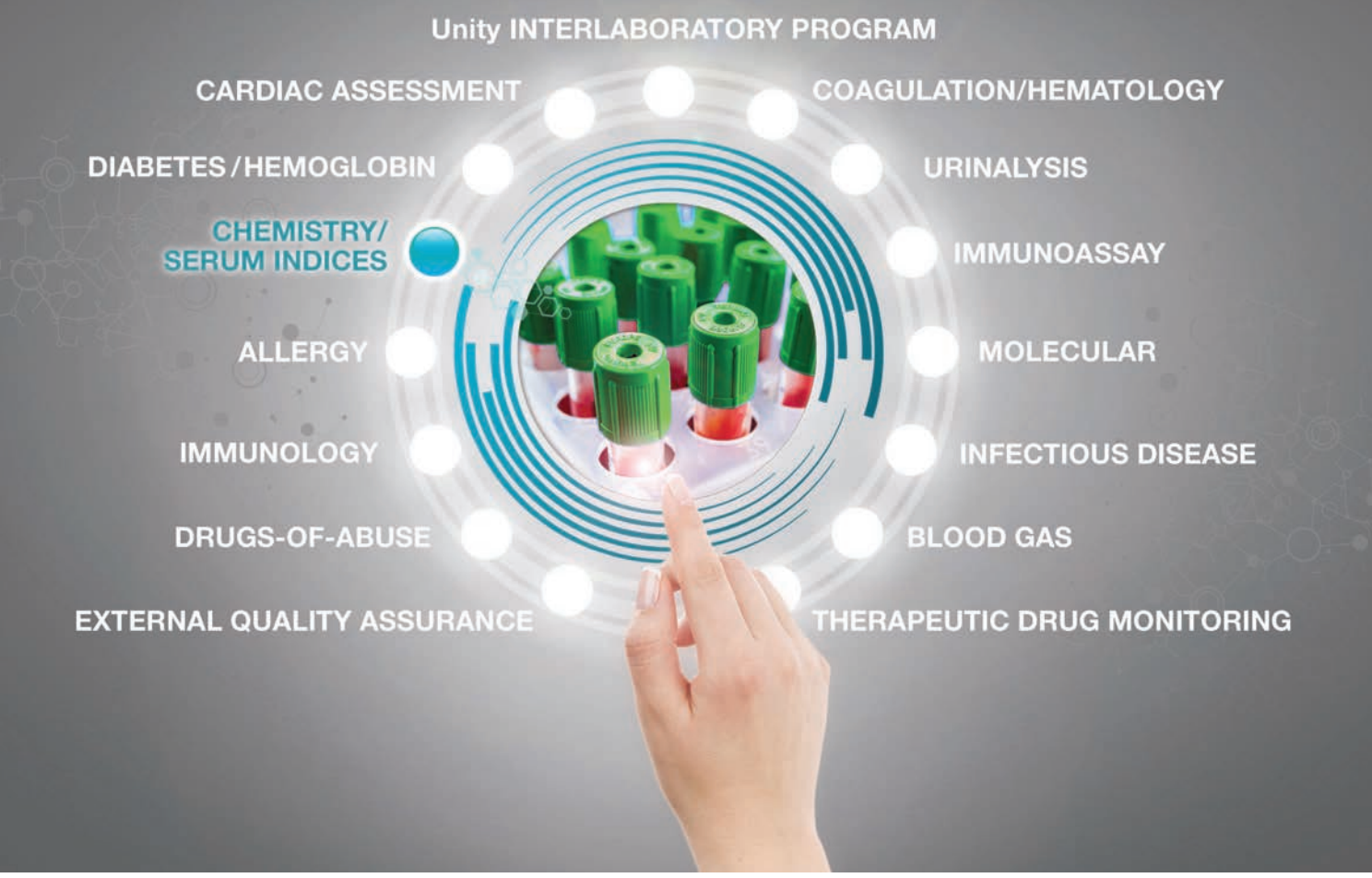
The importance of corporate culture

Finally, corporate culture is paramount to the efforts to provide quality products. An overarching focus on customers and their needs, coupled with a commitment to achieving and maintaining the highest possible quality—from product inception through development, production, packaging, and shipping protocols—ensures the optimal activity and consistency of the product. A company that continually incorporates feedback from customers is also in a better position to rectify any product shortcomings. A reasonable expectation of the consumer is a level of transparency regarding QCs, exceptional technical support, and timely response to feedback.

Life science research is demanding, and many factors can hinder scientific advancements. Furthermore, publications and new attention to erroneous, or irreproducible findings erode the credibility of research. The responsibility of life science reagent providers in contributing to reliable, trustworthy research is to provide the scientific community with the highest quality products so that this variable is taken out of the equation at the outset.

Joanne Gibson, PhD, is a Technical Writer at **New England Biolabs, Inc**. Joanne completed a PhD at the University of Sydney, Australia in 2005, and then held positions as a Postdoctoral Fellow & Associate at Massachusetts Institute of Technology and an Editor at American Journal Experts, before joining Biolabs in 2018.

MONITOR AN INSTRUMENT'S ABILITY TO DETECT PRE-ANALYTICAL INTERFERENCES



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[1]Plebani M. The detection and prevention of errors in laboratory medicine. Ann Clin Biochem 2010; 47:101-10. http://dx.doi.org/10.1258/acb.2009.009222.

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BIO-RAD

A self-reflection on recruitment and retention

By Carleen Van Siclen, MS, MT (ASCP)CM, TS (ABB)

For decades we have heard that the laboratory personnel shortage is coming. Today that shortage seems more evident than ever before. We have read about the main reasons contributing to the personnel shortage including the closure of laboratory training programs, increased number of retiring laboratorians, and decreased number of individuals entering our profession. Now we need to ask ourselves, "How can we be a part of the solution?" For me, it's all about recruitment and retention.

Recruitment

How old were you when you were first asked the question, "What do you want to be when you grow up?" You may have answered actor, musician, teacher, athlete, doctor, firefighter, or even police officer. Regardless of how you answered, surely it was a career that you had knowledge of. The truth is that our profession—clinical laboratorians—has an identity crisis. We know who we are and what we do, but it's a big secret to the general public. Don't you think that it's about time to let the cat out of the bag?

Never too young

Is there an age that is too young to start career exploration? Cahill and Furey's research concluded that there is value and benefit to children as young as three to eight years old learning about potential careers.[1] Pre-school and elementary school aged children identify with workers and careers in their neighborhood and community. They are curious about exploring what adults do for work. One of my favorite recruiting activities for elementary school is reading the book titled, *I Had a Lab Test* by Joyce McCreary, MT(ASCP). It's fun to get dressed in scrubs with a white lab coat, gloves, and goggles as I walk into the classroom carrying a biohazard bag filled with a rainbow of vacutainer tubes and a throat culturette swab.

Middle school

More than 5 million Instagram hashtags include the word slime (#slime). It seems as if every middle school aged child loves playing with slime. This is an amazing opportunity to introduce young scientists to *Hands-On Grossology* by Sylvia Branzei.[2] What student doesn't want to participate in really gross science experiments? As an educator, the child in me enjoys creating simulated laboratory specimens such as blood, urine, stool, and vomitus. However, it is even more fun to watch the reaction of these students as each specimen container is opened. That's what you call a real attention getter!

High school

Recruitment activities for high school students include partnering with STEM (Science, Technology, Engineering, and Math) education teachers, medical magnet schools, HOSA (Future Health Professionals, formerly known as Health Occupations Students of America), students, and career immersion programs. Last summer, Mayo Clinic School of Health Sciences offered a Medical Laboratory Science Career Immersion Program in Jacksonville, FL. Twelve diverse high school students spent four days immersed in Transfusion Medicine:

- Day one promoted blood donation awareness. Students were introduced to blood donor facts, including that 4.5 million Americans would die each year without life-saving blood transfusions and that donating one pint could help save three lives.
- On day two, the students toured the Department of Laboratory Medicine and Pathology. Each lab section participated and explained their valuable contribution to a patient's diagnosis.
- Day three was spent at a local community college in the MLT student laboratory where students performed routine ABO and Rh blood typing.
- On day four, the Career Immersion Program concluded with a simulated life-saving blood transfusion.

College-aged youth

How can we get college students interested in the medical laboratory? The National Center for Education Statistics states that approximately 110,000 biological/biomedical science students graduate each year with a Bachelor of Science degree.[3] This is an opportunity to invite college faculty to invest in career exploration by allowing their students to take a tour of our laboratories in lieu of completing their three hour lab class on campus. In Florida, college students majoring in microbiology are surprised to learn that they must complete a laboratory training program in order to work in a clinical microbiology lab due to state licensure. For those interested, explore the opportunity of inviting the student back to spend one day observing each of the specialty areas of the laboratory. It's rewarding to our staff and they take pride in sharing their vital role as an integral part of the healthcare team.

Educational resources

Now that the recruitment phase was successful, let's direct students to readily-available educational resources such as the National Accrediting Agency for Clinical Laboratory Sciences (www.naacls.org) and the American Society for Clinical Laboratory Science's (ASCLS) Education Scientific Assembly's (ESA) Medical Laboratory Education Online Directory (www.ascls.org/careers-ascls/mls-programs-lists). In Florida, the Board of Clinical Laboratory Personnel lists all Florida approved training programs on the Department of Health website. It's then up to the student to find a Medical Laboratory Science program that best fits their needs.

The Mayo Clinic School of Health Science Medical Laboratory Science Program is committed to training undergraduate and post-baccalaureate students in laboratory medicine, quality assurance, and professional practice. Our faculty members promote academic excellence, instill professionalism, and encourage the pursuit of lifelong learning. We strive to retain excellent

students for employment and promotion at Mayo Clinic. Florida-appointed students enrolled in the 4+1 track of the medical science certificate program complete 12 months of didactic courses and clinical laboratory rotations within the Department of Laboratory Medicine and Pathology at Mayo Clinic. Eight months of didactic courses and clinical laboratory rotations are completed at Mayo Clinic's campus in Rochester, Minnesota, and the remaining four months are at Mayo Clinic's campus in Jacksonville. There are more than 3,000 laboratory positions at Mayo Clinic alone and 100 percent of our graduates find employment within three months of graduation. Our program has a three-year average placement rate of 100 percent.

Retention

Now that we have hired the new employee, how do we as managers retain them? Doig and Beck's research on clinical laboratory personnel retention cited salary, work independence, and work appreciation as the most important factors to retaining lab staff.[4,5] All laboratorians want to feel valued and appreciated. Many may think that it starts at the top, however, I would argue that it starts at the bottom with coworkers. The benefits of peer-to-peer praise leads to significantly higher levels of employee performance and engagement, as well as increased customer loyalty and retention.[6] It creates a sense of teamwork within the work unit. It also motivates employees to continue doing their best even when performing routine tasks. It reduces employee turnover because coworkers feel appreciated for their hard work and extra effort. It also adds to an employee's overall job satisfaction and loyalty to the employer. That is why many healthcare facilities invest in formalized employee recognition programs.

Employee recognition programs

You've heard the adage, "People leave managers, not companies," right? A 2018 Gallup data poll revealed that the most memorable recognition comes most often from an employee's manager.[7] Their recommendation is that recognition should be given on a regular basis (weekly) and timely so the employee understands the impact of their recent achievement(s).[5] The Gallup research also revealed that only one in three U.S. employees reported that they had received recognition for their work performance within the last week.[7] How often do you catch your employee doing great work such as catching an error, staying late for shift coverage, or sharing a rare laboratory finding? Do you take the opportunity to thank them in real time? Do you recognize the employee again at your monthly staff meeting or team huddle?

As a manager, do you take the opportunity to share how proud you are of your staff to others within the organization? Appreciation by other healthcare professionals and hospital administrators enables the laboratory staff to feel valued. What is the culture at your institution? Do the pathologists value the medical laboratory scientists? Do they greet each other by name? Do the Department Chair, Medical Director, and Operations Administrator share their appreciation to the staff for embracing workflow changes, validating newly installed equipment, and completing successful inspections? Is staff appreciation given on a regular basis or is it only shared during National Lab Week or Employee Recognition Day? As leaders, we lead by example. It can be as simple as sending out a general email and having lab leadership reply thanking the staff for their valued contributions.

Rothenberg states that job satisfaction is tied to workload, recognition, and salary.[8] Staffing to workload is a hot topic and is an institutional expectation in most healthcare institutions today. The personnel shortage leaves those on the workbench working overtime, double shifts, and with fewer staff. However, the customer's expectation is that the same level of service will be provided, and the same high quality of lab results will be reported as if the lab is fully staffed. As a result, poor working conditions often lead to fatigue, increased error rates, and employee burnout.[9]

The Florida trend

It's estimated that the number of individuals over 65 will double over the next 30 years.[10] Many retirees relocate from the frozen tundra to sunny Florida. As a Floridian, it amazes me to know that there are 919 newcomers to Florida every day.[11] *The Florida Trend* predicts that within the next five years Miami, Fort Lauderdale, and Jacksonville will each have over 1 million residents each.[11] How will the demand for medical laboratory scientist keep pace with the state's population growth? The Florida Department of Health's Board of Clinical Laboratory Personnel reports that there are approximately 18,244 licensees; including 244 directors, 5,534 supervisors, 10,631 technologists, and 1,835 technicians.[12] With estimates that there are only 10,000 MLS graduates per year in the U.S., one must ask themselves, "Has the demand now exceeded the supply in Florida?"

I'll ask my first question again, how can we be part of the solution? For me, it's all about recruitment and retention.

Visit www.mlo-online.com for references.

Carleen Van Siclen, MS, MT (ASCP)CM, TS (ABB), serves as Manager of Laboratory Staff Education and Professional Development at Mayo Clinic in Jacksonville, Florida. Carleen has been a medical laboratory scientist for over 35 years and is board certified by the American Society for Clinical Pathologists (ASCP) and the American Board of Bioanalysis (ABB).

The MARC Program at UTSA

How a Texas university steers young scientists to research careers

By Gail P. Taylor, PhD, J. Aaron Cassill, PhD, and Edwin J. Barea-Rodriguez, PhD

At the University of Texas at San Antonio (UTSA), we have a diverse student population that includes many aspiring scientists. To support these budding researchers, UTSA has been a training site for the federally funded Maximizing Access to Research Careers (MARC) research training program for more than four decades.

Since 1980, we've admitted 250 undergraduate students to enroll in this competitive research-focused track. In this two-year program, our MARC students are immersed in a culture of science as they prepare to complete a biomedical, research-focused higher degree program. UTSA is one of 57 active MARC programs across the country. Our success is always focused on one student at a time. Alumni of the program have gone on to complete graduate research training at leading institutions including Stanford, University of Pennsylvania, UC Berkeley, and Harvard Medical School.

MARC programs vary according to a campus' infrastructure, its student population, and the strategies it uses to prepare its trainees for doctoral program admission. UTSA's MARC program is supported by 40 full-time faculty in the Departments of Biology, Chemistry, Physics, Biomedical Engineering, and Psychology. Our MARC scientists work in the laboratory alongside these nationally recognized researchers for 15 hours per week during the school year. In the first summer, their programs become more intense and they complete 40 hours.

Along with research access, UTSA MARC provides students with a curriculum that stresses scientific integrity,

UTSA MARC Program Activity Schedule

Throughout: Responsible conduct in research training, intramural research, individual PI meetings, annual conference, departmental seminars, individual poster and oral coaching, outreach/broader impact

Friday workshop/Seminar series: Role model, networking and recruiting seminars, technology transfer 101, leadership training, strengths quest, budgeting 101, basics of teaching, summer program orals, three minute thesis competition.

Summer 1	Fall 1	Spring 1-RCPSD-3
MARC JumpStart Summer Program • Why a PhD? • Scientific papers: finding, reading, organizing • Research plan • Introduction to wrting & abstracts • Introduction to IDP • Building a CV • Oral laboratory report • Poster creation and end of summer presentations	**Foundations for PhD program preparation (1 credit)** • Revisit summer topics (late admits) • Scientific culture & cultural capital • Introducing yourself in science • Foundations for future proposals • What happens in grad school and planning • Summer program preparation: facts, apps, and statements • Intro to oral presentations/final orals	**Scientific integrity, communication and critical thinking (1 credit)** • Critically approaching research • Impact of "bad" or incomplete research • Rigor bingo paper analysis • Experimental design, problem solving • Group proposals and presentations • Scientific culture and your culture • 3-minute thesis training
Summer 2	**Fall 2**	**Spring 2-RCPSD-5**
Extramural summer program	**Moving toward the PhD (1 credit)** • Progressive creation of NSF grant application • PhD applications: analyzing schools, PIs, statements, application strategy • Interview skills and mock interviews	**Successful transitions (biweekly meetings)** • Updates and interviews • Academics, mentor choice, professional behavior, survival skills • Networking meetings with former graduates in PhD programs

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oral communication, critical thinking, and the importance of technology transfer. Specifically, we discuss experimental design, problem solving, and practical skills such as three-minute thesis training and how to write winning National Science Foundation (NSF) grant proposals. Our MARC graduates leave the program with a strong curriculum vitae (CV) and experiences that develop scientific rigor, including experience in peer reviews where their research papers get measured against the highest standards.

The National Institutes of Health (NIH) requires all MARC trainees to be full-time students. It also recommends selection of students who are underrepresented in sciences, financially disadvantaged, or have a disability. At UTSA, we serve a large Hispanic and first-generation college student population. We focus on providing our students with extra support such as credited curriculum to develop vision casting/goal setting and independent development plans (IDP). The IDP works in concert with the CV to help trainees plan for careers in science and map out their final two undergraduate years.

The typical undergraduate IDP includes a course schedule and application deadlines, as well as a summer reserved for an extramural research internship, abstract deadlines, dates to attend a professional conference, a GRE timeline, and application deadlines for desired doctoral programs.

At UTSA, we go one step further by having our students prepare for the extremely prestigious National Science Foundation Graduate Research Fellowship due in October of their senior undergraduate year. This past year three of our MARC trainees won this prize.

The NSF Graduate Research Fellowship Program (GRFP) helps ensure the vitality of the human resource base of science and engineering in the United States and reinforces its diversity. The program recognizes and supports outstanding graduate students in NSF-supported science, technology, engineering, and mathematics disciplines who are pursuing research-based master's and doctoral degrees at accredited U.S. institutions.[1]

As the oldest graduate fellowship of its kind, the GRFP has a long history of selecting recipients who achieve high levels of success in their future academic and professional careers. The reputation of the GRFP follows recipients and often helps them become life-long leaders that contribute significantly to both scientific innovation and teaching.[1]

Since 1952, NSF has funded over 50,000 Graduate Research Fellowships out of more than 500,000 applicants. Currently, 42 Fellows have gone on to become Nobel laureates, and more than 450 have become members of the National Academy of Sciences. In addition, the Graduate Research Fellowship Program has a high rate of doctorate degree completion, with more than 70 percent of students completing their doctorates within 11 years.[1]

Due to the comprehensive training that our students receive in research laboratory practice, as well as the PhD application process, during the 2011 to 2016 award period, 67.6 percent of our MARC graduates continued their education to pursue a doctorate degree.

Our program also has an impact on laboratory and ancillary scientific skills by opening the door to engagement in scientific research for most trainees. On a research evaluation, UTSA MARC participants gave the program an overall rating of 4.89 out of 5 on a Likert Scale.

Recent UTSA graduate Robert Trevino said, "I am forever grateful to the MARC program as I do not think I would even have the dreams that I have without the experiences I have had in this program. I am looking forward to a career as a clinical scientist, and I understand that I owe that to the MARC program."

The future of UTSA MARC will change as another NIH-funded program will be adopted. UTSA will transition into the Research Initiative for Scientific Enhancement (RISE; R25) program which will take the best of the MARC curriculum to continue to innovate and improve the pipeline that trains the next generation of scientists and researchers.

REFERENCE

1. NSF Graduate Research Fellowship Program. https://www.nsfgrfp.org/general_resources/about. [Accessed July 10, 2019.]

Gail P. Taylor, PhD, serves as Associate Director for STEM Initiatives for the UTSA College of Sciences. Gail has also been serving as Assistant Program Director and Training Specialist for the UTSA RISE and MARC programs for almost 20 years. She was honored in 2014 with the UTSA President's Distinguished Diversity Award and the COS Distinguished Diversity Award for her devotion to assisting underrepresented students achieve their educational goals as biomedical researchers.

J. Aaron Cassill, PhD, serves as Director of STEM Initiatives for the College of Sciences and a Professor of Biology. Cassill joined the UTSA faculty in 1993. He received the Howe Award for Outstanding Service to Undergraduate Students at UTSA in 2002 and the UT Regents' Outstanding Teaching Award in 2012. In 2013, he received the Piper Professor Award and was inducted into the UTSA Academy of Distinguished Teachers.

Edwin J. Barea-Rodriguez, PhD, serves as the program director of the MARC-U*STAR (Undergraduate Student Training in Academic Research), and RISE (Research Initiative for Scientifc Enhancement) all of which aim to increase underrepresented minority participation in STEM fields. He received UTSA's Richard S. Howe Award for Excellence in Service to Undergraduate Students in 2006 and 2017.

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Multi-modal PET drives interdisciplinary preclinical imaging

By Sonica Van Wyk

Tomography is an imaging technique used across a wide variety of fields, ranging from radiology and nuclear medicine, to geophysics and materials science. It provides three-dimensional information about a subject based on its sections or projections, and common examples include X-ray, computed tomography (CT), positron emission tomography (PET), and single-photon emission computed tomography (SPECT). CT scanning provides information on the anatomy of the subject, while PET provides functional imaging which shows the spatial distribution of biomolecular activity in the body. PET was developed as a technology for both clinical diagnostic and preclinical purposes in the 1950s, the scope of which was expanded by the development of radiopharmaceuticals—a group of pharmaceutical drugs which emit radiation and commonly includes radiotracers.

Preclinical imaging (PCI) plays a vital role in understanding the biological processes behind disease states at the organ, tissue, cell, and molecular level. Elucidating how the body responds to physiological or environmental change is important in the search for therapeutic agents to fight disease. PCI is also critical to the evaluation of new treatment effectiveness and safety, by informing researchers of drug distribution patterns in tissues. PET in preclinical studies enables users to conduct repeat experiments on the same animal subjects, providing strong statistically valuable data and, therefore, reducing the number of animals required for a study. For this reason, it has become increasingly important to use non-invasive *in vivo* imaging techniques to optimize the use of each animal used. Multi-modal tomographs, such as PET/CT, allow the correlation of the functional imaging obtained using PET with the anatomic imaging obtained with CT scanning. PET can also be combined with other technologies, such as magnetic resonance imaging (MRI), to bring functional imaging together with soft tissue morphological imaging. PET/MR is gaining ground in preclinical imaging applications, as it offers superior soft tissue contrast, imaging without the CT's ionizing radiation risk, and multiparametric data.

Preclinical PET applications

PET, PET/CT, SPECT/CT, PET/MR, and PET/SPECT/CT multi-modal imaging techniques are used across a number of life science applications, including oncology and neurology. Total body PET imaging is also possible and enables researchers to determine the pharmacokinetics of new drugs in all the body's organs and tissues at low masses.

Oncology

Preclinical researchers are interested in understanding the biology of tumor development, response to cancer treatment, and drug toxicity. There are various types of tumors, some of which have not yet been well characterized, so imaging technologies such as PET can shed light on the mechanisms of progression for many different tumor types, and how treatment affects them.

Many cancers are associated with a higher metabolic turnover than normal cells so, using PET and an injected radiolabeled glucose analogue tracer such as fluorine-18 (^{18}F)-fludeoxyglucose (^{18}F-FDG), glucose uptake can be quantified and tumor burdens detected. This method can also be used to detect molecular biomarkers to contribute to cancer detection and treatment response assessment. PET/CT and, more recently, PET/MR are used to determine the accumulation regions of ^{18}F-FDG, to obtain a semi-quantitative standardized uptake value (SUV) to assist in the diagnosis of tumor malignancy.

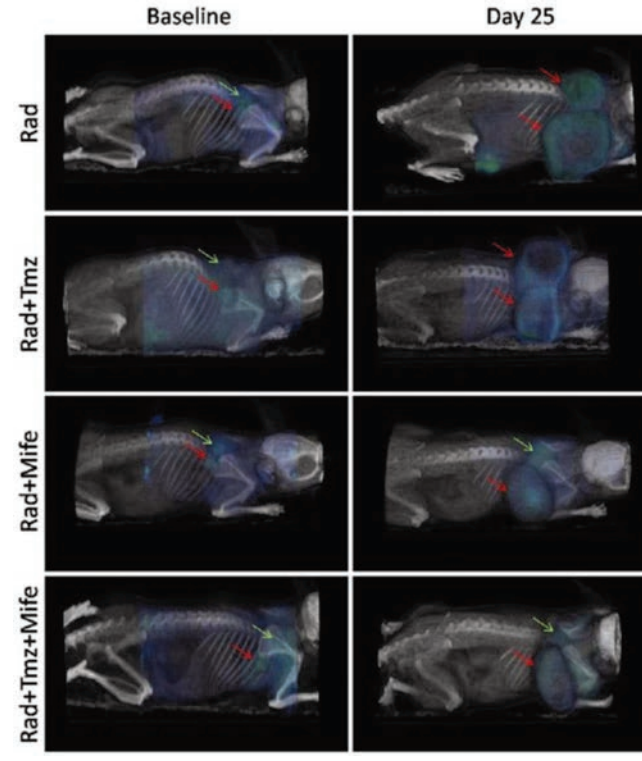

Figure 1. PET/CT images showing ^{18}F-FDG tumor uptake, in four treatment combinations, at the beginning of treatment and 25 days later. Red arrows indicate tumor location at baseline and day 25, green arrows show sites of typical ^{18}F-FDG uptake in brown adipose tissue (BAT). Reproduced from reference [1] in accordance with the Creative Commons License (https://creativecommons.org/licenses/by/2.0/).

Combination cancer therapies are often desired for their ability to address multiple molecular targets, as well as a reduced chance of drug resistance. A relevant study used preclinical PET/CT imaging to monitor ^{18}F-FDG tumor uptake for different treatment combinations: Radiotherapy (Rad) alone, Rad + Temozolamide (Tmz), Rad + Mifepristone (Mife), and Rad + Mife + Tmz. Rad + Tmz is the typical treatment regime for glioblastoma, but the study found that using Mife as a priming

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agent suppressed tumor growth more than the other treatment combinations **(Figure 1)**.[1] The mechanism of this chemo-radio-sensitizing effect of Mife is yet to be fully characterized, but studies such as this help researchers make important steps toward improving available cancer treatments.

Preclinical laboratories are increasingly aware of the benefits of PET/MR for oncology research. Thanks to MRI's unique ability for imaging soft tissue, users can visualize the true tumor margin and evaluate tracer distribution within individual tumors to generate a desired volume of interest (VOI) and calculate SUVs more accurately. Tumor margin detection is a unique and significant enhancement to preclinical cancer PET studies.

Neurology

Neuroscientists benefit from PET imaging technologies to obtain metabolic information about the brain, for example to detect changes in brain metabolic activity that might be indicative of abnormalities, potentially leading to conditions such as Alzheimer's Disease (AD), Parkinson's Disease (PD), stroke, memory loss, and cognitive decline. PET imaging is also used for the study of addiction and psychiatric disorders. By using PET in preclinical studies on the brain's impact on behavior and cognition, researchers can advance their understanding about nervous system processes in healthy individuals, in addition to various disease states, and elucidate abnormalities in its organization and connectivity.

PET/MR is particularly useful in neurology as it provides synchronized soft-tissue images with metabolic imaging, enabling scientists to investigate the brain's anatomical structures, pathologies, and metabolic abnormalities in preclinical animal models. Researchers can use PET and MRI to localize molecular markers in brain tissue, and image brain microstructure, connectivity, vasculature, and activity at high resolution.

Neurodegenerative diseases, such as AD, PD, multiple sclerosis, and Huntington's disease are a key focus of preclinical research, with MRI technology providing the high spatial resolution *in vivo* imaging required to determine the structure and function of central nervous system tissues. Used in tandem with MRI, PET imaging enables scientists to investigate the pathological hallmarks of neurodegenerative disease, such as amyloid-β (Aβ) and tau protein depositions in AD models.

Similarly, to oncological applications, glucose metabolism is a useful biomarker for many neurological disorders. Normal brain glucose metabolism is modified by many disease states and can be easily monitored by ^{18}F-FDG-PET. Currently, most AD treatments are targeted toward the disease's symptoms, rather than the underlying causes. Some studies have investigated the possibility of halting AD progression with therapeutics that target the early stage causes of the disease. For example, one experiment found that a new candidate therapeutic synthetic cannabinoid, JWH, a selective CB_2 agonist, significantly increased metabolic activity in the hippocampus and cortical regions of mice, measured by ^{18}F-FDG-PET.[2] The mice also showed reduced neuroinflammation and an increase in Aββ clearance when administered with JWH, improving overall cognitive performance.

Advances in PET technology

There are a number of performance criteria that PET systems must meet to provide the highest quality imaging results. Resolution and sensitivity depend, in part, on the material in the detector stopping the gamma rays (the scintillator) and the detector design. A very dense material is needed to stop as many gamma rays as possible. Dense and thick scintillator crystals that convert the gamma energy into light are therefore the material of choice in PET detectors. The size of the crystal impacts PET resolution. Diameter of the ring and depth of interaction (DOI) correction must also be optimized for high-resolution imaging. Crystal technology also underpins PET sensitivity and has undergone a number of advances in recent years. The industry has been dominated by pixelated crystals, tightly packed together, but the use of continuous crystals has shown to better measure light distribution and, therefore, provides greatly improved resolution and sensitivity.

New advanced PET instruments combine continuous crystal scintillators with novel light detection technology for superior imaging capabilities. Rather than using traditional avalanche photodiodes (APD) or photomultiplier tubes (PMTs), continuous crystals are coupled with silicon photomultiplier (SiPM) photosensors to allow the accurate determination of all three spatial coordinates of the gamma photon interaction within the detector crystal. The result is sub millimetric spatial resolution, regardless of the positron, a term known as full field accuracy (FFA). FFA results in more reproducible data, independent of variable sample positioning, and more reliable imaging of large samples or multiple animals across the field of view (FOV), to facilitate accuracy and throughput in preclinical imaging.

Preclinical PET in the future

Multi-modal PET imaging is enabling scientists to break new ground in preclinical research spanning a number of fields. As a highly sensitive, non-invasive technique, PET can help improve the understanding of the underlying causes of disease, improving methods of detection and treatment. Preclinical PET studies facilitate the development of imaging biomarkers, with the goal to translate these to the clinical to identify patients at risk or in the early stages of disease.

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Sonica Van Wyk serves as Market Product Manager, Nuclear Molecular Imaging at **Bruker BioSpin**. Sonica has 15 years of extensive experience in the preclinical imaging industry. Her expertise includes various aspects of marketing, product management, sales and channel programs, numerous product launches, campaigns, and helping firms (re)brand to stay ahead of the ever-evolving life sciences landscape.

HOLOGIC®

Aptima® Mycoplasma genitalium Assay from Hologic is the First and Only FDA-Cleared Diagnostic Test to Detect This Emerging Health Threat

FDA clearance makes clinically validated assay available for sexually-transmitted infection listed as emerging threat by the CDC.

The U.S. Food and Drug Administration recently granted clearance for the first and only FDA-cleared test for detection of *Mycoplasma genitalium*, an under-recognized but increasingly common sexually transmitted infection (STI). The Aptima® Mycoplasma genitalium assay from Hologic, Inc., cleared through the FDA's De Novo request process, provides laboratories with a highly sensitive and specific molecular diagnostic method to identify infections and enable effective treatment.

First discovered in the early 1980s, *Mycoplasma genitalium* (*M. genitalium*) was listed as an emerging public health threat by the U.S. Centers for Disease Control and Prevention (CDC) in 2015. Current estimates indicate that *M. genitalium* may affect more than 15 percent of men and women in certain high-risk populations, and its prevalence is growing. Because of the lack of an FDA-cleared test until now, *M. genitalium* has often been misdiagnosed as other STIs and, in some cases, treated with the wrong antibiotics. This often leaves the underlying infection untreated, which can lead to increased transmission and recurrent infections.

"Although *Mycoplasma genitalium* is typically more common than gonorrhea, there is very little public awareness of this rising sexually transmitted infection, which can cause serious and potentially devastating health problems," said Tom West, president, Diagnostic Solutions at Hologic. "The introduction of the Aptima Mycoplasma genitalium assay gives healthcare professionals the opportunity to provide optimal care for their patients and reflects Hologic's commitment to developing innovative solutions that address emerging public health threats."

In men, *M. genitalium* symptoms may include urethritis, the swelling and inflammation of the urethra. In women, *M. genitalium* has been linked to cervicitis, the swelling and inflammation of the cervix. If left untreated, infections can lead to infertility in women and increased risk of HIV acquisition and transmission.[2] Patients infected with *M. genitalium* may be asymptomatic or experience symptoms similar to those associated with a chlamydial infection, so accurate diagnostic tests are critical to help healthcare professionals and their laboratory partners identify these bacterial infections and treat them appropriately. Research has shown as many as 50 percent of women and 42 percent of men with *M. genitalium* may have an antibiotic-resistant strain, further emphasizing the importance of early detection and regular screening.[3]

In published research, Hologic's ribosomal RNA-based *M. genitalium* assay displayed greater sensitivity than lab-developed or CE-marked DNA-based tests.[7,8] Hologic introduced the first FDA-cleared diagnostic test kit for STIs in the 1990s using its innovative RNA-based technology. Since then, Hologic has expanded its Aptima STI portfolio to include assays for chlamydia, gonorrhea, human papillomavirus (HPV), herpes simplex viruses (HSV 1 & 2), trichomonas, and Zika* virus. The Aptima virology portfolio also includes quantitative assays for the human immunodeficiency virus (HIV) and hepatitis B and C (HBV and HCV). All are available on Hologic's fully-automated Panther® system. In 2017, the Aptima assays helped an estimated 40 million patients obtain fast, high-quality test results.[9]

Including the first IVD for the detection of *Mycoplasma genitalium*, Hologic's Panther and Panther Fusion® system now offers 14 FDA-cleared or approved assays that detect more than 20 pathogens, making it the only high-throughput molecular diagnostic platform in the United States to combine comprehensive sexual health, cervical health, viral load, respiratory testing and open channel[10] functionality on a fully automated system.

For more information on the Aptima assays, visit **HealthDxS.com**.

Aptima® Mycoplasma genitalium Assay

* The Aptima Zika Virus assay has not been FDA cleared or approved; this test has been authorized by FDA under an EUA for use by authorized laboratories; this test has been authorized only for the detection of RNA from Zika virus and diagnosis of Zika virus infection, not for any other viruses or pathogens; and this test is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of in vitro diagnostic tests for detection of Zika virus and/or diagnosis of Zika virus infection under section 564(b)(1) of the Act, 21 U.S.C.§ 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner. For additional availability in other countries beyond the U.S., please contact your local sales representatives or distributor.

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Urinalysis chemistry test strip procedures

Monitor the precision of urinalysis chemistry test strip procedures by using Bio-Rad's qUAntify Advance Control. This assayed, human-urine solution based control is offered in liquid form in two individual levels (Normal and Abnormal) with 31 day open-vial stability for all analytes. **Bio-Rad Laboratories**

Hemoglobin measurement & hematocrit calculation

The HemoPoint H2 Hemoglobin analyzer provides a hemoglobin measurement and a hematocrit calculation within approximately 25 seconds. HemoPoint H2 is CLIA waived. Features include the 'soft load' cuvette holder which prevents optics contamination, a backlit touchscreen, and a large memory that saves 4,000 results. The point-of-care analyzer also has an integrated rechargeable battery that provides 100 hours of use from each charge, allowing the analyzer to be used in the field for large scale screening programs. The 'always ready' stand-by function reduces energy consumption and allows users to quickly start running tests without needing to switch HemoPoint H2 on and off. **EKF**

Critical care blood gas analyzer

The Stat Profile Prime Plus is a comprehensive, whole blood critical care analyzer that offers blood gases, electrolytes, metabolites, hematology, co-oximetry, and 32 calculated results in a simple, compact device. Prime Plus combines maintenance-free, replaceable cartridge technology for sensors and reagents with patented, new, maintenance-free and non-lysing whole blood co-oximetry technology. Test menu includes pH, PCO2, PO2, Na, K, Cl, iCa, iMg, Glucose, Lactate, Urea, Creatinine, Hct, Hb, SO2%, and Co-Ox with results from the full panel available in about one minute. **Nova BioMedical**

Rapid testing

Point-of-care testing (POCT) gives patients fast, accurate diagnostic test results while they wait, so you can provide the right treatment as quickly as possible. Sekisui Diagnostics delivers your POCT lab a broad range of high quality rapid tests, molecular point of care, and fast immunoassay systems. These diagnostic tests allow you to cost-effectively diagnose at the point of care in one visit—reducing labor and follow-up time while increasing patient satisfaction. **Sekisui Diagnostics**

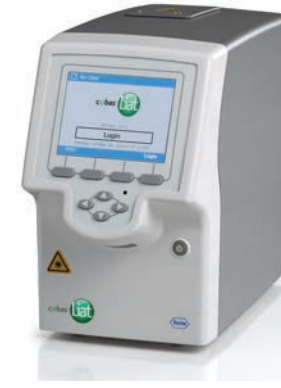
POCT management and integration software

Orchard Trellis point-of-care testing (POCT) management and integration software simplifies the complexities of diverse POCT situations and helps POC coordinators more easily oversee POCT and manage their workload. Trellis integrates POCT results into your LIS and/or EHR to achieve the rapid turnaround time that makes your POC tests valuable to providers. Trellis tracks training and competency assessments, managing operators and devices across locations to help ensure quality of testing and meet regulatory requirements. Automated billing and remote handling of POCT QC, decision-support rules, and a full menu of reports are Trellis features that make POCT integration, administration, and oversight more manageable. **Orchard Software**

Urinalysis dipstick control

Dipper POCT Urinalysis Dipstick Control is a single-use liquid quality control that enables improved performance and efficiency with three months room temperature and three years refrigerated stability. Dipper POCT is made with a simulated human urine matrix and formulated with native ketones. The pouch design allows users to visually verify full immersion of the dipstick and minimizes the risk of contamination. Dipper POCT is designed for use in every testing environment including central laboratories, reference laboratories, nursing stations, and doctors' offices. **Quantimetrix**

CLIA-waived PCR testing



This real-time polymerase chain reaction (PCR) system is CLIA-waived for Influenza A/B, RSV, and Strep A testing and delivers results in 20 minutes or less. The cobas Liat System brings lab-quality molecular testing to the point of care. It's designed for STAT testing to support time-sensitive diagnoses and treatment decisions. There's no need to confirm negative test results at the time of visit, so caregivers can make the right treatment decision right away. About the size of a single-serve coffee maker, the cobas Liat System is ideal for use in satellite laboratories or point-of-care locations. **Roche Diagnostics**

New FDA Regulations, Hospital Glucose Meters

FDA Product Code PZI, 2019:
"Blood Glucose Meter for Near-Patient Testing"①

FDA Product Code NBW, 2016:
"Blood Glucose Test System, Over the Counter."② "These device types are not intended for use in healthcare or assisted-use settings such as hospitals, physician offices, or long-term care facilities because they have not been evaluated for use in these professional healthcare settings."③

Use of a meter cleared by the FDA as NBW is considered "OFF LABEL" when used anywhere in a hospital. Is your hospital glucose meter cleared as FDA Product Code PZI for hospital use or NBW cleared and off label for hospital use?

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① U.S. Food and Drug Administration. Product classification [Product Code PZI]. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm?id=678

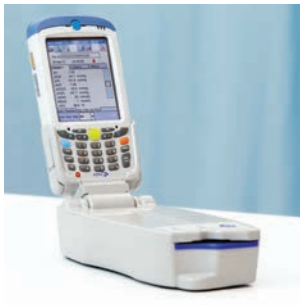
② U.S. Food and Drug Administration. Product classification [Product Code NBW]. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm?id=631

③ U.S. Food and Drug Administration. Self-monitoring blood glucose test systems for over-the-counter use. Draft guidance for industry and Food and Drug Administration staff. Silver Spring, MD: 2018.https://www.fda.gov/media/119828/download

Controlled venous sampling

Sarstedt's S-Monovette POC Collect Kit provides controlled venous sampling from vascular access lines, and precise dispensing for point-of-care testing (POCT). This dual technology reduces POC test rejection by helping prevent overfilling, underfilling, or air bubbles in the cartridge. This enables decreased turn-around-times and improved patient outcomes. After POC dispensing, the analyzer-ready S-Monovette tube can be sent directly to the lab if confirmation testing is required, facilitating patient blood management. **Sarstedt**

Blood analysis testing



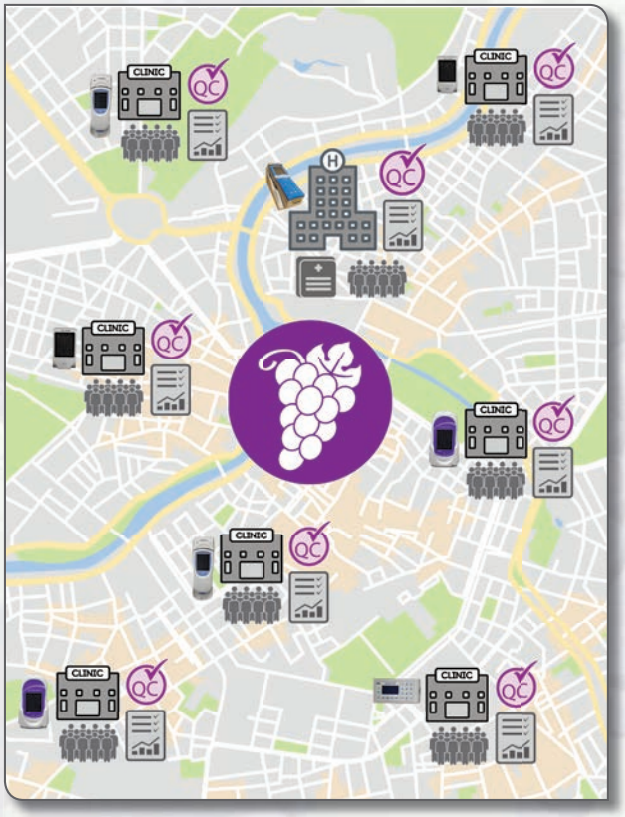
The epoc Blood Analysis System is a handheld, wireless solution to enable comprehensive blood analysis testing at the patient's side on a single room-temperature test card, with results in under one minute. The epoc system accelerates clinical decision making with customized critical ranges and fast, wireless transmission of patient results, which are able to be integrated into any LIS. To streamline patient testing workflow, the full-panel test card offers 13 analytes and automatic calibration prior to analysis. Further, an integrated bar-code reader provides identification of patient and operator IDs. The full menu includes pH, partial pressure of oxygen, partial pressure of carbon dioxide, sodium, potassium, ionized calcium, hematocrit, glucose, lactate, creatinine, chloride, BUN, and TCO2. Only 92 µL of blood is required for the full panel of tests. **Siemens Healthineers**

Fluorescent immunoassay analyzer

Sofia Influenza A+B FIA with Sofia 2 uses fluorescent technology to deliver automated, objective, and accurate results, with demonstrated sensitivity and specificity as high as 100 percent. Sofia 2 is a small benchtop fluorescent immunoassay analyzer with flexible workflows to accommodate any laboratory environment and testing volume. Results store automatically on Sofia 2 and can optionally be exported, printed, sent directly to your LIS, or viewed remotely with Quidel's secure, HIPAA-compliant Virena data management system. Sofia 2 CLIA waived assays include Sofia Influenza A+B FIA, Sofia RSV FIA, Sofia Strep A+ FIA, and Sofia 2 Lyme FIA. **Quidel**

BRIDGE THE POCT GAP

Software to Help Track POCT Across Locations



Having POCT take place across multiple locations, on disparate devices, and performed by a multitude of different operators makes any POCT program a challenge. To help, Orchard Software offers a configurable, centralized POCT management and integration software solution—Orchard® Trellis™—that is flexible enough to help make POCT administration easy to manage from a central location.

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Education:
Four year Bachelor's degree with National Certification as a Medical Technologist preferred, other Bachelor's degree in biomedical sciences considered with adequate clinical laboratory experience. Additional training in billing, compliance, and coding desirable.

Experience:
Four years of experience in a Clinical Laboratory setting. One year of experience with Laboratory and Pathology coding, medical billing, and data base management preferred.

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An interview with Carmen L. Wiley, PhD, DABCC, FAACC, AACC President

How long has AACC's Society for Young Clinical Laboratorians (SYCL) program been in existence and can you share a success story? The SYCL was launched in 2004 with the goal of helping the next generation of laboratory medicine leaders flourish in their careers with crucial networking, mentorship, and recognition opportunities. I served as a SYCL chair member in 2010 and am very proud of what we have accomplished with this program. Being a part of SYCL has been beneficial to the careers of many young clinical laboratorians. Here is one example:

When AACC member Dr. Robert Nerenz was attending his first AACC Annual Scientific Meeting in 2013, he decided to attend the annual ABCC-SYCL reception. This popular networking and recognition event is where the American Board of Clinical Chemistry (ABCC) acknowledges new diplomates and where SYCL presents a series of awards and honors. Amid the professional appreciation, the ABCC-SYCL reception also offers attendees from across the career spectrum the opportunity to meet and greet each other. Nerenz was doing exactly that—meeting and greeting—when he felt a tap on his shoulder. Turning to face the person behind the tap, he saw his fellowship program director, Dr. Ann Gronowski, who had someone she wanted him to meet. That someone was Dr. Ronald Whitley, a professor at the University of Kentucky in Lexington, who at that time was recruiting for a position. Based on a brief conversation with Whitley, Nerenz applied for and ultimately landed his first post-fellowship position, an assistant professor of pathology and laboratory medicine.

"Raising the profile" of clinical laboratorians includes both diagnostics and regulatory affairs. For those of us who can't attend Capitol Hill briefings, what can we do? Raising the profile of laboratory medicine is indeed an important goal for the field, and in fact is one of the goals under AACC's new Strategic Plan. In the new plan, we aim to quantify and demonstrate the value of laboratory medicine.

We will begin this work by increasing the evidence base demonstrating the link between lab tests, lab data, outcomes, and costs. We will also develop materials that give members the tools to serve as healthcare consultants in their organizations. We are also considering investing in a physician and a public awareness campaign showcasing the value the lab brings to patient care. We'll share much more information about this as the plan progresses.

Who is utilizing Lab Tests Online and to whom is this service marketed toward? As you know, clinical laboratory tests provide essential answers to clinicians so that patients get accurate diagnoses and effective treatment. Lab Tests Online is a health information web resource designed to help patients, caregivers, and medical professionals understand the many laboratory tests that are a vital part of medical care.

Lab Tests Online is available in 12 languages through 14 country sites. The content on each site is translated and adapted to policy and practice specific to that country. Countries with Lab Tests Online sites include: The United States, Australia, Brazil, China, Czech Republic, France, Greece, Hungary, Italy, Korea, Poland, Spain, Turkey, and the United Kingdom.

What highlights can attendees look forward to at the 71st AACC Annual Scientific Meeting & Clinical Lab Expo in Anaheim, CA this year? The cornerstone of every AACC Annual Scientific Meeting is the lineup of five plenary sessions delivered by world-renowned scientists. This year's stellar plenaries will look in-depth at how to accelerate the adoption of new biomarkers in clinical practice, as well as how biomarkers are guiding targeted breast cancer treatments. The plenaries will also explore how genetics influence behavior and neurological disorders, advances in clinical genomics that are enabling more personalized patient care, and what's next for emerging "extreme" molecular diagnostic methods that can be performed in seconds.

Additional highlights of the meeting will include:

- A special session that will shed light on the little-understood nuances of direct-to-consumer genetic tests, with a focus on how healthcare professionals can enable patients to benefit from these tests while also raising public awareness about these tests' limitations.
- The AACC Disruptive Technology Award Session, which will feature innovative tests for sepsis and colon cancer, as well as a new diagnostic platform based on lab-on-cartridge and artificial intelligence technology.
- Brand new ePoster sessions during which select presenters will display their abstracts on an interactive screen that can zoom in on figures. These sessions will supplement the existing printed poster sessions and will enable presenters to discuss their innovative research with a larger audience.

The Clinical Lab Expo will feature more than 800 companies exhibiting the latest clinical laboratory products and services. This year, attendees will have the opportunity to explore the cutting edge of laboratory medicine in the new AACC Innovation Zone located in the exhibit hall. The Innovation Zone will showcase presentations on groundbreaking technology from numerous pioneers in the diagnostic sphere, including the AACC Disruptive Technology Award semi-finalists and finalists.

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