MLO-online.com

MEDICAL LABORATORY OBSERVER

JANUARY 2019 ■ Vol 51 ■ No 1

MLO®

The Peer Reviewed Management Source for Lab Professionals since 1969

CE

Management of CMV in HSCT

The cost of quality

Impact of MDx economics

Somatic microchimerism

EXECUTIVE SNAPSHOT

Nancy Stratton
CEO
COLA

Crack pneumonia cases faster.

Get fast, comprehensive results with the BioFire® FilmArray® Pneumonia Panel.

Respiratory infections can arise from a variety of pathogens. The BioFire Pneumonia Panel utilizes a syndromic approach—simultaneously testing for the most likely organisms to cause similar signs and symptoms. Our simple, rigorous test identifies specific pathogens—as well as levels of organism present in a given sample—all in about one hour. The BioFire Pneumonia Panel drastically improves turnaround time to organism identification, delivering fast, comprehensive results that ultimately aid in diagnosis.

Learn more at **biofiredx.com**

The BioFire Pneumonia Panel

Bacteria (semi-quantitative)
Acinetobacter calcoaceticus baumannii complex
Enterobacter cloacae complex
Escherichia coli
Haemophilus influenzae
Klebsiella aerogenes
Klebsiella oxytoca
Klebsiella pneumoniae group
Moraxella catarrhalis
Proteus spp.
Pseudomonas aeruginosa
Serratia marcescens
Staphylococcus aureus
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

Atypical Bacteria (qualitative)
Chlamydia pneumoniae
Legionella pneumophila
Mycoplasma pneumoniae

Viruses (qualitative)
Adenovirus
Coronavirus
Human Metapneumovirus
Human Rhinovirus/Enterovirus
Influenza A
Influenza B
Parainfluenza virus
Respiratory Syncytial virus

Resistance Markers
Carbapenemase
- IMP
- KPC
- NDM
- Oxa48-like
- VIM

ESBL
- CTX-M

MRSA
- *mec*A/C and MREJ

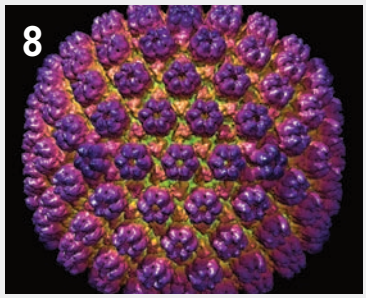
BIOFIRE®
A BIOMÉRIEUX COMPANY

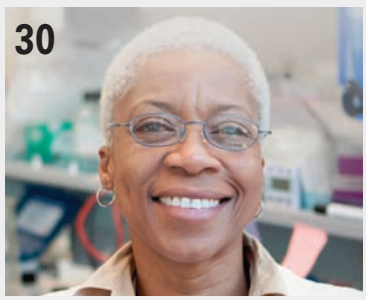
Syndromic Testing: The Right Test, The First Time.

IN THIS ISSUE...

JANUARY 2019 | Vol. 51, No. 1

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





DNA debate

By Janette Wider
Editor

Before the holidays, my co-editor enthusiastically inquired whether I had ever completed a consumer DNA test, or if I had plans to do so. The two most popular brands—23andMe and Ancestry—were advertising Cyber Monday sales. I have not—I'm on the fence on whether I want to.

There are two reasons why: accuracy and privacy.

Regarding accuracy, according to *Scientific American*, "In critiquing this business, it seems fair to assume the data generated is accurate. But there have been some bizarre cases of failure, such as the company that failed to identify the sample DNA as coming not from a human, but from a dog."[1]

I can't find a statistic for how many times dog DNA was identified as human, but I understand mistakes happen. As laboratory professionals, it is important to keep in mind that people are invested in getting accurate test results—whether for their own health or just for curiosity's sake.

Most of the positions of interest in our DNA are determined by experiments by Genome-Wide Association Studies that recruit a number of people—as many as possible—that share a common characteristic. This works well for a disease like cystic fibrosis (a spike in chromosome 7) but not so well for traits that the consumer may be interested in—like taste—because of the dozens of variants that emerge, therefore only offering a probability of predisposition toward a behavior as measured by a population.[1]

There is certainly a small downside—not being able to know for sure if you are a supertaster or not for example—but there's certainly an upside. I have an eye disease that can be related to genetics (I don't carry the gene), but perhaps my DNA, and others who have the same condition, overtime could reveal something that isn't yet known.

My main concern is privacy. Over 92 million account details from genealogy and DNA testing service MyHeritage were found on a private server, according to a release made by the company on June 4, 2018.[2] DNA data wasn't breached, but isn't that still cause for concern?

Also, when using these services, the companies ask you to agree (or make it clear that you have to specifically opt out) to share your DNA with their research partners. More than 80 percent of 23andMe users have opted in to sharing their DNA.[3] I'm sure their intentions are philanthropic in nature—as mine would be, but can we be guaranteed that our DNA is being safeguarded?

The answer is, we can't.

With the way healthcare is advancing, especially with the potential good DNA can do for research into genetic diseases/predispositions, all healthcare professionals should do their part in ensuring that patient and consumer information is safe from harm by following proper protocols—whether that's not leaving your password on a sticky note on your monitor, or shredding old facimilies, or something further.

The heritage part of the test really interests me the most. I'd love to see if what my family has told me is true. Honestly, I hope to be a small percentage of Neanderthal. But that aside, I think I may give one of the tests a try. I won't get as good of a deal as my co-editor did on Cyber Monday though, that's for sure.

I'll be keeping my fingers crossed that the powers that be do everything they can to keep my DNA safe.

Please visit mlo-online.com for references.

Janette Wider

MEDICAL LABORATORY OBSERVER

MEDICAL LABORATORY OBSERVER Vol.51, No.1

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

VERIFIED AUDIT CIRCULATION

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

sysmex | Lighting the way with diagnostics

FOR PRECIOUS PATIENT SAMPLES TIME IS PRECIOUS.

GloCyte®
CSF Cell Counter

TIMELY RESULTS YOU CAN COUNT ON

Sysmex America is now the exclusive distributor of GloCyte, an automated cell counter for cerebrospinal fluid (CSF) that provides rapid and accurate red cell and total nucleated cell counts at clinically relevant low levels. With its fluorescence technology, highly specific reagents, and intelligent counting algorithm, GloCyte can handle all of the CSF specimens that enter your laboratory, providing quick and precise results for your most critically ill patients.

www.sysmex.com/glocyte

FAST FACTS

Diabetes

Here are some interesting statistics about diabetes in the United States:

30 million
is the number of people in the U.S. who have diabetes.

1 in 4
is the number of people out of the 30 million that don't know they have diabetes.

84 million
adults have prediabetes.

90 percent
of those 84 million don't know they have prediabetes.

90-95 percent
of all diagnosed cases of diabetes are type 2.

5 percent
of all diagnosed cases of diabetes are type 1.

193,000
Americans under the age of 20 are estimated to have diagnosed diabetes.

252,806
is the number of death certificates listing diabetes as an underlying or contributing cause of death in 2015.

$327 billion
is the total costs of diagnosed diabetes in 2017.

Sources: https://www.cdc.gov/diabetes/basics/quick-facts.html, http://www.diabetes.org/diabetes-basics/statistics/

Cancer

New blood test detects early stage ovarian cancer. Research on a bacterial toxin first discovered in Adelaide, Australia has led to the development of a new blood test for the early diagnosis of ovarian cancer, a global disease which kills over 150,000 women every year.

The new blood test has the potential to dramatically improve early detection of the disease, although it will require further testing before it is available for clinicians.

A research team from the University of Adelaide and Griffith University have been studying the interactions between the toxin and an abnormal glycan (sugar) expressed on the surface of human cancer cells and released into the blood.

The team has now engineered a harmless portion of the toxin to enhance its specificity for the cancer glycan and used this to detect it in blood samples from women with ovarian cancer.

A paper published in *Biochemical and Biophysical Research Communications* has shown that the new test detected significant levels of the cancer glycan in blood samples from over 90 percent of women with stage 1 ovarian cancer and in 100 percent of samples from later stages of the disease, but not in any of the samples from healthy controls.

"Ovarian cancer is notoriously difficult to detect in its early stages, when there are more options for treatment and survival rates are better. Our new test is therefore a potential game changer," says Professor James Paton, Director of the University of Adelaide's Research Center for Infectious Diseases.

Professor Michael Jennings, Deputy Director of the Institute for Glycomics at Griffith University said, "Detection of this tumor marker may also play a role in a simple liquid biopsy to monitor disease stage and treatment."

The team is currently seeking scientific and commercial partners to further test the technology with larger numbers of patient samples and to adapt it for mass screening.

Technology

Cellphone technology developed to detect HIV. The management of human immunodeficiency virus (HIV), which cripples the immune system by attacking healthy cells, remains a major global health challenge in developing countries that lack infrastructure and trained medical professionals.

Investigators from Brigham and Women's Hospital have designed a portable and affordable mobile diagnostic tool, utilizing a cellphone and nanotechnology, with the ability to detect HIV viruses and monitor its management in resource-limited regions. The novel platform is described in a paper published recently in *Nature Communications.*

"Early detection of HIV is critical to prevent disease progression and transmission, and it requires long-term monitoring, which can be a burden for families that have to travel to reach a clinic or hospital," said senior author Hadi Shafiee, PhD, a principal investigator in the Division of Engineering in Medicine and Renal Division of Medicine at the Brigham. "This rapid and low-cost cellphone system represents a new method for detecting acute infection, which would reduce the risk of virus transmission and could also be used to detect early treatment failure."

Traditional virus monitoring methods for HIV are expensive, requiring the use of polymerase chain reaction (PCR). Shafiee and his colleagues sought to design an affordable, simple tool that makes HIV testing and monitoring possible for individuals in developing countries with less access to medical care.

Utilizing nanotechnology, a microchip, a cellphone, and a 3D-printed phone attachment, the researchers created a platform that can detect the RNA nucleic acids of the virus from a single drop of blood. The device detects the amplified HIV nucleic acids through on-phone monitoring of the motion of DNA-engineered beads without using bulky or expensive equipment. The detection precision was evaluated for specificity and sensitivity.

Researchers found that the platform allowed the detection of HIV

with 99.1 percent specificity and 94.6 percent sensitivity at a clinically relevant threshold value of 1,000 virus particles/ml, with results within one hour. The total material cost of the microchip, phone attachment and reagents was less than $5 per test.

"Health workers in developing countries could easily use these devices when they travel to perform HIV testing and monitoring. Because the test is so quick, critical decisions about the next medical step could be made right there," said Shafiee. "This would eliminate the burden of trips to the medical clinic and provide individuals with a more efficient means for managing their HIV."

"We could use this same technology as a rapid and low-cost diagnostic tool for other viruses and bacteria as well," said lead author Mohamed Shehata Draz, PhD, an instructor in the Division of Engineering in Medicine and Renal Division of Medicine at the Brigham.

Shingles

Shingles vaccine in short supply as demand increases. At least 1 million people get shingles every year in the United States, and 1 in 3 will get it in their lifetime, according to the Centers for Disease Control and Prevention (CDC). Shingles is caused by the varicella-zoster virus, the same virus that causes chickenpox. So, once you've had chickenpox, the virus is in your body and you can develop shingles.

Even if you've never had chickenpox, a person with shingles can pass the virus to anyone who isn't immune to chickenpox. This usually happens with direct contact with the open sores from a shingles rash. But instead of shingles, the virus will produce chickenpox.

Shingles is more common in adults older than 50, but that doesn't mean younger people won't get shingles. For people younger than 50, it's typically not on their radar. Dr. Craig Dolven, with Orange Park Medical Center, said it should be.

Dolven said in rare cases shingles develops from the chickenpox vaccine even if the patient never got chickenpox. The vaccine is a live virus that can leave people susceptible to shingles. People who are vaccinated are still better off because they get a milder cause of chickenpox or shingles in most cases. But no vaccine offers a 100 percent guarantee.

Shingles can be triggered by stress or anything that weakens your immune system. Symptoms of shingles include a painful, blistering rash on one side of the body. It attacks the nerves under the skin, which is why it's so painful. Sufferers might also feel tingling or numbness.

For people 50 and older, there's a way to reduce the risk of getting shingles by more than 90 percent. Dolven speaks with great confidence about the shingles vaccine, Shingrix, which is 90 percent effective at preventing shingles. After the CDC designated Shingrix as the preferred shingles vaccine, demand prompted a shortage.

The CDC recommends two doses, two to six months apart, for adults age 50 and over, but the shortage has made getting the second dose within the recommended window difficult for some people.

Dolven said if you're having trouble finding the second dose, don't fret. It's still recommended to get the vaccine as soon as you can get it.

"The CDC says go ahead and give it to them if they're outside of that window and it should work just as good," Dolven explained.

If you want to see where the Shingrix vaccine is available, enter your ZIP code on the following website and it will reflect pharmacies where the vaccine is available: https://www.shingrix.com/index.html.

Parkinson's disease

Appendix linked to toxic Parkinson's protein. Parkinson's disease is a brain disorder that leads to shaking, stiffness, and difficulty with walking, balance, and coordination. Symptoms usually begin gradually and get worse over time. Parkinson's disease results from the loss of the dopamine-producing brain cells that control movement.

Many brain cells of people with Parkinson's contain Lewy bodies, which are unusual clumps of the protein alpha-synuclein. Clumps of this protein are thought to be toxic to the cells and lead to their death. This protein has also been shown to accumulate in the gut of Parkinson's patients. There is evidence that the protein may be able to travel from the gut to the brain via the connecting vagal nerve. Gastrointestinal symptoms are often associated with Parkinson's disease and can start up to 20 years before the symptoms of brain cell degradation.

A team led by Dr. Viviane Labrie at the Van Andel Research Institute in Grand Rapids, MI, sought to explore whether the gut could be involved in triggering Parkinson's disease. They focused on the appendix. Despite its reputation as a useless organ, the appendix is an immune tissue involved in the body's defense against microbes and helps regulate bacteria in the intestine.

The team analyzed the records of nearly 1.7 million people whose health information was tracked for up to 52 years. They compared the chances of developing Parkinson's disease among those who'd had their appendix removed with those who hadn't. The work was supported in part by NIH's National Institute on Deafness and other Communication Disorders and National Institute of Neurological Disorders and Stroke. Results appeared on October 31, 2018, in *Science Translational Medicine*.

People who'd had their appendix removed had a 19.3 percent lower chance of Parkinson's disease. Those who lived in rural areas and had an appendectomy had an even lower chance, 25.4 percent. People who'd had an appendectomy and developed Parkinson's showed a delayed onset of the disease relative to those who still had their appendix—an average delay of 3.6 years for those who'd had an appendectomy at least 30 years prior.

The team also found a build-up of the toxic form of alpha-synuclein in the appendixes of healthy volunteers, suggesting the appendix may be a reservoir for the disease-forming protein and may be involved in the development of Parkinson's disease.

CMV-specific immune system monitoring for management of cytomegalovirus in HSCT

By Ted Blanchard and William Cruikshank, PhD

Despite advances in diagnostic testing and treatment, cytomegalovirus (CMV) remains a cause of increased morbidity and mortality in allogeneic hematopoietic stem cell transplant (allo-HSCT). Anti-viral drugs are effective at reducing viral loads; yet, these drugs are expensive and have significant toxicity profiles. In general, treatment regimens are determined based on broad clinical risk stratifications, such as serostatus and haplotype matching for donor and recipient. However, a more personalized approach to risk stratification could potentially identify those individuals who may only require a reduced treatment strategy—or even no treatment strategy—thereby reducing both cost and toxicity exposure. An attractive alternative strategy consists of monitoring the patient's CMV-specific immune response either prior to or after allo-HSCT to better inform a risk stratification strategy.[1] This review will address current thinking in CMV-specific immune responses as a potential predictor of protection or susceptibility to CMV reactivation following allo-HSCT.

Viral latency

For most individuals with a healthy immune system, initial infection is either asymptomatic or is manifested by a transient period of malaise, which can present as mononucleosis or flu-like symptoms.[2] During this time the virus has infected a variety of cell types, but primarily found in cells of the monocytoid lineage such as monocytes and CD34+ myeloid progenitor cells,[3] where the virus persists intracellularly until changes in immune competence allows for reactivation and subsequent infection. This latency period is characterized by a homeostatic balance between viral replication and the immune response,[4] and has been defined by Lemmermann et al as, "a highly dynamic condition during which episodes of viral gene desilencing, which can be viewed as incomplete reactivations, cause intermittent antigenic activity that stimulates CD8 memory-effector T cells and drives their clonal expansion. These T cells are supposed to terminate reactivation before completion of the productive viral cycle."[5]

Therefore, if the infected individual remains healthy with a competent immune system, the virus will likely remain under control through immune surveillance for the life of that individual. The lifelong task of keeping the virus from uncontrolled replication results in a rise in CMV-specific T cells such as cytotoxic CD4+CD28- T cells,[6] as well as CD4+CD28+ and CD8+ CMV-specific T cells. In elderly individuals, CMV-specific T cells can increase to as high as 50 percent of all CD8+ T cells and 30 percent of all CD4+ T cells.[7]

CMV reactivation

The delicate balance that exists between viral replication and immune system control of viral replication would suggest that a prolonged decrease in immune competence might result in a viral advantage. Loss of this balance—as seen in association with disease or drug treatment—can lead to uncontrolled viral replication resulting in CMV reactivation and disease.[8] Uncontrolled viral replication can affect virtually any organ or tissue in the body and can manifest as neuropathy, pneumonia, hepatitis encephalitis, and myelitis.[9] In more severe cases of immunosuppression CMV disease can present as Guillain-Barre syndrome, myocarditis, thrombocytopenia, or meningoencephalitis.[10] Due to the necessity of inducing long-term immunosuppression prior to and post-transplantation, CMV reactivation, particularly for hematopoietic stem cell transplantation (HSCT), is one of the primary causes for infectious morbidity and mortality.[11]

CMV in HSCT

T lymphocyte ablation and immunosuppressive therapy for the HSCT recipient induces a loss of CMV-specific immunity. This loss creates a permissive environment for CMV reactivation which may approach a frequency of 70 percent when either the recipient or the donor is CMV seropositive.[12] Without a prevention strategy, the majority of CMV reactivation typically occurs during the first three months after HSCT. While several antiviral drugs exist for HSCT patients, they are not routinely administered as part of a CMV prophylaxis strategy, in contrast to

Human Cytomegalovirus depicting membrane and nucleoid components

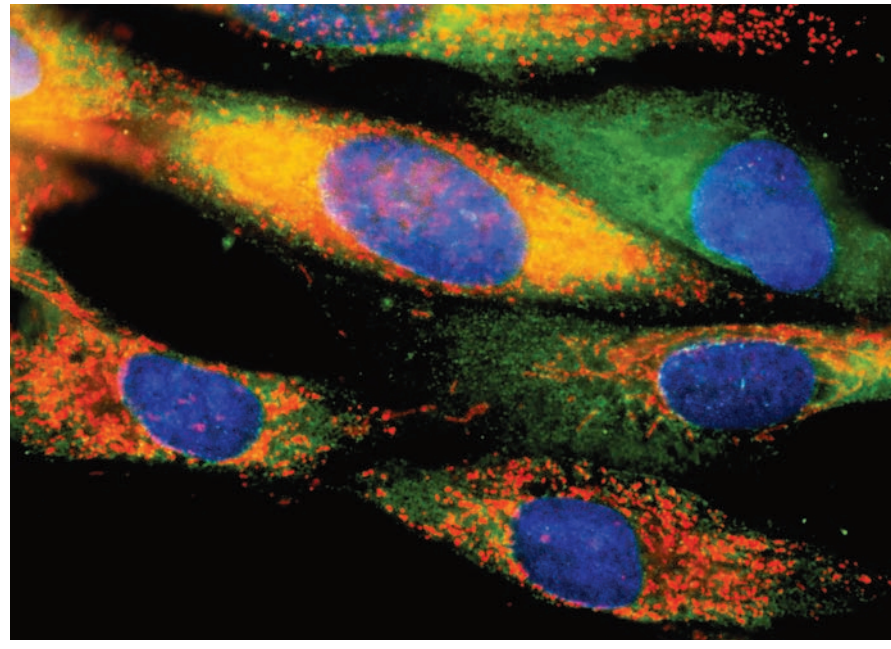
Earning CEUs

The test is available on page 10 or can be accessed online at www.mlo-online.com under the CE tab.

LEARNING OBJECTIVES

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

1. Identify the main challenges of standard CMV treatment regimens in HSCT patients.
2. Describe the process of the immune's response to CMV in terms of viral latency and reactivation.
3. Discuss CMV laboratory testing in HSCT patients and its limitations.
4. Discuss the physiology of the immune response to CMV in HSCT and the importance in monitoring this response in both the recipient and the donor.



Cellular Cytomegalovirus Infection as indicated by the red spots

solid organ transplant patients. Instead, a preemptive strategy of monitoring CMV viral load is commonly used to screen for infection or reactivation. Preemptive therapy is initiated when the viral load crosses a given threshold or if a significant rate of replication of the virus is detected. Preemptive strategy success depends on the early, detectable, presence of the virus in the blood before the onset of disease.[13] This usually involves frequent testing using the CMV antigenemia assay or quantitative real-time polymerase chain reaction (PCR) analysis until the likelihood of reactivation is significantly reduced, typically viewed as day 100 following transplant. While still used in some settings, antigenemia has been reported to miss up to 35 percent of PCR-positive CMV infections, and therefore a negative result may not necessarily rule out CMV infection.[14]

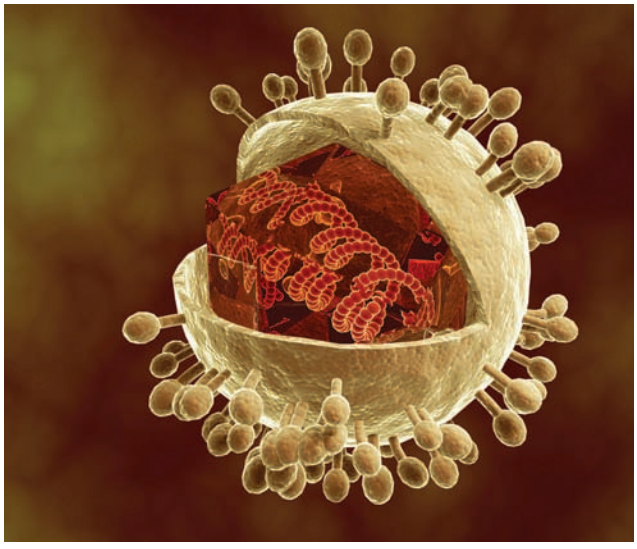
CMV nucleic acid testing (NAT), such as PCR, is one of the most common tests performed in clinical virology laboratories to identify CMV reactivation—however, there are important limitations of the test to consider. First, the viral load is simply a measure of infection; it is uninformative as to which patients may be able to—through their immune system—control infection without treatment and which patients may need treatment. Secondly, there are no validated viral load thresholds for initiation of antiviral treatment. Universal thresholds are difficult to establish because of differences in assay platforms including, but not limited to, specimen types (blood urine, CSF, and others), blood sample preparations (whole blood, plasma, serum, and leukocytes), nucleic acid extraction methods, and targets (various CMV genes, DNA versus RNA).[14] Therefore, the lack of assay standardization limits broad utility of the test results.

CMV-specific immune-monitoring

It is widely accepted that T-cell mediated cellular immunity is the most important factor in controlling CMV infection.[15] Both CD4+ and CD8+ T lymphocytes are associated with protection against CMV infection with a complex interaction involving a CD8+ T cell response producing IFN-γ as well as a number of other cytokines in response to the CMV virus.[16] IFN-γ has been shown to have a pivotal role in the control of CMV infection.[17] A lack of CD8+ T cells in HSCT patients is associated with CMV infection, whereas immune reconstitution of CD8+ T cells is correlated with protection against CMV.[18] Monitoring the patient's CMV immune status would assist clinicians in evaluating the patient's ability to successfully control the infection. Application of this approach may help reduce the duration and intensity of CMV monitoring, and the duration of antiviral therapy or prophylaxis in patients demonstrating a robust immune response. Alternatively, a low immune response would indicate a high likelihood of CMV reactivation and therefore indicate that continued viral monitoring or extended anti-viral treatment may be required.

Importance of early immune monitoring in patients

It is generally accepted that T lymphocytes from the transplant donor are the primary source of CMV control as the recipients immunity has been ablated prior to transplant. This may be the case for fully myeloablated transplant recipients, but there is evidence that in reduced-intensity myeloablated stem cell transplants, CMV specific T cells from a seropositive recipient contribute to CMV immunity, particularly early after transplant.[19] An immune response is initiated by CMV-specific T cells, primarily CMV-specific CD8 T cells, triggered by an onset of viral replication, resulting in expansion of responsive cells. Reconstitution of CMV-CD8 T cells appears to be somewhat comparable for both donor seropositive and seronegative individuals, indicating that in some cases early immune protection is conferred by recipient derived CMV-specific CD8 T cells.[20] Sellar et al demonstrated that in recipient seropositive/donor seronegative (R+/D-) patients, CMV-specific CD8 T cells detected early following transplant were entirely derived by the recipient and were protective against CMV infection.[20] This data indicates that recipient-derived CMV-specific CD8 T cells which had survived ablation treatment could establish a rapid reconstitution of anti-viral protection. Therefore, functional assessment of the individuals CMV-specific T cell response early, within a couple of weeks, following HSCT could provide a mechanism to establish a patient risk stratification for those likely to develop



Conceptual image of human cytomegalovirus. Cytomegalovirus is a genus of the viral family Herpesviridae.

CMV infection or CMV disease, from those for whom their immune response is sufficient to provide protection. This concept has demonstrated feasibility in a study conducted by Nesher et al[18] where detection of high levels of CMV-specific cells following allo-HSCT was associated with protection from CMV reactivation. While the study results are encouraging, continued research is required to fully explore the complex relationship between donor T cell reconstitution and recipient T cell survival, and how it relates to overall CMV-specific immune competence and protection against CMV reactivation.

Early identification—perhaps even prior to HCT—of patients likely to experience CMV reactivation could then be incorporated into treatment algorithms thereby helping to guide decisions on whom to treat, optimal treatment paradigms, and potentially, length of treatment. Several studies are ongoing which address assessment of CMV-immune responses prior to transplant or within several weeks following transplant. It is anticipated that data from these studies will help to establish its clinical utility to risk stratify patients for personalized treatment strategies.

REFERENCES

1. Yong MK, Lewin SR, Manuel O. Immune Monitoring for CMV in Transplantation. Curr Infect. Dis. Rep 2018 20:4 doi:10.1007/s11908-018-0610-4.

2. Styczynski J. Who is the patient at risk of CMV recurrence: A review of the current scientific evidence with a focus on hematopoietic cell transplantation. Infect. Dis. Ther. 2018. 7:1-16. doi:10.1007/s40121-017-0180-z.

3. Freer G, Quaranta P, Pistello M. Evaluation of T Cell Immunity against Human Cytomegalovirus: Impact on Patient Management and Risk Assessment of Vertical Transmission. Journal of Immunology Research. 2016;2016:9384813. doi:10.1155/2016/9384813.

4. Picarda G, Benedict CA. Cytomegalovirus: Shape-Shifting the Immune System. J. Immunol. 200:3881-3889. 2018. doi:10.4049/jimmunol.1800171.

5. Lemmermann NA, Böhm V, Holtappels R, Reddehase MJ. In vivo impact of cytomegalovirus evasion of CD8 T-cell immunity: facts and thoughts based on murine models. Virus Res. 2011;157(2):161–74. doi: 10.1016/j.virusres.2010.09.022.

6. Broadley I, Pera A, Morrow G, Davies KA, Kern F. Expansions of Cytotoxic CD4+CD28– T Cells Drive Excess Cardiovascular Mortality in Rheumatoid Arthritis and Other Chronic Inflammatory Conditions and Are Triggered by CMV Infection. Frontiers in Immunology. 2017;8:195. doi:10.3389/fimmu.2017.00195.

7. Fülöp T, Larbi A, Pawelec G. Human T Cell Aging and the Impact of Persistent Viral Infections. Frontiers in Immunology. 2013;4:271. doi:10.3389/fimmu.2013.00271.

8. Sissons JG, Wills MR. How understanding immunology contributes to managing CMV disease in immunosuppressed patients: now and in future. Med Microbiol Immunol. 2015;204: 307– 316.

9. Rafailidis PI, Mourtzoukou EG, Varbobitis IC, Falagas ME. Severe cytomegalovirus infection in apparently immunocompetent patients: a systematic review. Virology Journal. 2008;5:47. doi:10.1186/1743-422X-5-47.

10. Blyth E, Withers B, Clancy L, Gottlieb D. CMV-specific immune reconstitution following allogeneic stem cell transplantation. Virulence, 2016;7(8), 967-980.

11. Ljungman P, Hakki M, Boeckh M. Cytomegalovirus in Hematopoietic Stem Cell Transplant Recipients. Hematology/Oncology Clinics of North America. 2011;25(1):151-169. doi:10.1016/j.hoc.2010.11.011.

12. Ariza-Heredia EJ, Nesher L, Chemaly RF. Cytomegalovirus diseases after hematopoietic stem cell transplantation: a mini-review. Cancer Lett. 2014;342(1):1–8. doi: 10.1016/j.canlet.2013.09.004.

13. Boeckh M, Ljungman P. How we treat cytomegalovirus in hematopoietic cell transplant recipients. Blood. 2009;113(23):5711-5719. doi:10.1182/blood-2008-10-143560.

14. Razonable RR, Hayden RT. Clinical Utility of Viral Load in Management of Cytomegalovirus Infection after Solid Organ Transplantation. Clinical Microbiology Reviews. 2013;26(4):703-727. doi:10.1128/CMR.00015-13.

15. Boeckh M, Leisenring W, Riddell SR, et al. Late cytomegalovirus disease and mortality in recipients of allogeneic hematopoietic stem cell transplants: importance of viral load and T-cell immunity. Blood. 2003;101:407–14.

16. Harari A, Zimmerli SC, Pantaleo G. Cytomegalovirus (CMV)-Specific cellular immune responses. Hum Immunol 2004; 65:500–6.

17. Cummins NW, Deziel PJ, Abraham RS, Razonable RR. Deficiency of cytomegalovirus (CMV)-specific CD8+ T cells in patients presenting with late-onset CMV disease several years after transplantation. Transpl Infect Dis 2009; 11:20–7.

18. Nesher L, Shah DP, Ariza-Heredia E J, et al. Utility of the enzyme-linked immunospot interferon-γ-release assay to predict the risk of cytomegalovirus infection in hematopoietic cell transplant recipients. The Journal of Infectious Diseases. 2016;213:1701–1707.

19. Ogonek J, Varanasi P, Luther S, et al. Possible impact of Cytomegalovirus-specific CD8+ T cells on immune reconstitution and conversion to complete donor chimerism after allogeneic stem cell transplantation. Biol. Blood Marrow Transplant, 2017 Mar 23. pii: S1083-8791(17)30362-2. doi: 10.1016/j.bbmt.2017.03.027.

20. Sellar RS, Vargas FA, Henry JY. CMV promotes recipient T-cell immunity following reduced-intensity T-cell-depleted HSCT, significantly modulating chimerism status. Blood. 2015;125:731–739.

Ted Blanchard, MBA, serves as Senior Manager of Strategic Marketing at **Oxford Immunotec USA, Inc.** Blanchard has over 10 years' experience in clinical and market development of drug and diagnostic products in the U.S. and international markets.

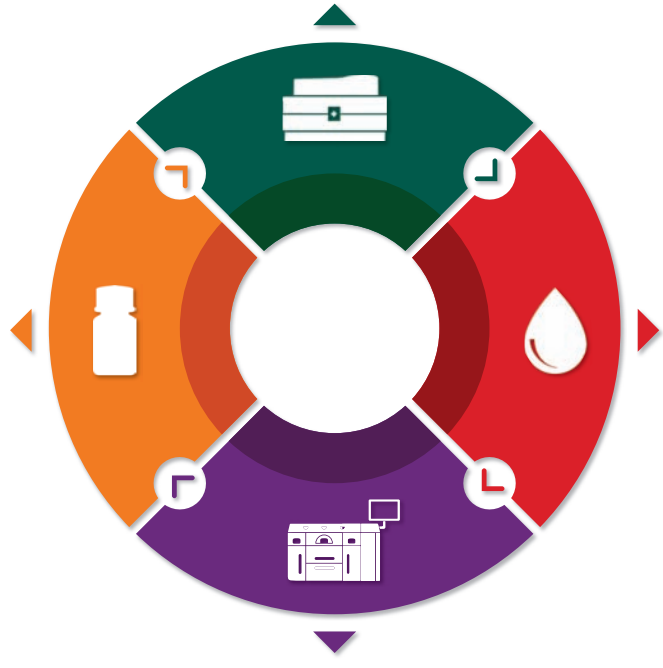
William Cruikshank, PhD, is Director of Medical and Scientific Affairs, Global at **Oxford Immunotec USA, Inc.** Cruikshank received his PhD degree in Biochemistry and has been studying pro-inflammatory cytokines for the past 40 years. His current interests involve understanding the immune's system regulation of M. tuberculosis and CMV infection in immunocompromised individuals.

RANDOX

DEDICATED TO IMPROVING HEALTH WORLDWIDE

RX SERIES

Five reliable and cost effective clinical chemistry analyzers on which to base your laboratory analysis, offering accurate results first time, every time.



QUALITY CONTROL

A complete laboratory QC solution comprising Third Party Controls, External Quality Assessment and Interlaboratory Data Management.

REAGENTS

The widest range of 116 clinical biochemistry tests, facilitating routine and niche testing on hundreds of routine biochemistry analyzers.

EVIDENCE SERIES

A range of immunoassay analysers that guarantee cost-effective, highly accurate and flexible testing solutions through utilising Biochip Array Technology.

marketing@randox.com

#ImprovingHealth

randox.com/improving-health

TEST QUESTIONS

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

1. **Which virus remains the main cause of morbidity and mortality in allogeneic hematopoietic stem cell transplant (allo-HSCT)?**
   - a. influenza
   - b. parainfluenza
   - c. norovirus
   - d. cytomegalovirus

2. **What are the main concerns with antiviral drugs that are effective at reducing viral loads?**
   - a. they are expensive
   - b. they have significant toxicity profiles
   - c. both a and b
   - d. none of the above

3. **In order to create a personalized risk stratification strategy to allo-HSCT patients receiving drugs for CMV, studies are being conducted that monitor CMV-specific immune response before or after the transplant.**
   - a. True
   - b. False

4. **The homeostatic balance between CMV viral replication in a host and the host's immune response to that replication is**
   - a. viral declination.
   - b. viral reactivation.
   - c. viral latency.
   - d. none of the above

5. **Which immune cells are responsible for keeping CMV from uncontrolled replication?**
   - a. T cells
   - b. B cells
   - c. Antigen presenting cells
   - d. all of the above

6. **Uncontrolled CNV viral replication can only affect the organs of the body.**
   - a. True
   - b. False

7. **Viral replication of CMV can present as all but the following**
   - a. encephalitis
   - b. pneumonia
   - c. osteomyelitis
   - d. neuropathy

8. **How soon does CMV reactivation typically occur after HSCT?**
   - a. 1 year
   - b. 9 months
   - c. 6 months
   - d. 3 months

9. **There are several antiviral drugs that are administered routinely as a part of CMV prophylaxis strategy in post-HSCT patients.**
   - a. True
   - b. False

10. **In order for a preemptive strategy to detect viral load to be successful, the virus must be detected**
    - a. before the onset of disease.
    - b. at the onset of disease.
    - c. after the onset of disease.
    - d. all of the above

11. **Which two testing methods are commonly used to monitor the viral load of CMV reactivation?**
    - a. PCR and viral culture
    - b. PCR and antibody immunoassay
    - c. antigenemia assay and biomarker assays
    - d. antigenemia assay and PCR

12. **When is the likelihood of CMV viral reactivation significantly reduced?**
    - a. 75 days post-transplant
    - b. 100 days post-transplant
    - c. 250 days post-transplant
    - d. 500 days post-transplant

13. **A main limitation in the utility of PCR results in detecting CMV viral load is that there is a lack of assay standardization limits for this patient population.**
    - a. True
    - b. False

14. **Which cytokine plays an important role in the control of CMV infection in HSCT patients?**
    - a. IFN-γ
    - b. IL-1
    - c. TNF-R
    - d. TNF-α

15. **Monitoring a lack of, or reconstitution of _____ cells can assist physicians in whether the patient is able to successfully control a CMV infection.**
    - a. CD4+ T
    - b. CD4+ B
    - c. CD8+ B
    - d. CD8+ T

16. **A study performed by Sellar et al. determined that in _____ patients, the CMV specific immune cells have originated from the recipient and was protective against CMV infection.**
    - a. R+/D+
    - b. R+/D-
    - c. R-/D-
    - d. R-/D+

17. **In order to provide a mechanism to establish risk stratification for the development of CMV, assessment of recipients' T cell response to CMV should occur within _____, following HSCT.**
    - a. a couple of days
    - b. a couple of weeks
    - c. a couple of months
    - d. a couple of years

18. **Once algorithms are developed based on studies of CMV-immune response in HSCT patients, decisions can be made about which/what factor(s)?**
    - a. optimal treatment standards
    - b. length of treatment
    - c. whom to treat
    - d. all of the above

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

PLEASE PRINT CLEARLY

NAME _____ MAILING ADDRESS _____ ☐ HOME ☐ WORK

CITY _____ STATE _____ ZIP _____ INSTITUTION/FACILITY _____

PHONE _____ E-MAIL ADDRESS _____

Send your $20 check payable to Northern Illinois University with this form to: University Outreach Services, Northern Illinois University, DeKalb, IL 60115-2860 Phone: 815-753-0031
FEE NOT REFUNDABLE OR TRANSFERABLE

P = Poor; E = Excellent

1. **To what extent did the article focus on or clarify the objectives?** P ① ② ③ ④ ⑤ E
2. **To what extent was the article well-organized and readable?** P ① ② ③ ④ ⑤ E
3. **How will you use the CE units?** ☐ state license ☐ employment ☐ recertification ☐ other

CE Licensure Information for FL and CA:

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

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

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

It’s what’s inside U.

Unity QC Data Management Solutions –
Your strategy to elevate your entire team’s quality performance.

Streamline workflow. Automate processes.
Increase confidence in reporting patient results.

Download infographic to discover how www.qcnet.com/unity

BIO-RAD

Hemoglobin A1c testing and diabetes management

By Jessica Pawlak, Ralph Ito, Catherine Cahill, Michael Sweatt

The Diabetes Research Institute Foundation has estimated a 50 percent increase in the number of people living with diabetes mellitus in the United States over the past decade.[1] With more than 400 million people living with and managing diabetes worldwide, the ability to accurately diagnose and track patient management is a growing need. The diagnosis of diabetes mellitus uses a combination of measurements: fasting serum glucose levels, presentation of symptoms, two-hour plasma glucose levels during a glucose tolerance test, and hemoglobin A1c (HbA1c) levels.[2] Current patient management includes diet, exercise, medication, daily monitoring of blood glucose, and HbA1c monitoring.

Mayo Clinic Laboratories emphasizes the value of controlling glucose levels to prevent long-term complications such as retinopathy, neuropathy, and cardiovascular disease. However, solely measuring and monitoring blood glucose levels has some limitations as the test only measures glucose levels at the time of testing and it relies on the patient to consistently test their levels at home, using a point-of-care device. To address these limitations and provide a broader indication of long-term glycemic control, HbA1c testing is used. It is typically performed in a laboratory setting and the test indicates the patient's average levels of blood glucose over the past 8 to 12 weeks. The NGSP, originally called the National Glycohemoglobin Standardization Program, supports the American Diabetes Association's recommendations that patients who are meeting glycemic goals be tested for HbA1c twice a year, while patients not meeting glycemic goals or patients with changes to therapies be tested every three months.[2,3] The American Diabetes Association sets a normal patient at < 5.7 percent, prediabetes patients at ≥ 5.7-6.5 percent, and diabetic patients at ≥ 6.5 percent HbA1c.[4]

Hemoglobin is the protein in red blood cells that transports oxygen.[5] HbA1c is a form of hemoglobin that is generated by a non-enzymatic glycation pathway, following a Schiff's base reaction and an Amadori rearrangement that occurs between glucose and the N-terminal valine of the hemoglobin beta chain.[2] This glycosylation is irreversible and occurs continually over the entire 8 to 12 week life span of a given erythrocyte.[3,5] This binding reaction reflects the average level of glucose that young and old red blood cells are exposed to over the course of 8 to 12 weeks. A blood sample will have a population of young-to-old red blood cells and the percent of HbA1c that is measured is a result of an average glucose level in the patient's sample over this time period. HbA1c is an excellent analyte to monitor a patient's glycemic control or therapeutic intervention.

Methods for measuring HbA1c include high pressure liquid chromatography based (HPLC), antibody based (immunoassay), and enzyme based (enzymatic) methods. Table 1 lists, in alphabetical order, twelve of the most common HbA1c assays with their claimed reportable ranges and reaction methods. The advantages and disadvantages of each should be considered in order to choose a method that best fits the patient population for which the laboratory is reporting results.

Table 1-HbA1c Assays and Linear Ranges

	A1c	Hb	NGSP HbA1c (%)	IFCC HbA1c (mmol/mol)	Method
Abbott Architect Chemistry			4.0-14.0	20-130	Enzymatic
Abbott Architect Immunoassay			4.0-14.5	20-135	Chemiluminescent*
Beckman Coulter AU		7.0-23.0	3.2-14.5	11-135	Turbidimetric*
Beckman Coulter UniCel DxC	0.3-5.0	6.0-24.0	4.0-17.0	20-162	Turbidimetric*
Bio-Rad VARIANT			3.5-19.0	15-184	HPLC
Ortho Vitros	0.08-2.53	5.0-30.3	3.0-15.4	9-145	Turbidimetric Endpoint*
Roche COBAS INTEGRA	0.3-2.6	4.0-40	4.2-20.1	22-195	Turbidimetric*
Roche cobas	0.3-2.6	4.0-40	4.2-20.1	22-195	Turbidimetric*
Siemens ADVIA			3.8-14.0	18-130	Turbidimetric*
Siemens DCA Vantage			2.5-14.0	9-130	Monoclonal Antibody Agglutination Reaction*
Siemens Dimension	0.3-2.6	5.0-25.0	3.6-16.0	16-151	Turbidimetric*
Tosoh HLC-723			3.4-18.8	14-182	HPLC

*Turbidimetric, chemiluminescent and agglutination methods are antibody based assays

With treatment standards being set by various governing associations across the world, it is critical that the values being reported to patients and professional caretakers be accurate. Prior to standardization, results were observed to vary ±4-8.1 percent on the same sample.[5] The accuracy of commercially available HbA1c tests has been improved by the International Federation of

Roche Point of Care

ACCU-CHEK® Inform II

FACT CHECK.

When it comes to professional blood glucose monitoring systems, you need a partner you can trust to deliver not only reliable results but also reliable information.

Roche is the only professional total glucose monitoring solution provider with meter/strips, lancets and a data management system.

Roche submitted data in November 2018 to the FDA seeking to expand existing claims for use of the Accu-Chek Inform II System with venous, arterial, and neonate arterial and heel stick samples in all hospitalized patients.[1]

System integrity checks and 24/7/365 live support give you confidence you can count on.

More POC glucose tests have been performed worldwide by the Accu-Chek® system than by any other company.*

Contact your Roche account executive to make sure you know the facts: go.roche.com/informfacts

1 The expanded use of venous whole blood, arterial whole blood, and neonate arterial and heel stick whole blood samples throughout all hospital and all professional healthcare settings including patients receiving intensive medical intervention/therapy is pending 510(k) clearance with the FDA and is not available in the US.

*Roche data on file 2018.

ACCU-CHEK®

Table 2-HbA1c Assay Interference with Hb Variants. Table is derived from NGSP Table.[3]

Method	HbC Interference	HbS Interference	HbE Interference	HbD Interference	Elevated HbF Interference
Abbott Architect c Enzymatic	No	No	No	No	—
Beckman AU system (reagent lot OSR6192, lot B00389 not yet evaluated)	**Yes** interference causes higher results	**Yes** interference causes higher results	No	No	No specific method data, assumes interference above 10-15%
Beckman Synchron System	No	No	No	No	No specific method data, assumes interference above 10-15%
Bio-Rad Variant II NU	No	No	No	No	No <10% HbF
Bio-Rad Variant II Turbo	No	No	**Yes** interference causes higher results	**Yes** interference causes higher results	No <5% HbF
Bio-Rad Variant II Turbo 2.0	No	No	No	No	No <25% HbF
Ortho-Clinical Vitros	No	No	No	No	No specific method data, assumes interference above 10-15%
Roche Cobas Integra Gen.2	No	No	No	No	No specific method data, assumes interference above 10-15%
Siemens Advia A1c (new version)	No	No	No specific method data, assumes no significant interference	No specific method data, assumes no significant interference	No specific method data, assumes interference above 10-15%
Siemens DCA 2000/Vantage	No	No	No	No	No <10% HbF
Siemens Dimension	No	No	No	No	No specific method data, assumes interference above 10-15%
Tosoh G7	**Yes** interference causes lower results	No	**Yes** interference causes lower results	No	No ≤30% HbF
Tosoh G8	**Yes** interference causes lower results (No for ver. 5.24)	**Yes** interference causes lower results (No for ver. 5.24)	**Yes** interference causes lower results (No for ver. 5.24)	**Yes** interference causes lower results (No for ver. 5.24)	No ≤30% HbF

Clinical Chemistry Working Group (IFCC-WG) on HbA1c.[3] This group established reference materials and methods for HbA1c that include values assigned by mass spectrometry and capillary electrophoresis.[3] A master equation was developed to demonstrate the relationship between NGSP measurements expressed as the %HbA1c of total hemoglobin and IFCC expressed in SI units (mmol/mol), where the relationship is: NGSP = (0.09148 * IFCC) + 2.152.[3] The IFCC primary reference material uses a mixture of purified HbA1c and HbAo that were isolated using cation exchange and affinity chromatography and is considered the only valid standardization for HbA1c.[3]

Accurately reporting HbA1c levels can be further complicated by patients with other clinical conditions or high levels of hemoglobin variants that interfere with HbA1c results. For example, patients with clinical conditions that lengthen the lifespan of their red blood cells (polycythemia) can produce falsely high HbA1c results, while patients with red blood cells with shorter life spans (hemolytic anemia) may produce HbA1c values lower than actual.[2,5] Patients with homozygous or double heterozygous forms of abnormal hemoglobin (CC, SS, EE, SC) have no hemoglobin A present and therefore no HbA1c can be measured in these patients.[2] Table 2 is a summary from the NGSP website of potential hemoglobin variants and their effect on common methods. The NGSP criteria used to determine whether or not a method shows interference that is clinically significant is > ±7 percent at 6 percent and/or > ±7 percent at 9 percent HbA1c.[3] The table shows that HbC and HbD do not interfere with the majority of the methods, with the exception of the Beckman AU and Tosoh G8 and G7. The advantage to HPLC methods (e.g. Tosoh and BioRad systems) is that the variants that can affect results will be detected in the chromatogram analysis and samples can be retested if necessary.

Establishing, validating, and verifying the linear reportable range claims of these methods is another critical component to reporting accurate patient results. Calibration Verification and Linearity experiments are standard procedures of practice in order to fulfill CLIA '88, CAP, ISO 15189, COLA, JCAHO, and JCI testing requirements and occurs on a frequency of at least once every 6 months and ideally using materials which are commercially available.[6,7] They are manufactured to predefined concentrations and

► You are Invited to Attend an Educational Webinar ◄

Consequences of FDA Changes to Critically Ill Bedside Glucose Testing Regulations

Clinical Consequences

Venous, Arterial and Now Capillary Samples are All FDA Cleared for Critical Care Patient Testing – Are All Specimen Types Analytically and Clinically Equivalent?

7KHFKRLFHRI VSHFLP HQWSHLVDQLP SRUWDQWFRQVLGHUDWLRQSDUWLFXODUO\ IRUWKHFULWLFDOO\ LOO7KLVSUHVHQWDWLRQZ LOOGLVFXVV WKHDQDO\WLFDOSHUIRUP DQFHGLIIHUHQFHVEHWZ HHQGLIIHUHQWVSHFLP HQWSHVDQGWKHLUFOLQLFDOVLJQL¿FDQFH 7KHGDWDLVEDVHG RQWKHUHVXOWVRI DQ)' $ FRP SDULVRQVWXG\ RI SDLUHGSDWLHQWWHVWUHVXOWV

Learning objectives:

- $ QDO\WLFDOSHUIRUP DQFHGLIIHUHQFHV
- &OLQLFDOVLJQL¿FDQFHRI WKHVHGLIIHUHQFHV
- 6XJJHVWHGEHVWSUDFWLFHWHVWLQJ SURFHGXUHV

Presenter:

Jeffrey A. DuBois, PhD.
9 3 RI 0 HGLFDODQG6FLHQWL¿F$ IIDLUV
Nova Biomedical

Regulatory/Legal Consequences

Regulatory Requirements for Off-Label Testing and Consequences of Non-Compliance

1 RYD6 WDW6WULS LV)' $ FOHDUHGDQG&/,$ Z DLYHGIRUXVHZ LWKDOOSDWLHQWVLQFOXGLQJ FULWLFDOO\ LOO8 VHRI DOORWKHUP HWHUV Z LWKDQ\ FULWLFDOO\ LOOSDWLHQWSRSXODWLRQLVFRQVLGHUHGRII OÐEHOE\ )' $ DQG&0 6 + RVSLWDOVFDQQRWFKDQJH)' $ RII ODEHOWHVWLQJ GHVLJQDWLRQVXVLQJ WKHLURZ QWHVWLQJ RUGH¿QLWLRQV 7KLVSUHVHQWDWLRQZ LOOGLVFXVVWKHKLVWRU\ DQGUDWLRQDOH IRUUHFHQW)' $ FKDQJHVWRFULWLFDOO\ LOOEHGVLGHWHVWLQJ DQGWKHUHJXODWRU\ DQGOHJDOFRQVHTXHQFHVRI RII ODEHOWHVWLQJ WR FDUHJLYHUVDQGKRVSLWDOV

Learning objectives:

- 5 HYLHZ WKHKLVWRU\ DQGUDWLRQDOHIRU)' $ FKDQJHVWREHGVLGH JOXFRVHWHVWLQJ
- : KHQEHGVLGHJOXFRVHWHVWLQJ LVRII ODEHO
-)' $ WHVWLQJ UHTXLUHP HQWIRURII ODEHOEHGVLGHJOXFRVHWHVWV
- 3DWLHQWULVNVIL RII ODEHOWHVWLQJ LVXVHGIRUFULWLFDOO\ LOOSDWLHQW
- &DUHJLYHU¶VSHUVRQDOOLDELOLW\ ULVNVZ KHQSHUIRUP LQJ RII ODEHO JOXFRVHWHVWLQJ
- + RVSLWDOOLDELOLW\ ULVNVZ KHQSHUIRUP LQJ RII ODEHOJOXFRVHWHVWLQJ
- &/ ,$ ULVNVZ KHQSHUIRUP LQJ RII ODEHOJOXFRVHWHVWLQJ

Presenter:

1 DWDOLD0 D]LQD (VT LVDQ)' $ FRP SOLDQFH DWWRUQH\ VSHFLDOL]LQJ LQP HGLFDOGHYLFHDQG SKDUP DFHXWLFDOODZ 6KHDGYLVHVSK\VLFLDQV DQGFRUSRUDWLRQVRQ)' $ FRP SOLDQFHP DWWHUV LQFOXGLQJ P HGLFDOGHYLFHXVHDQG SKDUP DFHXWLFDORII ODEHOSUHVFULELQJ 6KH DXWKRUHGWKH$ %$ + HDOWK/ DZ SXEOLFDWLRQ ³5 HFHQW' HYHORSP HQWVLQ2 II / DEHO8 VHDQG / HJDO,P SOLFDWLRQVWR3K\VLFLDQV´

► Date and Time ◄

Thursday, February 7th, 2019 • 1 PM Eastern Standard Time

► Educational Credits ◄

1. This webinar provides 1 contact hour for P.A.C.E. continuing education credits. Nova Biomedical is approved as a provider of continuing education programs in the clinical laboratory sciences by the ASCLS P.A.C.E program. P.A.C.E. is a registered trademark of the American Society for Clinical Laboratory Science
2. This meeting has been approved for a total of 1.0 contact hours of Continuing Education Credit toward fulfillment of the requirements of ASHRM designations of FASHRM (Fellow) and DFASHRM (Distinguished Fellow) and towards CPHRM renewal.
3. This Program Has Been Approved by the American Association of Critical-Care Nurses (AACN) for 1.00 Synergy CERP Category A

► Registration ◄

Go to www.novabio.us/webinars

nova® biomedical
www.novabiomedical.com

have recovery targets optimized to the claimed reportable range for various instrument vendors (e.g. Roche cobas 6000 and Tosoh G8). It is important to select materials that are designed to the type of method. For example, materials used on the Tosoh G8 analyzer (an HPLC method) must preserve all forms of hemoglobin integrity, thus limiting aberrant chromatography peaks caused by hemoglobin alterations or degradation. Immunoassay methods must preserve the specific epitope recognized by the antibodies for HbA1c that the manufacturer employs for the method.

Alongside the increasing number of people living with and managing diabetes, the ability to accurately diagnose prediabetes and diabetes patients also becomes critical. Standardization of results across platforms, and worldwide by the IFCC-WG, has resulted in more accurate results and it now becomes the reagent manufacturer's responsibility to continue to ensure their methods are traceable to the IFCC reference material and method. Laboratories have the continued responsibility to ensure the methods they are using to report HbA1c values are providing accurate results by running Internal Quality Controls (IQC), Calibration Verification and participating in Proficiency Testing, and External Quality Assurance (EQA) schemes.

The more recent trend toward point-of-care testing for HbA1c adds value to professional caretakers, providing visibility to the patient's HbA1c trends and allowing for real-time adjustment to patient care plans. However, as this test moves out of the laboratory and toward point-of-care where regulations are different, considerations for the specificity, precision, accuracy, and reportable range of these methods needs to be a focus.[5]

REFERENCES

1. What is Diabetes? Diabetes Research Institute Foundation website https://www.diabetesresearch.org/what-is-diabetes. Accessed November 26, 2018.
2. Test ID: HbA1c. Mayo Clinic Laboratories website https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/82080. Accessed November 26, 2018.
3. Clinical Use, HbA1c Assay Interferences and IFCC Standardization. NGSP website http://www.ngsp.org/index.asp. Updated October 2018. Accessed November 26, 2018.
4. Diagnosing Diabetes and Learning about Prediabetes. American Diabetes Association website http://www.diabetes.org/diabetes-basics/diagnosis/?loc=db-slabnav. Accessed November 26, 2018.
5. Gupta S, Jain U, Chauhan N. Laboratory Diagnosis of HbA1c: A Review. Journal of Nanomedicine Research. 2017; 5(4):00120. DOI: 10.15406/jnmr.2017.05.00120.
6. Linearity and Calibration Verification FAQs. LGC Maine Standards website https://www.mainestandards.com/support/faq-calibration-verification.php. Accessed November 27, 2018.
7. CLIA '88. 42 CFR 493 in section 493.1253. Code of Federal regulations website. https://www.gpo.gov/fdsys/pkg/CFR-2003-title42-vol3/xml/CFR-2003-title42-vol3-part493.xml#seqnum493.1253. Accessed November 27, 2018.

Jessica Pawlak, holds a Bachelor of Science in Biochemistry from Boston College, and a Master of Science in Biochemistry from the University of Maine. Her career includes work in both academia and industry, as well as an internship at the National Institutes of Health. Jessica joined **LGC Maine Standards** in February 2010 as a Research Scientist I and is currently the R&D Manager overseeing LGC Maine Standards new product development and product support activities including the HbA1c product line.

Michael Sweatt serves as General Manager, **LGC Maine Standards**
Ralph Ito serves as Chief Scientific Officer, **LGC Maine Standards**
Catherine Cahill serves as Technical Support Supervisor/Product Manager, **LGC Maine Standards**

HOLOGIC®

FUSION SEASON

Impact patient care when needed most.

PANTHER FUSION® Flu A/B/RSV Assay

PANTHER FUSION® AdV/hMPV/RV Assay

PANTHER FUSION® Paraflu Assay

FLU SEASON *READY*

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

PANTHER FUSION®

Microchimerism—when you're just not yourself

By John Brunstein, PhD

It's generally taken for granted that all cells in an organism share identical chromosomal DNA sequences, since they originated from a single cell zygote fused of parental gametes which undergoes rounds of cell division and differentiation to form what is eventually the mature organism. In fact, it's this concept which is the basis for applications of pluripotent stem cells in regenerative medicine. Almost nothing in biology is absolute however and in this month's edition we're going to look at some of the cases where this "truth" doesn't hold true—that is, somatic microchimerism.

By definition, this is a situation where some somatic cells in the organism have sequence variations from other cells in the organism (chimerism); where this is only a small fraction of the total cells, we append the "micro" part. Note that this is sequence only and doesn't concern itself with epigenetic variations which we already accept can vary between cells. An immediate example of microchimerism which readers will be familiar with, is in various B and T cell lineages, where V/D/J recombinational events give rise to cell populations with relatively small variations from their progenitors. We could also envision this happening through de novo mutation; a cell gets a DNA lesion leading to a sequence change, and then any products of its division will inherit this change. Since we've already said this is a somatic cell, these changes won't however transmit to offspring, and will be limited to whatever proportion of cells originated from the point of mutation. If this happens to occur very early in gestation, we might even expect a sizeable proportion of adult tissue to bear this change relative to surrounding tissue; as a proportion of genome variation from the bulk average though it's still likely quite small. (If it were not small, there's a higher chance of the mutation and its impacted progeny cells having serious deleterious effects up to and including embryonic lethality, so there's a selective pressure on these types of somatic microchiomerisms being relatively small). Note that in these cases, the amount of genetic variation from source genome is pretty small as well—from single nucleotide polymorphisms (SNPs) through indels—but overall, the genome between mutant and non-mutant cells is nearly identical.

Bigger differences—cells from another source

In addition to these examples with small proportional variations in genotype, there is also ways for an adult human to be walking around with a small fraction of their cells bearing very dramatically different genotypes than the rest. These are the more interesting examples of somatic microchimerism. How do they arise, do they have any clinical impacts, and what sorts of lab results would detect them?

One way this can arise is during pregnancy: if fetal cells cross the placenta and engraft themselves in maternal tissue. While this could presumably happen with fetuses of either gender, it's easiest to detect by looking at long term (i.e., years) postpartum mothers of male offspring with a molecular test for cells bearing holandric markers (ones from the nonhomologous part of the Y chromosome) and most studies have focused on this easily discernable group. Actually, it turns out that such male-specific markers can be also be detected in a significant fraction of women who haven't delivered male children; postulated sources include miscarried or non-implanted male embryos or a vanished fraternal male twin. Regardless of source, it turns out that it's not rare for adult females carry detectable male cells which can't be explained as simple short-term residual from transplacental bloodstream mixing in their bodies, with one representative study[1] reporting prevalence on the order of 10 to 20 percent. Another study which specifically examined what we would normally consider to be an immunologically privileged zone, the brain, and reported finding evidence of this in an amazing 63 percent of women tested[2]—perhaps because the body is less able to clear out foreign cells from this compartment.

Health effects?

Are there direct consequences of this long-term persistence of "foreign" cells in the body? The short answer for now seems to be "perhaps." It's known that autoimmune diseases predominantly effect women by a ratio of about four to one, and fetal microchimerism has been postulated as one cause of this. A number of studies have examined women with and without autoimmune conditions for their levels of detectable holandric markers, with results ranging from no significant correlation to strong correlation of disease state with detectable residual male cells. This disparity in results has come from a wide range of specific autoimmune presentations including progressive systemic sclerosis, systemic lupus erythematosus, Sjogren's syndrome, Hashimoto's thyroiditis, rheumatoid arthritis, and others. Are some of these more likely to be triggered by residual fetal cells than others? Maybe. Alternatively, is there perhaps some issue with what tissue or sample type was taken between different studies, with the studies finding no correlation missing the tissue(s) where male cells were resident? Again, "maybe." While there are some tantalizing hints that fetal derived microchimerism may be playing a role here, it seems that further studies will be needed to clarify if that's so.

Just to add a further twist to that story, it's also been suggested that these persisting fetal derived cells may provide health benefits to the mother. Some studies have provided

evidence that these cells can be found associated with healed wounds, suggesting either they partake an active role in wound healing or that the wound healing environment selectively supports their proliferation and persistence. The fetal tissue in brain study referenced above observed an inverse prevalence between male derived cells in female brains and incidence of Alzheimer's disease, again possible suggesting they may provide a protective role.

We noted above that "vanished fraternal twin"—more properly known as tetragametic chimerism—is one possible source of somatic microchimerism. This occurs during a fraternal twin pregnancy setting where one embryo in effect absorbs the other, usually early on and without anyone's knowledge. It can presumably occur without gender bias toward the surviving newborn, meaning we might expect to find examples of both adult men and women with detectable traces of this event. Although exceedingly rarely detected (possibly because we don't normally look for it), around one hundred clear cases of this exist in the literature where overt evidence was present. The most commonly detected manifestation of this seems to be where a person carries multiple blood types and is picked up in blood typing. A few more spectacular cases even made it into public literature, where DNA testing has revealed cases of parents (both male and female) where their offspring didn't appear to be theirs. Of course, in such cases there are less exotic possible causes of the findings, but in these particular instances other reasons were ruled out and the only possible solution was determined to be that the "non-parent" was generating at least some gametes which were, really, genetically those of a fraternal twin. While most of these cases of somatic microchimerism appear to be harmless or likely even unnoticed, in at least some cases they have been found to cause autoimmune health issues where two complete, but different immune cell lineages are circulating.

A less exotic way for limited somatic microchimerism to occur can also be through blood transfusion. Specifically, if nonleukoreduced blood products are transfused, there's good evidence of long-term persistence of the donor white cells in a significant number of cases; on the order of half of trauma patients who received nonleukoreduced red cells have detectable donor cells in circulation two to three years later.[3] It's interesting to speculate on whether this might in and of itself lead to health outcomes, although this author is not aware of any data yet suggesting this to be the case.

Where and when do we see this?

From the preceding overview it's apparent that in most cases there is little to no overt evidence of somatic microchimerism; as such it's likely underreported and as deep sequencing methods are deployed on larger numbers of patients, more examples (and a more accurate appreciation for the true frequency at which it occurs) will be uncovered. This should provide a better data set from which to assess whether there are significant links of this condition to health outcomes. For the meantime, should your lab be facing a case with discordant genetic results, human and process errors in sample collection and labeling are still prime candidates for source of confusion. If, however, repeat samples keep giving you these same strange results, keep in mind there's a very, very small but nonzero chance that you may be looking at microchimerism.

For those readers interested in learning more about this topic, in addition to the specific references cited below a good starting point would be the review article listed as reference [4].

REFERENCES

1. Lambert NC, Pang JM, Yan Z, et al. Male microchimerism in women with systemic sclerosis and healthy women who have never given birth to a son. *Annals of the Rheumatic Diseases* 64:845-848 (2005).
2. Chan WF, Gurnot C, Montine TJ, Sonnen JA, Guthrie KA, Nelson JL. Male microchimerism in the human female brain. PLoS One. 7(9) (2012).
3. TH Lee, T. Paglieroni, GH Utter, et al. High-level long-term white blood cell microchimerism after transfusion of leukoreduced blood components to patients resuscitated after severe traumatic injury. Transfusion 45(8) 1280-1290 (2005).
4. Maureen A. Knippen. Microchimerism: Sharing Genes in Illness and in Health. ISRN Nursing 2011, Article ID 893819.

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

2019 Primer Topics

FEBRUARY
PCR for Antibiotic Resistance Markers – Not the Whole Story?

MARCH
Limits of Detection: What's the Probability Your Negative Sample is Actually Negative?

APRIL
WGS vs WES: Why the Exome Isn't the Whole Story

MAY
Long Term Persistence of Pathogen DNA

JUNE
Quantitative Trait Loci – Uncovering Genes for a Continuously Variable Trait

JULY
Warfarin: Lessons in Pharmacogenomics

AUGUST
Jumping Genes: Alu Elements in Human Disease

SEPTEMBER
Getting to the End: Telomeres in Clinical Settings

OCTOBER
Histone Acetylation: An Emerging Target

NOVEMBER
Reverse Transcriptase Inhibitors: NRTIs vs NNRTIs

DECEMBER
What's With Hot Start? A Tale of Mispriming

Automation advancements continue to meet evolving urinalysis laboratory needs

By Danette Godfrey, MS, MT(ASCP)

Testing of urine samples for diagnostic purposes began more than 6,000 years ago. From ancient times, to the technique's pinnacle of popularity in the Middle Ages, and then into the Victorian era, a patient's urine was used to both diagnose and foretell. Fast forward to modern times, urine tests are one of the most commonly ordered tests. No longer recorded on clay tablets, laboratories are pressured to produce accurate, valid, and high-quality results that provide clinical value to the physician, all while meeting turnaround time expectations with less staff and tightened budgets. Decreasing reimbursements, increased test utilization oversight, and regulated clinical quality metrics add to the stress of reducing clinical laboratory test volumes and budgets while increasing quality assurance monitoring and documentation. Because of the challenges faced by today's labs, solutions are required that streamline workflow and reduce the labor-intensive manual processes of traditional urinalysis methods while minimizing operating and capital expenditures.

State of urinalysis

In the mid 90's, automated quantitative analysis of formed elements in urine combined with flow cytometry technology lead to a reduction in the fundamental need for laboratory technicians and technologists to perform manual microscopy in the urinalysis department. However, samples that were flagged as abnormal by the analyzers still needed to be confirmed visually, so laboratories centrifuged samples and performed sediment reviews. Such manual methods lacked precision, leading to potential variation in results. Just two years ago, improvements in automation brought standardization to urinalysis testing. Today, clinical laboratories are focusing on integrated systems with features such as calibration, sample transport technology, and test scheduling capabilities; however, these systems remain incomplete, missing the benefits of either flow cytometry or urine digital imaging.

While extensive advancements have been made in urinalysis, especially with automation, there is still much room for improvement. Physicians could enjoy greater confidence in diagnostic decision making if given more accurate and precise results. There is a need for better sensitivity and specificity in bacteria detection, as well as a need for more efficient differentiation of Gram-Negative and Gram-Positive bacteria to support treatment options.

Advancements in quality control and quality management practices could also benefit the urinalysis lab. Performing laborious manual reviews of quality statistics is time consuming and current systems do not enable an efficient approach to meeting regulatory compliance requirements. And while closed-tube sampling (CTS) technology or cap piercing offers many user benefits including efficiency and safety, a low-cost standard for this feature means many laboratories don't get to experience the benefits of cap piercing. This is especially challenging for high-volume laboratories.

The dream urinalysis department

Take a few moments to imagine the perfect urinalysis department. This dream department is equipped with a "fully" automated urine particle analyzer, reducing the need for manual slide reviews and delivering first-pass accuracy and unprecedented workflow efficiency. The ideal automation consists of a modular system that offers the flexibility to meet every laboratory's needs—in other words, this dream lab is fully customizable. Multiple instrument configuration options would offer simple upsizing and downsizing should physician order profiles change, or solution splits become necessary. Throughput could be increased by adding chemistry analyzers, flow cytometers, or digital image analysis components as needed. Decreased specimen handling would eliminate the opportunity for clerical errors. More accurate test results could be achieved with greater standardization and advanced automation. This dream analyzer would have intelligent software that allows for rules-based workflow management and result interpretation that is specific to the laboratory policies. It would be an innovative system with automated quality control monitoring and the ability to send messages to laboratory managers or service representatives when the device requires attention. It would also provide laboratory personnel with easy-to-read troubleshooting guidance and real-time reporting of analyzer status. This dream urinalysis department is supported with advanced tools, training, and quality control options, offering the best of modern technology and personal support to ensure the laboratory's success.

Tools

Advanced tools and powerful software systems are specifically designed to drive greater insight into—and control over—both processes and information across the healthcare network. Automating instrument calibration and calibration verification programs offers a reduction of non-productive analyzer time. Business intelligence reporting allows improvement of clinical performance, productivity, and staffing decision-making. Mobile technology tools enable sharing of analyzer performance history, workflow analytics, and educational requirements throughout an organization.

Quantimetrix®

We've got you covered from the central lab to the point-of-care!

New
Dipper POCT®
Single-Use Liquid Urinalysis Dipstick Control*

New
CHROMA
SCOPICS®
Liquid Urinalysis Control with Microscopics
Designed for Siemens Clinitek Novus & Atellica

Urinalysis QC, however you need it!

Learn more @
quantimetrix.com

*Dipsticks not included.

Training

Training is essential to expanding the diagnostic knowledge of staff and helping laboratories deal with the growing challenges of personnel shortages. It plays a key role in ensuring that laboratories get the most out of the investments they make in both hardware and software. In-person training, regional conferences, and user groups are good options for continuing education, but access is limited, and labs may incur expenses and/or inconvenience. Conversely, web-based training programs ensure that all technologists receive standardized training from the manufacturer, assuring consistent knowledge within a lab or across a lab network. Webinars, e-learning, and self-paced training platforms also enable better efficiency and lower costs of training employees.

Quality control and management

New and inventive approaches to simplified, fully integrated, and automated analyzers lend themselves to web-based quality control and management. Such innovation will streamline the process of running controls and verifying result acceptability. This occurs by identifying issues systematically through routine and traditional quality control approaches, so problems can be resolved before the laboratory even knows one exists. Predictive monitoring will take data interpretation to the advanced level that is needed to overcome today's challenges.

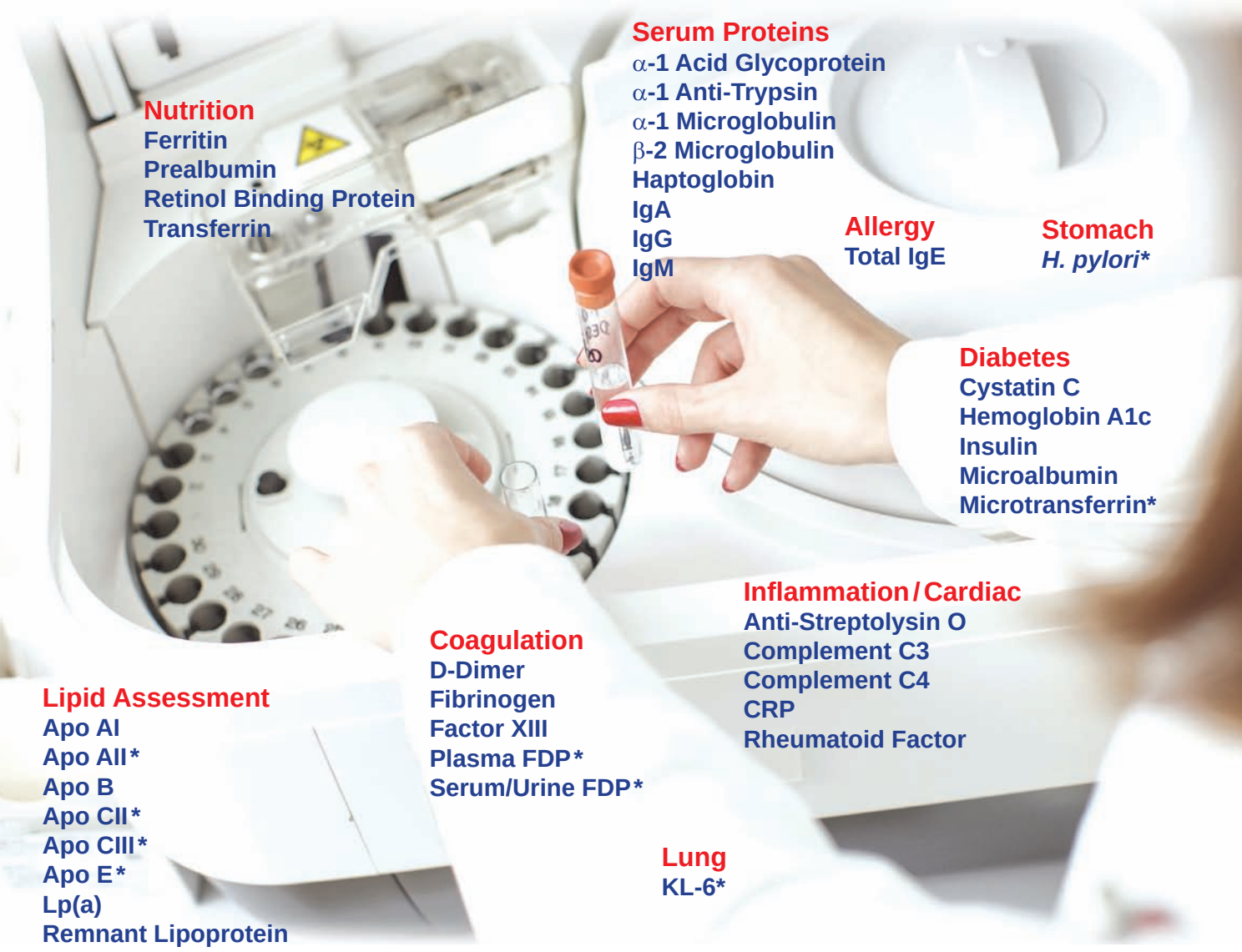
While the pressures of staffing challenges and declining reimbursement combine with growing demands for result accuracy and workflow efficiency, the need for new and innovative products becomes more apparent. Manufacturers will be expected to provide automated processes, tools, and service support that maximize instrument uptime. Current lab leadership will need to form partnerships with healthcare diagnostic companies to bring such solutions to market in the future. Laboratory purchase decisions will continue to be based on quality and reliability, as well as system flexibility and superior technology, all of which are needed to give technicians more time to apply their expertise analyzing test results.

Danette Godfrey, MS, MT(ASCP), serves as director of IVD product marketing at **Sysmex America, Inc.** She is responsible for product, service, and integrated technology solutions marketing for hematology, urinalysis, and flow cytometry testing. Danette's 25 years of healthcare experience includes both medical laboratory technical and marketing positions.

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

Immunoassay Reagents for chemistry analyzers™

Over 37 different assays available



Nutrition
Ferritin
Prealbumin
Retinol Binding Protein
Transferrin

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

Allergy
Total IgE

Stomach
*H. pylori**

Diabetes
Cystatin C
Hemoglobin A1c
Insulin
Microalbumin
Microtransferrin*

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

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

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

Lung
KL-6*

New Products Now Available!!

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

* Research Use Only

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

Exploring cost of quality in the lab

By Andy Quintenz and Paul Williams

A statement frequently used in healthcare medicine which also applies to quality systems used in the clinical laboratory is, "prevention is better than cure." There's little doubt that anyone who works in a lab knows that the prevention of adverse incidents is preferable to implementing corrective actions once an issue occurs. However, in today's healthcare economic environment, many lab management teams are finding their resources are stretched to the breaking point, forcing them to make worrisome cuts that could potentially affect the quality of patient tests. Applying cost of quality principles is a solution that assists labs in making fiscally sound decisions while maintaining high standards of quality.

Quality processes have a clear relationship with laboratory costs. If more money is invested in good quality processes, there will be both fewer errors and decreased costs related to failure recovery. If little attention is given to good quality processes, failures (and the corresponding cost of poor quality) will increase.

A cost of quality mindset not only works to streamline lab processes, reduce waste, and cut unnecessary expenses, but invests in positive quality processes that can ultimately drive down overall failure costs for both the short and long term.

It is important to remember that quality issues are usually due to inefficient or flawed laboratory processes, and high failure costs are rarely the fault of lab staff.[1]

Why quality principles are so essential

Customers, clinicians, and patients should always be the first priority for a healthcare business. Every laboratory should strive to provide customers with superior and dependable services, including implementing a cost of quality approach. While implementing additional quality processes might seem like an unnecessary expense, the subsequent reduction of high failure costs more than justifies the initial expenses. It takes both effort and financial investment to produce high quality services, but it is far more costly to deal with the failures that arise from neglecting quality. High quality efforts reduce waste and help the laboratory maintain a more strategic and effective budget.

Keep in mind, if money is not spent on quality activities, the number of errors and failures will be much higher, potentially presenting daunting economic consequences.

What are the costs of quality?

First, to understand how quality costs affect the lab, it is important to recognize that there are both good and poor quality costs. *Good quality costs* are divided into two categories:

1. Prevention costs—spent on quality activities intended to proactively prevent problems from occurring, and
2. Appraisal costs—spent on quality activities intended to identify current issues and prevent them from happening again.

Poor quality costs attempt to deal with the consequences of quality failures (also called non-conforming events) which can be very expensive. *Poor quality costs* are also divided into two categories:

1. Internal failure costs—spent on resolving errors before they leave the lab's control, and
2. External failure costs—spent on resolving errors after they have left the lab's control. These are the highest quality costs.

While good quality costs are usually easy to identify in a lab budget, poor quality costs are not always as straightforward; failure costs don't have their own category and are often folded into the rest of the budget.

For example, it is easier to identify how much is being spent on proficiency testing or preventive maintenance than it is to determine how expired materials or invalid instrument runs affect the budget. This means that labs may not have a clear picture of how much money and time failures are costing them. Chances are, a laboratory is spending far more on failure costs than expected.

Types of quality cost

Prevention costs prevent problems from happening in the first place. Examples include:

- Quality management system
- Quality planning
- Quality improvement activities
- Quality education
- Validation of lab processes before they are implemented
- Initial staff competency assessments
- Preventive maintenance

Appraisal costs assess service and product quality. Examples include:

- Ongoing competency assessments
- Tracking quality indicators
- Internal audit programs
- External accreditations
- Instrument calibration
- Sample and reagent inspections
- Quality control (QC) materials and data evaluation
- Proficiency testing

Internal failure costs resolve failures while they are still under laboratory control. Examples include:

- Pre-examination issues (insufficient/flawed/mislabeled samples, data entry errors, etc.)
- Invalid instrument runs
- Expired reagents/materials
- Rework, repairs, retesting
- Downtime

External failure costs resolve problems once they have left laboratory control. Examples include:

- Lost/erroneous reports
- Customer complaints
- Report recalls
- Misdiagnoses
- Damaged reputation
- Lost revenue
- Lawsuits

Understanding the cost of quality in practice

Quality control (QC) materials are an example of a "key appraisal activity." If QC isn't run frequently enough, a laboratory might not realize an instrument is malfunctioning and producing invalid results.

For example, let's assume QC that is typically run once per day is reduced to once per week. If something changes after the

QC is performed, the laboratory will not know that the instrument is functioning incorrectly until the following week. The entire week's results will be called into question. Those results need to be re-evaluated, and if any affected information was submitted from the laboratory, it will need to be retracted. If the results leave the laboratory and reach the customer, those invalid results could negatively affect patient treatment, and have major economic consequences for that laboratory. Dealing with this QC failure quickly becomes much more costly than it would have been to simply run QC more frequently.

How to identify and track quality costs

In order to implement strategic cost of quality procedures, the lab team first needs to understand how it is currently spending money on quality costs. From there, it can identify target areas with high failure rates and opportunities for more comprehensive prevention activities.

It is a good practice to create a list of good quality costs and then ask the laboratory's budget administrator to help find those costs in the budget. While these costs are relatively easy to identify, it is worth noting that some good quality costs also require labor, which may not be captured. The lab should decide if the amount of labor is high enough relative to the hard costs to make it worthwhile to calculate; if not, they may choose to ignore it.

In order to understand exactly how much money a laboratory is losing on failure costs, it is helpful to take a practical approach to those costs.

How to identify and calculate failure costs

Tackling the identification and calculation of specific failure costs may seem somewhat overwhelming at first but doesn't have to be. A good place to start is with is Key Performance Indicators (KPIs) or Non-Conforming Events (NCEs). Most laboratories will have statistics about the frequency of failures being tracked as KPIs or NCEs, which will make this first task significantly easier to manage.

First, *determine key non-conforming events*. These incidents (i.e., lost reports, unacceptable samples, or any other instances of quality failures) can cost the laboratory a great deal of money. When focusing on high severity or non-conforming events, it can be helpful to prioritize those that have the greatest effect on patient care or those that occur the most often.

Next, *calculate the failure cost for each non-conforming event*. These costs should include all materials needed to recover from the failure and, if necessary, to re-perform the tests. It should also include any labor costs needed to troubleshoot and fix the problem, including time documentation and supervision.

Examine the budget and identify the relevant costs (labor, material, etc.) that were expended because of that non-conforming event. Add up these costs to get an estimate of how much money that specific quality failure cost the laboratory. Each time a non-conforming event occurs, the lab now has a pre-calculated estimate of how expensive that quality failure is.

Last, *track how much money each non-conforming event costs the laboratory*. Achieve this by simply multipling the failure cost by how many times that event occurs over a certain period of time. This will estimate how much money this recurring quality failure is costing the laboratory over time.

How to reduce failure costs

Laboratories can reduce failure costs through a combined system of prevention and appraisal activities that minimizes waste and variation in lab processes.

It might seem logical to tackle each problem as it presents itself, but relying too heavily on retroactive problem solving can be expensive and inefficient, and makes for very high appraisal costs. Investing more money in advance will actually prevent most problems from occurring in the first place, while still effectively dealing with any issues.

Four strategies for reducing the cost of poor quality

1. Begin routinely identifying and tracking quality costs in the budget. This will allow the lab to understand how much is spent on quality and where those quality costs are used.
2. Recognize key non-conforming events that affect patient safety, have negative trends, or result in large failure costs. Can these be reduced by prevention or appraisal activities?
3. Start reporting Cost of Poor Quality (CoPQ) data, and include failure costs in lab quality reports or non-conforming incident reports. If failure costs are clearly displayed, they will draw attention to areas for improvement. Consistently reporting CoPQ data will also allow laboratories to track how failure costs are affected by various quality improvement efforts.
4. Educate staff at every level about cost of quality principles, and share CoPQ data throughout the organization. When everyone understands why certain measures or approaches are implemented, they can work together towards a more cost-effective quality system. CoPQ data will also facilitate healthy conversations with lab administrators or finance departments on the value of quality programs.

Reporting failure costs

When reporting failure costs, make sure they are clear and easy to understand. It is more important to have a useful, practical, straight- forward estimate than a highly specific figure that took extensive time and resources to determine. A simple estimate will serve as usable, actionable information and simplify communication and comprehension.

Conclusion

Instead of conducting limited quality activities and dealing with failures as they occur, it is more cost-effective to develop comprehensive preventive procedures and efficient problem-solving strategies. Integrating cost of quality principles works to the advantage of the lab, the customers, and the budget. Devoting more attention to strategic quality processes can lower costs while making the lab more efficient and reliable.

REFERENCE

1. Plebani, Mario. The Detection and Prevention of Errors in Laboratory Medicine. *Annals of Clinical Biochemistry: International Journal of Laboratory Medicine*. December, 2009.

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

Paul Williams is President of **MediaLine Communications** and serves as a communications and education consultant to leading health and science organizations around the world.

The importance of implementing a quality management system in the laboratory

By Joanne P. Christopher, MA, ELS

Laboratory quality can be defined as accuracy, reliability, and timeliness of reported test results. To be useful, laboratory results must be as accurate as possible, all aspects of the laboratory operations must be reliable, and reporting must be timely. Some significant consequences of poor quality in the laboratory can include:[1] unnecessary treatment or treatment complications, failure to provide correct treatment, delayed diagnosis, and unnecessary follow-up diagnostic testing. These consequences result in increased cost in time and work, as well as poor patient outcomes. Two facets of quality management in the laboratory are quality control (QC) and quality assurance (QA).

Quality control vs quality assurance

QC is defined by the International Organization for Standardization (ISO) as the part of quality management focused on fulfilling quality requirements.[2] QC requirements are mandated by regulatory agencies and must be followed by the laboratory to fulfill accreditation requirements set forth by those regulatory agencies. ISO's standard *Medical laboratories–requirements for quality and competence* (ISO 15189: 2012) delineates a set of requirements the laboratory must fulfill to pass accreditation requirements set forth by accrediting agencies.[3] Some accrediting organizations use the information in ISO 15189 to guide the inspection and accreditation process. While the ISO standard provides broad-based guidance on implementation of regulatory requirements, other standards are available for the laboratory that gives step-by-step detailed guidance on how to fulfill these requirements.[4]

QA is the part of quality management focused on providing confidence that quality requirements will be fulfilled.[2] Implementation of a quality management system (QMS) is an effective way to ensure QC and QA goals are met and maintained in the laboratory.

The quality management system

Laboratory error can be minimized by the implementation of an effective quality management system (QMS). A laboratory QMS is a systematic, integrated set of activities to establish and control the work processes from preanalytical through postanalytical processes, manage resources, conduct evaluations, and make continual improvements to ensure consistent quality results.[5] All aspects of the laboratory operation—including the organizational structure, processes, and procedures—need to be attended to in a QMS. In the U.S., a QMS is a Clinical Laboratory Improvement Amendment (CLIA) requirement.[6] A laboratory that implements the QMS model can expect the following outcomes:[4] better ability to reduce or eliminate error, higher likelihood of meeting customer expectations, more effective and efficient operations, and greater potential for successful governmental and accreditation assessments.

The quality management system model for laboratory services, shown in Figure 1 (available online at www.mlo-online.com), organizes all laboratory activities into 12 quality system essentials.

The quality system essentials

The quality system essentials (QSE) are the building blocks of a QMS. All 12 QSEs must be included in the QMS to assure accurate, reliable, and timely laboratory results. The 12 QSEs may be implemented in the order that is most effective for each individual laboratory. Implementing a QMS does not guarantee an error-free laboratory, but it can help maintain a high-quality laboratory that detects errors and prevents them from recurring.[1]

The 12 quality system essentials are:[4]

1. **Organization:** Describes key leadership responsibilities that are integral to a laboratory's success in achieving and maintaining a systematic approach to quality and meeting regulatory, accreditation, customer, and internal requirements.
2. **Customer focus:** Describes the need to design work to meet the expectation of laboratory customers. It also describes methods for seeking customer input to confirm that expectations are continually met.
3. **Facilities and safety:** Provides information about the maintenance and safety programs needed to support the laboratory. The laboratory needs to establish and maintain a facility that provides adequate space, workflow, and environmental conditions to support the quality of work and safety for all staff, in compliance with requirements.
4. **Personnel:** Describes obtaining and retaining an adequate number of qualified, well-trained, and competent laboratory staff to perform and manage the activities of the laboratory.
5. **Purchasing and inventory**: Describes agreements that the laboratory has with customers and outside vendors to ensure that specified requirements for critical supplies and services are consistently met.
6. **Equipment**: Describes selection and installation of equipment, equipment maintenance and calibration, documentation of equipment-related problems, and record maintenance.
7. **Process management:** Describes processes directly and indirectly related to the laboratories path of workflow to meet requirements and maintain efficient use of resources.

8. Documents and records: Describes the creation, management, and retention of the policy, process, and procedure documents for the QSEs and path of workflow.

9. Information management: Provides guidance for managing the information generated and entered into laboratory recordkeeping systems (e.g., patient demographics, examination results and reports, interpretations).

10. Nonconforming event management: Describes processes for detecting and documenting nonconformances, classifying nonconformances for analysis, and correcting the problems they represent.

11. Assessments: Describes the use of external and internal monitoring and assessments to verify that laboratory processes meet requirements and to determine how well those processes are functioning.

12. Continual improvement: Describes mechanisms for identifying opportunities for improvement and developing a strategy to continue this improvement.

Conclusion

Implementing a QMS in the laboratory is essential to providing quality test results and patient care and is a requirement for passing and maintaining laboratory accreditation in the U.S. under CLIA regulations.

Joanne P. Christopher, MA, ELS is a content specialist for the **Clinical and Laboratory Standards Institute (CLSI)**. She is a board certified life sciences editor and a member of the American Medical Writers' Association (AMWA) and the Board of Editors in the Life Sciences (BELS). Joanne has been writing for the healthcare industry for 15 years.

REFERENCES

1. World Health Organization. Laboratory quality management system: handbook, Version 1. Geneva: World Health Organization, 2011.

2. ISO. Quality management systems. Fundamentals and vocabulary. ISO 9000. Geneva, Switzerland: International Organization for Standardization; 2015.

3. ISO. Medical laboratories. Requirements for quality and competence. ISO 15189. Geneva, Switzerland: International Organization for Standardization; 2012.

4. CLSI. *Quality Management System: A Model for Laboratory Services; Approved Guideline—Fourth Edition.* CLSI document QMS01-A4. Wayne, PA: Clinical and Laboratory Standards Institute; 2011.

5. Carey RB, et al. 2018. Implementing a quality management system in the medical microbiology laboratory. Clin Microbiol Rev 31:e00062-17. https://doi.org/10.1128/CMR .00062-17.

6. U.S. Department of Health and Human Services, Centers for Medicare and Medicaid Services. 2003. Medicare, Medicaid and CLIA programs; laboratory requirements relating to quality systems and certain personnel qualifications. Final rule. 42 CFR 493. Fed Regist 68:3640 –3714.

The clinical impact of MDx economics

By Ilan Danieli

Recent years have produced a wealth of discovery in the molecular diagnostics (MDx) field, as the identification of new genes and mutations has pointed to clinically relevant diagnostic, prognostic, and therapeutic information. The application of newly developed targeted therapies is increasingly driven by molecular mutational analysis that indicates the patient's response or resistance to those therapies. In this article, I'll discuss one particular application of molecular tests that have become key diagnostic indicators in two substantial hematopoietic disease classifications, i.e., myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN); the economics facing these diagnostic indicators; and the clinical impact observed.

MDS and MPN account for approximately 40 percent of all hematopoietic cancers. The National Comprehensive Cancer Network guidelines recommend testing for the JAK2, MPL, and CALR genes[1-3] as part of the diagnostic workup of patients being assessed for MDS or MPN, to provide both diagnostic and prognostic guidance in treating the patient. Labs are now expected to incorporate molecular workups into a routine evaluation of a bone marrow biopsy, as well as with peripheral blood specimens, to provide a comprehensive evaluation of the specimen, and provide the treating clinician with a complete picture of the patient's diagnosis and prognosis. These molecular tests play a critical part in that comprehensive evaluation.

Molecular test economics

Like any test, the evaluation of molecular markers requires both testing reagents as well as negative and positive controls. The cost of these reagents (and in particular, the controls) is often influenced by how often the mutation presents itself clinically. The less frequent the mutation is, the more challenging it is to create positive controls, hence the more expensive they become. Since a positive control is required per run and not per each sample testing, in order to reduce the overall costs of the tests, laboratories will typically batch samples. Given the low frequency of mutations in the JAK2, MPL, and CALR genes, the corresponding reagents and controls are increasingly expensive. **Table 1** provides a simple mathematical example to illustrate this. While batching is a sensible economic decision in order to increase the profitability of a lab, there is a negative potential clinical impact on the turnaround time provided to a clinician who awaits their patient's diagnosis.

Table 1.

Positive control costs		$500.00
Batch size	Cost/sample	Reduction
2	$250.00	50%
10	$ 50.00	90%
20	$ 25.00	95%

Workup timeline

A typical bone marrow workup requires between seven to 10 days, and will include a morphologic assessment, histology, flow cytometry, and cytogenetics testing. As the diagnosis is being identified, molecular tests are often added to complete the diagnostic picture. Upon surveying the leading labs, we found that the molecular workup for these three genes takes between two to three weeks. This means that, in order for a pathologist to include the results of the molecular tests in the final workup, the results are often delayed by two to three weeks. For a clinician awaiting the diagnosis to begin treatment, this is a significant delay; for the patient facing the diagnosis of a deadly disease—an eternity.

Solutions

While these mutations (JAK2, JAK2 exon 12, MPL, and CALR) are important to obtaining a full diagnostic picture, the data shows that they present in patients quite infrequently; more than 80 percent of patients return a negative answer on these molecular tests.[4-6] A screening test would be beneficial in identifying those negative patients; and if this screen was low-cost, thus lowering the batching threshold, laboratories could, while maintaining reasonable economics, provide a quick response to the majority of patients which have a negative result. Furthermore, if the screen were to indicate which genes were positive, a follow-up confirmation would be substantially less expensive since it would require both infrequent testing (one in five patients, or the remaining 20 percent who are positive); and it would only require testing one of the three genes. This would result in a 1:15 reduction in the overall cost factor for the positive confirmation.

A potentially significant advance in this area has been made with the recent commercial launch of a novel, proprietary test, HemeScreen, which screens for mutations in the JAK2, JAK2 exon 12, MPL, and CALR genes. The test is offered to hospital labs as a send-out test in our CLIA lab. This assay is capable of delivering negative results within two days, and positive results within five days. Precipio offers both commercial insurance and government payor billing for the test, as well as direct bill, providing the hospital with a financial benefit.

Technological innovations suggest an exciting future as the molecular diagnostics field seeks solutions that are both more efficient, providing a faster answer to the clinician and their patient, and are substantially more cost-effective than those currently available by other providers.

Please visit mlo-online.com for references.

Ilan Danieli, serves as CEO of **Precipio, Inc.**, and is the developer of HemeScreen, a novel proprietary test for mutations in hematologic cancers.

The vitamin D epidemic includes deficiency, supplementation, and over-testing

By Sean T. Campbell, PhD

From 2000 to 2010, Medicare reimbursements for vitamin D testing increased by 83-fold[1]—phenomenal increase.

Yet in 2011, the Endocrine Society released guidelines for vitamin D insufficiency, including raising their upper level of insufficiency to 30 ng/mL and including instructions for testing and screening.[2]

Almost concurrently, the Institute of Medicine (IOM) released their new guidelines for vitamin D supplementation, declaring their own level of deficiency at 20 ng/mL, and tripling the recommended dose for deficient patients,[3] adding to the belief that vitamin D insufficiency was more common than previously thought.

But even as supplementation and testing increased, a narrative review published in 2016[4] indicated there was still a shortage of reliable studies backing up many of the beliefs surrounding vitamin D supplementation.

This creates a tension. Even as recommendations expanded, qualifying more patients as "insufficient," the evidence for supplementation as a solution was simply not there. Even more concerning, the risks of over-testing are clear and range from pure monetary waste (to the tune of millions of dollars at just one hospital in Maine[5]), to delays in accurate diagnosis of other issues, to the serious consequences of vitamin D mega dosing, such as increased fractures and mortality.[4]

So where does this tension originate from? There are many possibilities. First, the guidelines themselves may be partially to blame. For instance, the Endocrine Society guidelines state, "considering that vitamin D deficiency is very common in all age groups and that few foods contain vitamin D, the Task Force recommended supplementation at suggested daily intake and tolerable upper limit levels, depending on age and clinical circumstances." But this misses the unequivocal statement in the next paragraph: "We do not recommend population screening for vitamin D deficiency in individuals who are not at risk."

Second, the IOM guidelines give similar advice, showing that average serum concentrations of vitamin D were well above the level for deficiency, regardless of latitude, and stating in equally stark terms that, "Of great concern recently have been the reports of widespread vitamin D deficiency in the North American population. Based on this committee's work…the concern is not well founded."

In addition, the two societies also released several papers after the guidelines were published, relating the differences between the two groups' recommendations.[6,7] In these, again, the societies reiterated the same basic points: deficiency is rare and screening should not be done on the general population, and that the non-skeletal benefits of Vitamin D were not proven. Similarly, in 2016 several members of the original IOM committee published yet another article detailing that even the IOM cutoff of 20 ng/mL was too high, and the vast majority of patients had sufficient blood levels.[8]

Yet, despite the very bodies drafting the guidelines recommending less testing, overtesting is rampant. In 2012-2014, a group at Maine Medical Center found that an average of 23 percent of patients with no indications for vitamin D testing were being tested for vitamin D, with over a third of those being tested multiple times.[5] To compound issues, associated diagnosis codes with a third of this testing were for non-specific symptoms that are not associated with deficiency, such as fatigue. All of this totaled an estimated 9.5 million dollars in waste over the two-year span.

So, what are the next steps? As mentioned, the expert opinion panels were in agreement in 2011: routine testing of the general population is simply not advisable. While deficiency may be common compared to other vitamin deficiencies, there is simply no good evidence to suggest testing should be conducted on non-symptomatic patients.

A systematic review by the Agency for Healthcare Research and Quality (US) in 2014 concluded that there was no established evidence linking vitamin D with any symptom outside of bone health,[9] and the previously mentioned narrative review published in 2016[4] concluded similarly, collating evidence that supplementation did not resolve problems that were not associated with bone health. Thus, the benefits of supplementation are limited and yet the dangers of over-supplementation of vitamin D have also been studied, in some cases showing an increase in the exact indices that are being treated such as falling and fracture risks.[4]

The guidelines and studies have all been rather clear: the healthy population does not need to be screened for vitamin D deficiency. In addition, supplementation above relatively modest levels is unnecessary and possibly harmful. In the end, it is the clinician's and laboratorian's duty to push back against unnecessary testing and medication.

REFERENCES

1. Shahangian S, Alspach TD, Astles JR, Yesupriya A, Dettwyler WK. Trends in Laboratory Test Volumes for Medicare Part B Reimbursements, 2000–2010. *Arch Pathol Lab Med*: February 2014, 138(2):189-203.
2. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al., Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab,* 2011, 96(7):1911–1930.
3. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. Dietary reference intakes for calcium and vitamin D. Washington, DC: The National Academies Press (US), 2011.
4. Allan GM, Cranston L, Lindblad A, et al., Vitamin D: A Narrative Review Examining the Evidence for Ten Beliefs. *J Gen Intern Med,* 2016, 31(7):780-791.
5. Murray KA, Rosen CJ, Hillyer RL, Fairfield KM. Low Value Vitamin D Screening in Northern New England. *5th Annual Lown Institute Conference,* 2017.
6. Rosen CJ, Abrams SA, Aloia JF, Brannon PM, et al., IOM Committee Members Respond to Endocrine Society Vitamin D Guideline. *J Clin Endocrinol Metab,* 2012, 97(4):1146-1152.
7. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al., Guidelines for Preventing and Treating Vitamin D Deficiency and Insufficiency Revisited. *J Clin Endocrinol Metab,* 2012, 97(4):1153-1158.
8. Manson JE, Brannon PM, Rosen CJ, Taylor CL. Vitamin D Deficiency — Is There Really a Pandemic? *N Engl J Med,* 2016, 375(19), 1817-1820.
9. Newberry SJ, Chung M, Shekelle PG, Booth MS, et al., Vitamin D and Calcium: A Systematic Review of Health Outcomes (Update). AHRQ Publication No. 14-E004-EF. Rockville, MD: Agency for Healthcare Research and Quality. September 2014.

Sean T. Campbell, PhD, is a trained biochemist and clinical chemist and currently serves as Assistant Director of Hematology and Coagulation at **Montefiore Medical Center** in the Bronx. Sean's research passions are in hemoglobinopathy testing, mass spectrometry assays, and science based medicine.

12 steps to CD4 testing Part II—HIV treatment

By Beckman Coulter Life Sciences

The 2016 and 2017 World Health Organization (WHO) guidelines provide guidance on the diagnosis of human immunodeficiency virus (HIV) infection, the care of people living with HIV, and the use of antiretroviral (ARV) drugs for treating and preventing HIV infection.

CD4 provides guidance on when to start ART[6]:

When to start ART in adults (>19 years old)	ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count.
	As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with a **CD4 count ≤350 cells/µL**
When to start ART in adolescents (10–19 years of age)	ART should be initiated in all adolescents living with HIV, regardless of WHO clinical stage and at any CD4 cell count.
	As a priority, ART should be initiated in all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adolescents with a **CD4 count ≤350 cells/µL**
When to start ART in children younger than 10 years of age	ART should be initiated in all children living with HIV, regardless of WHO clinical stage or at any CD4 cell count: • Infants diagnosed in the first year of life • Children living with HIV 1 year old to less than 10 years old
	As a priority, ART should be initiated in all children <2 years of age or children younger than 5 years of age with WHO clinical stage 3 or 4 or **CD4 count ≤750 cells/µL** or **CD4 percentage <25%** and children 5 years of age and older with WHO clinical stage 3 or 4 or **CD4 count ≤350 cells/µL**
Timing of ART for adults and children with TB	ART should be started in all TB patients living with HIV regardless of CD4 count. TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment.
	HIV-positive TB patients with profound immunosuppression (e.g. **CD4 counts less than 50 cells/µL)** should receive ART within the first two weeks of initiating TB treatment.
	ART should be started in any child with active TB disease as soon as possible and within 8 weeks following the initiation of antituberculosis treatment regardless of the CD4 cell count and clinical stage.

While these guidelines recommend lifelong antiretroviral therapy (ART) regardless of CD4 cell count ("treat all policy") and analysis of viral load (VL) as the preferred monitoring approach, they also provide clear guidance on the indispensable role of CD4 in assessing baseline risk of disease progression—particularly for individuals presenting with advanced disease—decisions regarding starting and stopping prophylaxis for opportunistic infections (OIs), and prioritization decisions regarding ART initiation in settings where universal treatment is not possible. CD4 cell count measurement may also be important for people who are failing ART.

As a recap, the following copy is a continuation from last month's "Part I: HIV Testing."

3. PRIORITIZATION OF TREATMENT INITIATION

Prioritization of antiretroviral therapy (ART) initiation is outlined in the chart to the left entitled, "CD4 provides guidance on when to satart ART." [6]

4. RAPID INITIATION OF ART

Recommendation for rapid initiation of ART

People with no contraindication to rapid ART initiation should be fully informed of the benefits of ART and offered rapid ART initiation, including the option of same-day initiation.[7]

Rapid ART start is especially important for people with very low CD4 cell count, for whom the risk of death is high.[7]

Although no longer a requirement for ART initiation, **baseline CD4 cell count testing should be performed** to determine whether the patient has advanced HIV disease.[7]

5. DIAGNOSING TREATMENT FAILURE

Monitoring response to ART and diagnosing treatment failure in absence of viral load testing in individuals who are not stable on ART

Viral load is recommended as the preferred monitoring approach to diagnose and confirm treatment failure.[8]

If viral load testing is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure, with targeted viral load testing to confirm viral failure where possible.[8]

In settings where routine viral load monitoring is available, CD4 cell count monitoring can be stopped in individuals who are stable on ART and virally suppressed.[8]

A patient is considered stable on ART based on the following criteria:[8] on ART for at least one year, no current illnesses, good understanding of lifelong adherence, and evidence of treatment success (two consecutive viral load measurements below 1,000 copies/ml).

6. IDENTIFYING IMMUNOLOGICAL FAILURE

The role of CD4 in identifying immunological failure

The 2016 WHO guidelines point out the role of CD4 in the identification of immunological failure for the decision to switch ART regimens:[9]

- **Adults and adolescents:** CD4 count at or below 250 cells/ul following clinical failure OR persistent CD4 levels below 100 cells µ/L
- **Children younger than 5 years:** Persistent CD4 levels below 200 cells µ/L
- **Children older than 5 years:** Persistent CD4 levels below 100 cells µ/L

10. TREATMENT ADHERENCE

Adherence support interventions

The 2016 WHO Guidelines strongly recommend to provide adherence support interventions to people on ART.[16] The following interventions demonstrated benefit in improving adherence and viral suppression:[16]

- Peer counselors
- Mobile phone text messages
- Reminder devices
- Cognitive-behavioral skills training/medication adherence training
- Fixed-dose combinations and once-daily regime

Follow this space next month in MLO's Special Feature for the final technical overview of Beckman Coulter Life Sciences' "12 Steps to CD4 Testing."

REFERENCES

6. World Health Organization (2016): Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection; recommendations for a public health approach – 2nd ed., page xxxi.

7. World Health Organization (2017): Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, page 20.

8. World Health Organization (2016): Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection; recommendations for a public health approach – 2nd ed., page xxxiv.

9. World Health Organization (2016): Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection; recommendations for a public health approach – 2nd ed., page 131.1.

16. World Health Organization (2016): Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection; recommendations for a public health approach – 2nd ed., page xlii.

A dialogue with COLA's new Chief Executive Officer, Nancy Stratton

Congratulations on your new position! What do laboratorians not familiar with COLA need to know? I am really excited and honored to be chosen by the COLA Board of Directors to serve in this capacity. Having been a customer, I've experienced firsthand the knowledge, talent, and skills of the COLA surveyors. The one thing that impresses me most is that each and every person—out in the field and at the home office—genuinely cares about serving our customers. This, combined with rock solid technical expertise, makes COLA a special organization. Staff members are completely enthusiastic about our mission. Teamwork is not something we work on, but rather the natural way we do our work. There is a high degree of collaboration and communication within COLA, which is important to providing exceptional customer service.

What advantages does a COLA certified lab have over one that is not? Clearly, the federal CLIA framework is the recognized government standard that all laboratories must meet. However, it is incredibly difficult for government authorities to pass laws and/or promulgate new regulations to keep pace with the tremendous innovation underway in laboratory science and the exponential growth in new methodologies. At COLA, we do everything we can to stay current on new developments and assist our customers to navigate their dynamic environment. Due to the complexity of government regulations, we're available to translate these regulations into accreditation criteria that can be practically applied and evaluated through a comprehensive, relevant, on-site survey. When compliance problems are found on site, we mentor labs to help them identify workable solutions. We expect laboratories to apply the highest standards of quality in their day-to-day operations and demonstrate continued accuracy and reliability of testing through successful performance of proficiency testing.

Our online customer portal can monitor a laboratory's accreditation status in real-time, access educational materials and laboratory templates, upload documentation (including plans to achieve required improvements), and communicate changes as they occur.

Finally, COLA is an organization which holds itself to the highest standards as evident by the fact that we are the only laboratory accreditation organization that has pursued, and has been awarded, ISO certification for our Laboratory Accreditation Program. We participate in routine third-party external audits to ensure our quality-engineered processes that guide accreditation actions are operating as intended.

What are the steps for a lab to be accredited by COLA and what is the average turn-around-time? To enroll with COLA, a laboratory manager can fill out an application on our website or call to enroll. Once enrolled, we send the new customer a link to the COLA Accreditation Manual and a detailed Laboratory Information Packet to gather additional information.

Next, we provide online access to COLA's Customer Portal. There the laboratory can complete a self-assessment based upon COLA criteria. Using the self-assessment report, laboratories can then make the improvements needed.

The COLA on-site lab survey is the centerpiece of the accreditation process. The surveyor will interact with lab staff and observe work in progress in addition to reviewing policies, procedures, and records. Preliminary survey findings are shared with the lab staff and educational guidance offered during the summary conference. COLA also provides the laboratory with a detailed survey report, citing all non-compliant issues identified at the time of the survey. In addition, COLA provides laboratories with educational materials, technical coaching, and advice. The lab then develops and implements a corrective action plan, providing us with appropriate documentation to demonstrate compliance. Upon successful completion of the survey and any required follow-up actions, the lab receives a COLA Certificate of Accreditation. Approximately 85 percent of labs receive their certificate within 90 days of their on-site survey.

When a laboratory enrolls with COLA, their initial on-site survey occurs within 11 months. Subsequent surveys occur every two years. COLA accredited laboratories are continuously accredited, without gaps, as long as they continue to stay in compliance with COLA criteria for accreditation, permit a survey every two years, and pay their accreditation fees.

How many laboratories does COLA currently serve? COLA accredits nearly 7,500 medical laboratories, which makes us the largest independent clinical laboratory accreditor in the U.S. COLA has long held the position that owners, directors, and laboratory managers should have a choice in terms of the accreditation of their laboratory. While this is a small industry in terms of the number of accreditors, I've discovered that while we are well known among physicians with office labs, small independent community reference labs, and some small community hospitals, we are not as well-known in other segments of the clinical lab market. Certainly, the consolidation of laboratories and the integration of healthcare providers are trends we are watching closely.

What profession other than your own would you like to attempt? I have always had a passion for laboratory medicine and patient care and honestly couldn't imagine myself doing anything else. However, I would continue my work with veterans and horses. Back in Texas, I own and operate a horse ranch, which was part of the national nonprofit "Horses4Heroes." This organization makes the dream of affordable horseback riding a reality for our troops, veterans, wounded warriors, and their families. Besides working with COLA, helping those people has been one of the most rewarding things I have done. The more we give, the more we receive.

Read the full interview at mlo-online.com.

COLA

Your Source for Laboratory Excellence

With COLA, you have access to:

A Mentoring Approach to Accreditation
Helps you identify areas for improvement through "starter" self-assessments, compliance coaching, and more.

Knowledgeable Customer-Focused Surveyors
Bring COLA's unique customer-centric training and many years of laboratory management experience to your team.

COLAcentral Client Portal
Gives you the tools you need to run an efficient lab and produce accurate test results, all in one place.

On-Demand Competency Improvement Materials
Makes it easy for you to build a culture of consistent quality in your lab—even through staff turnover.

Superior Customer Experience
As the only laboratory accreditor that's ISO 9001 Certified, COLA strives to deliver a standardized, consistent accreditation process and outstanding customer experience for every lab, every time, nationwide.

Contact us today to learn about the enrollment process.
www.cola.org/enroll | (800) 981-9883

sysmex | Lighting the way with diagnostics

RESHAPING SCALABLE AUTOMATION

XN-Series™ Automated Hematology Systems

XN-9100

XN 20

THE **XN-20** AUTOMATED HEMATOLOGY ANALYZER

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

FULL AUTOMATION HAS CHANGED FOREVER

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

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

www.sysmex.com/us