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Cover: Laboratory Services representatives from across the Sentara organization. Photo: Steve Budman

FEATURES

THE PRIMER
18 Oncogene panels: a window into the individuality of cancers
By John Brunstein, PhD

CLINICAL ISSUES
22 mRNA-based hrHPV assay in cotesting for cervical cancer screening
By Juan Felix, MD

EDUCATION
24 Emerging applications in clinical mass spectrometry
By Lisa Thomas, BS, MBA

LAB MANAGEMENT
30 MLO’s 2016 Lab of the Year: Sentara Laboratory Services
By MLO Staff

SPECIAL FEATURE
38 Solving the thrombocytopenia puzzle with immature platelet testing
By Maggie Fischer RN, BSN, MS, and Krista Curcio, BS, MBA

MANAGEMENT MATTERS
42 CDC’s more restrictive policy on child lead testing means more positives and high QC
By Robert Kapler

FUTURE BUZZ
46 The laboratory’s role in the transformation to patient-centered care
By Donna Beasley, DLM(ASCP)
48 In pursuit of patient-centered care
By Chrystal Adams

CONTINUING EDUCATION
12 Diagnosing androgen deficiency in adult men
By Michael Samoszuk, MD
16 CE Test
Tests can be taken online or by mail. See page 16 for testing and payment details.

DEPARTMENTS
4 From the editor
6 The observatory
44 Tips from the clinical experts
50 Letters to the editor
51 New products

PRODUCT FOCUS
40 Rapid testing

MARKETPLACE
51 Advertiser index

EXECUTIVE SNAPSHOT
52 Developing blood biomarker tests for the detection of cancer
James R. Jett, MD
Chief Medical Officer
Oncimmune
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- IgM

Allergy
- Total IgE

Diabetes
- Cystatin C
- Fructosamine
- Hemoglobin A1c
- Insulin
- Microalbumin

Inflammation/Cardiac
- Anti-Streptolysin O
- Complement C3
- Complement C4
- CRP
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- D-Dimer
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FROM THE EDITOR

By Alan Lenhoff, Editor

Health—it’s not just for women anymore!

YEARS AGO, I worked for a company that produced customized magazines for HMOs and hospital systems; I edited some of them. “Women’s Health” was a popular topic requested by clients, particularly hospitals eager to highlight centers of excellence related to pregnancy/prenatal and HMOs urging breast cancer screenings, for example. Women’s health was such a priority of our clients that one of my fellow editors and I joked that an alien from another planet, judging what life was like on Earth only from those publications, would conclude that “health” was an attribute possessed only by women, that only women had health issues, (I guess you had to be there….) It is true that healthcare publications, and individuals and organizations dedicated to educating healthcare consumers, in general have been somewhat tardy in addressing men’s health issues. But that is changing. An increased awareness of prostate cancer has been one of the drivers in the progress toward the growing interest in men’s health; another has been increased study of the effects of low testosterone in men.

In that context, MLO is proud to present this issue’s important Continuing Education article, “Diagnosing androgen deficiency in adult men,” by Michael Samoszuk, MD (pages 12-14). The article convincingly demonstrates that the clinical understanding of laboratory testing for low T in men must catch up with the growing demand for testing and treatment.

News of recent studies confirms that men’s health, seen as a category of healthcare knowledge and research, is coming into its own. For one example, researchers from the Perelman School of Medicine at the University of Pennsylvania, and twelve other medical centers in the United States, in partnership with the National Institute on Aging, recently found that testosterone treatment improves sexual activity, walking ability, and mood in men over 65. As men age, testosterone levels decrease, but prior studies of the effects of administering testosterone to older men had been inconclusive.

The Testosterone Trials, or T Trials, are a coordinated group of seven trials, and researchers have analyzed the results of the first three—sexual function, physical function, and vitality. They found that testosterone treatment increased the blood testosterone level in the study subjects to the mid-normal range for younger men. Testosterone also improved all aspects of sexual function. Testosterone treatment did not improve energy but did improve mood and depressive symptoms.

“The results of the T Trials show for the first time that testosterone treatment of older men who have unequivocally low testosterone levels does have some benefit,” says the principal investigator of the T Trials, Peter J. Snyder, MD. “However, decisions about testosterone treatment for these men will also depend on the results of the other four trials—cognitive function, bone, cardiovascular, and anemia—and the risks of testosterone treatment.” Stay tuned.

Another example: We often think of osteoporosis as largely a women’s problem, but men experience a loss in bone density as they age as well. Recent research from the University of Missouri-Columbia shows that men can forestall its effects by exercising in their teen and young-adult years. Work by Pamela Hinton, PhD, indicates that high-impact exercise during adolescence and young adulthood is linked to greater bone mass in middle-aged men.

Hinton analyzed data from the physical histories of 203 males aged 30 to 65 years. Participants’ sports and exercise histories varied, both in type and level of activity, and the length of time spent doing various physical activities differed. But her research found that exercise-associated bone loading during adolescence and young adulthood benefitted bone density in adulthood. Moreover, she found that high-impact activity during growth and adulthood is an important determinant for bone health later in life.

It’s an interesting finding—and more evidence that men’s health, as a subject for clinical research, is here to stay.

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**Infectious Disease**

New CDC laboratory test for Zika virus authorized for emergency use by FDA.

In response to a request from the Centers for Disease Control and Prevention (CDC), the United States Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for a diagnostic tool for Zika virus that will be distributed to qualified laboratories and, in the United States, those that are certified to perform high-complexity tests.

The test, called the CDC Zika IgM Antibody Capture Enzyme-Linked Immunosorbent Assay (Zika MAC-ELISA), is intended for use in detecting antibodies that the body makes to fight a Zika virus infection. These antibodies (in this case, immunoglobulin M, or IgM) appear in the blood of a person infected with Zika virus beginning four to five days after the start of illness and last for about 12 weeks. The test is intended to be used on blood samples from people with a history of symptoms associated with Zika and/or people who have recently traveled to an area during a time of active Zika transmission.

The FDA can use the EUA to permit use, based on scientific data, of certain medical products in certain circumstances, including when there is a determination by the Secretary of Health and Human Services that there is significant potential for a public health emergency that has significant potential to affect national security or the health and security of U.S. citizens. As there are no commercially available diagnostic tests cleared or approved by the FDA for the detection of Zika virus infection, it was determined that an EUA is crucial to ensure timely access to a diagnostic tool. The CDC's Zika MAC-ELISA is the first diagnostic test authorized for use in the U.S. for the detection of Zika virus during this situation in which there has been a determination that there is a significant potential for a public health emergency that has a significant potential to affect national security or the health and security of citizens living abroad and that involves Zika virus.

Results of Zika MAC-ELISA tests require careful interpretation. A positive test result indicates that a person was likely infected recently with the Zika virus. However, the test can give an incorrect positive. These false-positive results can occur when someone has been infected with another closely related virus (such as dengue virus). When positive or inconclusive results occur, additional testing (plaque reduction neutralization test) to confirm the presence of antibodies to Zika virus will be performed by the CDC or a CDC-authorized laboratory.

Moreover, a negative test result does not necessarily mean that a person has not been infected with Zika virus. If a sample is collected just after a person becomes ill, there may not be enough antibodies for the test to measure, resulting in a false negative. Similarly, if the sample is collected more than 12 weeks after illness, it is possible that the body has successfully fought the virus and antibody levels have dropped below the detectable limit.

As with any test, it is important that healthcare providers consult with their patients about test results and the best approach to monitoring their health.

The CDC began distributing the test last month to qualified laboratories in the Laboratory Response Network, an integrated network of domestic and international laboratories that can respond to public health emergencies. The test will not be available in U.S. hospitals or other primary care settings. Public health officials anticipate that distribution of the tests will improve laboratory testing capacity for Zika virus in the U.S.

Zika virus associated with meningoencephalitis. An 81-year-old man was admitted to the intensive care unit 10 days after he had been on a four-week cruise in the area of New Caledonia, Vanuatu, the Solomon Islands, and New Zealand; he was reported to have been in perfect health during that time.

On medical examination, he was febrile and comatose with hemiplegia of the left side, paresis of the right upper limb, a normal response to tendon reflexes, and a Babinski sign on the left side. The patient's trachea was intubated and mechanical ventilation began; a transient rash was observed within the next 48 hours. Magnetic resonance imaging (MRI) of the brain was suggestive of meningoencephalitis.

Computed tomographic angiography revealed an irregular narrowing of the right callosomarginal artery. A lumbar puncture was performed on day 1, and findings on analysis of cerebrospinal fluid (CSF) were suggestive of menigitis: the leukocyte count was 41 per cubic millimeter (with 98% polymorphonuclear leukocytes), the protein level was 76 mg per deciliter, and the ratio of CSF to blood glucose was 0.75. The patient was initially treated with amoxicillin, cefotaxime, gentamicin, and acyclovir, but these antimicrobial agents were stopped on day 5. Investigations in both CSF and blood for other infections were unrevealing except for a positive result for ZIKV on reverse-transcriptase–polymerase-chain-reaction assay of the CSF. ZIKV was grown in culture from the CSF on a Vero cell line. These findings all support the diagnosis of ZIKV-associated meningoencephalitis.

**New Studies**

Common blood test could predict risk of second stroke. A new discovery about ischemic stroke may allow doctors to predict a patient's risk of having a second stroke using a commonly performed blood test and their genetic profile.

The researchers have linked high levels of C-reactive protein, an enzyme found in the blood, with higher risk for recurrent ischemic stroke. C-reactive protein (CRP) is produced in the liver in response to inflammation, and it is already checked to measure risk of developing coronary artery disease. The new research suggests it could be a useful tool for ischemic stroke patients as well.

Researchers set out to determine how genes affect the levels of biomarkers such as CRP in the blood. Not only did they find that elevated CRP levels suggest increased stroke risk, but they identified gene variations that drive that risk.

Researchers envision a day when doctors might focus on CRP levels and a patient's genetic makeup to determine the overall risk for a second stroke. But CRP levels alone could be a useful tool in assessing risk after the initial stroke.

**Cancer**

Low vitamin D predicts aggressive prostate cancer. A new study provides a major link between low levels of vitamin D and aggressive prostate cancer. Northwestern Medicine research showed that deficient vitamin D blood levels in men can predict aggressive prostate cancer identified at the time of surgery. The finding is important because it can offer guidance to men and their doctors who may be considering active surveillance, in which they monitor the cancer rather than remove the prostate.

continued on page 10
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also known as ‘benzos,’ has increased more than four-fold since 1996—a public health problem that has gone under the radar,” says lead author Marcus Bachhuber, MD, MS. Overdoses from benzodiazepines have increased at a much faster rate than prescriptions for the drugs, indicating that people have been taking them in a riskier way over time.”

In 2013, benzodiazepine overdoses accounted for 31 percent of the nearly 23,000 deaths from prescription drug overdoses in the U.S. But little was known about the national trends in benzodiazepine prescribing or in fatalities from the drug.

The researchers’ analysis revealed that the number of adults purchasing a benzodiazepine prescription increased by 67 percent over the 18-year period, from 8.1 million prescriptions in 1996 to 13.5 million in 2013. For those obtaining benzodiazepine prescriptions, the average quantity filled during the year more than doubled between 1996 and 2013. Most crucially, the overdose death rate over the 18-year period increased from 0.58 deaths per 100,000 adults in 1996 to 3.14 deaths per 100,000 adults in 2013, a more than four-fold increase. Overall, the rate of overdose deaths from benzodiazepines has leveled off since 2010. But for a few groups—adults aged 65 and over, and blacks and Hispanics—the rate of overdose deaths after 2010 continued to rise.

**Alzheimer’s Disease**

Researchers identify virus and two types of bacteria as major causes of Alzheimer’s. A worldwide team of senior scientists and clinicians have come together to produce an editorial which indicates that certain microbes—a specific virus and two specific types of bacteria—are major causes of Alzheimer’s Disease (AD).

This major call for action is based on substantial published evidence into AD. The team’s landmark editorial summarizes the abundant data implicating these microbes, but until now this work has been largely ignored or dismissed as controversial. Therefore, proposals for the funding of clinical trials have been refuted, despite the fact that over 400 unsuccessful clinical trials for AD based on other concepts were carried out over a recent 10-year period.

“We are saying there is incontrovertible evidence that Alzheimer’s Disease has a dormant microbial component, and that this can be woken up by iron dysregulation. Removing this iron will slow down or prevent cognitive degeneration. We can’t keep ignoring all of the evidence,” Professor Douglas Kell says.

Professor Resia Pretorius, who also worked on the editorial, says “The microbial presence in blood may also play a fundamental role as causative agent of systemic inflammation, which is a characteristic of Alzheimer’s disease—particularly, the bacterial cell wall component and endotoxin, lipopolysaccharide. Furthermore, there is ample evidence that this can cause neuroinflammation and amyloid-β plaque formation.”

**Swedish study finds potential proteinomic biomarkers for Alzheimer’s in cerebrospinal fluid.** A mass spectrometry-based analysis of cerebrospinal fluid in Alzheimer’s disease (AD) patients has yielded a handful of potential biomarkers for the disease.

The researchers used label-free shotgun mass spectrometry to look at protein profiles in the cerebrospinal fluid of 10 AD patients and 10 healthy controls. They also performed protein depletion of high-abundance proteins to improve detection and quantification of low-abundance proteins.

The authors found eight proteins that were differentially expressed between the two study groups. “ApoM, LRG, FBLN3, and PTPRZ have functions related to cell adhesion, migration, and morphology,” and may also be associated with other aging-associated diseases like cancer and diabetes, they wrote. C1QB, C1QC, complement C1S, and SEZ6 may be implicated in synapse development.

“Cerebrospinal fluid is a proximal fluid in direct contact with the brain interstitial fluid that potentially reflects biochemical changes related to [the] central nervous system, making it a promising source of biomarkers in neurological disorders such as AD,” they added. While Alzheimer’s disease is associated with several proteomic markers, especially the protein tau and beta-amyloid peptides, those have limited value for monitoring disease progression.

In their paper, the authors also pointed out other factors that might have influenced results. In addition to the small study size, they noted that there was a slight age difference between the two groups, where the controls were, on average, nine years older than participants in the Alzheimer’s group; protein levels in cerebrospinal fluid are thought to change with age. The lower protein levels could also be the effect of protein depletion.
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In recent years, there has been an explosive increase in prescriptions for testosterone replacement therapy (TRT) in adult men who are thought to have adult-onset hypogonadism (i.e., androgen deficiency [AD], also known as low testosterone or “low T”). This increase has been fueled by changing demographics and by increased public awareness of low T syndrome due to extensive advertising and numerous articles in the lay press. Despite recent controversies about risks for cardiovascular complications in men receiving TRT, the trend of increased testing and treatment for low T is likely to continue. Hence, it is imperative for clinical laboratory professionals to have a good understanding of this important topic.

The diagnosis and treatment of adult-onset hypogonadism in men older than 45 years of age remains controversial. For example, there is lack of consensus on the thresholds of testosterone that are needed to diagnose AD. Furthermore, evidence shows that testosterone levels in men decrease with age, at approximately one percent per year, beginning at about 40 years old. Because testosterone levels are known to decline as men grow older, there is debate about whether or not to interpret lower testosterone values in older men as being physiologic (i.e., a “normal” part of aging) or abnormal and worthy of treatment. For this reason, a standard approach in older men has been to interpret blood tests for testosterone in the context of the other clinical features of the patient in order to establish a diagnosis of androgen deficiency that should be treated.

Continuing Education

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LEARNING OBJECTIVES
Upon completion of these articles, the reader will be able to:
1. Identify the limitations that are currently problematic when diagnosing androgen deficiency.
2. Describe the signs and symptoms of androgen deficiency.
3. List ways in which the criteria for diagnosing androgen deficiency can be improved upon.
4. Identify the metabolites of testosterone and their possible use for future laboratory diagnostic value.

Biology of testosterone
Testosterone is a steroid hormone that develops and maintains the primary and secondary sex characteristics in men (Figure 1). Its metabolites include estradiol (produced by aromatase enzyme found in fat and other tissues such as testes) and dihydrotestosterone (DHT)—an androgenic hormone that is approximately three to ten times more potent than testosterone. DHT is produced from testosterone by 5-alpha reductase, an enzyme that is found primarily in hair follicles, prostate, testes, and adrenal glands, but not in skeletal muscle.

Measuring total testosterone
Total testosterone can be accurately measured by immunoassay and by mass spectroscopy. Even in men with severe deficiency of testosterone, enzyme immunoassays will provide accurate and reliable results. There is no clinical advantage to using mass spectroscopy for measuring total testosterone, although the results may be more precise and accurate at very low levels that are not normally seen even in hypogonadal men.

In younger men, there is marked diurnal variation in testosterone levels, with the highest levels occurring in early morning upon awakening. The diurnal variation in total testosterone becomes less pronounced in older men. Nevertheless, current recommendations are that blood samples for total testosterone levels should be drawn before 10 a.m. in all men. There is currently no consensus regarding whether or not fasting is required, and most laboratories do not require it.

Total testosterone levels can vary considerably from day to day in the same man. Factors that can affect total testosterone on a day-to-day basis include sleep, diet, stress, illness, and exercise. Consequently, it is not advisable to make a diagnosis of low T on the basis of a single blood test result. Instead, two or even three tests taken on different days are recommended in order to ensure an accurate diagnosis.

Lack of consensus on diagnostic criteria
There are considerable variations in the reference intervals for total testosterone assays that are produced by various manufacturers of in vitro diagnostics and reference labs (Table 1). It is notable that the reference intervals are based on the range of values between the fifth and 95th percentiles of men of various ages. The populations of men that were used to derive these reference intervals are poorly defined with respect to age distribution and possible...
symptoms of low T, and it is unclear if these reference intervals provide a reliable basis for interpreting test results from men being tested for low T. Of particular concern are the lower limits of the reference intervals, which may be too low to identify the significant proportion of men who are truly hypogonadal but whose total testosterone levels still fall above the fifth percentile of the reference range.

Reference intervals for total testosterone levels reported by various reference laboratories also have considerable variation (Table 1). Once again, the variation is of particular concern at the low end of the reference interval, because many clinicians use this value to determine whether or not a man should be diagnosed as having low T.

An emerging approach to interpreting total testosterone levels in men is to use a clinical threshold cutoff value for the level. Based on recommendations from various sources, it appears that the clinical threshold for diagnosing low T probably lies somewhere between 300-500 ng/dL. Notably, this broad range lies considerably above the fifth percentiles for the testosterone values in Table 1. It should also be noted that all sources of the clinical thresholds recommend the primacy of clinical signs and symptoms when interpreting total testosterone values. For example, the Endocrine Society recommends “making a diagnosis of androgen deficiency only in men with consistent symptoms and signs and unequivocally low serum testosterone levels.”

To resolve this conundrum, many experts now recommend that numerical values for total testosterone should be interpreted only in the context of the other clinical features of the patient. For this purpose, various clinical criteria for diagnosing or suspecting low T in men have been proposed (Table 2, page 14). Although all of these signs and symptoms are somewhat nonspecific, the sexual symptoms appear to be the most useful indicators of potential low-T. Consequently, in men older than 45 years of age with complaints of erectile dysfunction or other sexual problems, there should be a high index of suspicion for low T.

**Testosterone binding and circulation**

Testosterone circulates in the blood in a free (unbound) form and a bound form. Sex hormone-binding globulin (SHBG) and albumin are the primary sources of binding of testosterone. Approximately two percent of total testosterone circulates in the free form. Current thinking is that free testosterone is mostly responsible for the biological activity of the hormone, and the bound form is thought to be mostly inactive.

The free and bound forms can be directly measured by a variety of methods, or a mathematical formula can be used to calculate the percentage of free testosterone, based on the values for total testosterone, SHBG, and albumin. Regardless of the method used to determine free testosterone, there is still substantial confusion and uncertainty regarding how to interpret the results. Some experts use both total testosterone and free testosterone to evaluate men presenting with symptoms of low T.
insufficient sleep are also associated with low T.21 Interestingly, poor sleep seems to be both a cause and an effect of low T.

Testing for dihydrotestosterone and estradiol
Testing for DHT levels is not a routine part of the workup for men being evaluated or treated for hypogonadism. At this time, it is not clear how to interpret the test results. It is likely that as our understanding of testosterone replacement therapy improves, there will be an increased interest in clinical testing for this metabolite of testosterone.

There is now considerable evidence that estradiol levels in men play an important role in modulating the effects of testosterone on sexual function, body fat, lean muscle mass, and bone density.21 Nevertheless, estradiol levels are still not commonly measured in men who are being evaluated or treated for low T. This is because the interpretive criteria for such testing are still not well understood. In some men, estradiol levels are measured in order to determine if testosterone therapy is causing an increase in estradiol due to aromatization of the testosterone. This can lead to symptoms of high estradiol such as bloating, fluid retention, and breast tenderness or gynecomastia.22 Some experts now recommend calculating a ratio of testosterone to estradiol, but this approach is not yet widely accepted. Nevertheless, it is likely that clinical laboratories will experience an increased demand for estradiol testing in men as our understanding and the prevalence of testosterone therapy increases.

Conclusion
From the preceding discussion, it should be apparent that our understanding of laboratory testing for low-T in men lags considerably behind the growing demand for testing and treatment of low T. Clinical laboratories, manufacturers of in vitro diagnostic tests, and clinicians should be aware of the many unanswered questions in this field. They should also begin to educate themselves about the important changes in this field that are likely to occur in the next few years.

REFERENCES

Table 2. Symptoms and signs of androgen deficiency in men.

<table>
<thead>
<tr>
<th>SEXUAL SYMPTOMS OF LOW T</th>
<th>NON-SEXUAL SYMPTOMS OF LOW T</th>
<th>SIGNS OF LOW T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diminished libido</td>
<td>Fatigue</td>
<td>Decreased bone density</td>
</tr>
<tr>
<td>ED</td>
<td>Decreased energy/motivation</td>
<td>Decreased bone density</td>
</tr>
<tr>
<td>Change in orgasm experience</td>
<td>Depressed mood/irritability</td>
<td>Body composition</td>
</tr>
<tr>
<td>Delayed or absent orgasm</td>
<td>Decreased muscle mass/strength</td>
<td>Anemia</td>
</tr>
<tr>
<td>Reduced ejaculate volume</td>
<td>Increased fat (abdominal)</td>
<td>Decreased sense of well-being</td>
</tr>
</tbody>
</table>

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### TEST QUESTIONS

#### 1. What factors have led to an explosive increase in the prescription of testosterone replacement therapy (TRT) in men?
   - a. increased public awareness
   - b. changing demographics
   - c. an increase in interest in weight-lifting by men
   - d. both a and b

#### 2. What risk factor has most recently added to the controversy associated with men receiving TRT?
   - a. kidney disease
   - b. muscular/joint complications
   - c. cardiovascular complications
   - d. none of the above

#### 3. Testosterone levels in men begin to decrease at what age and at approximately what rate?
   - a. 40 years old, 2% per year
   - b. 50 years old, 1% per year
   - c. 50 years old, 2% per year
   - d. 40 years old, 1% per year

#### 4. Currently, there is controversy regarding the diagnosis and treatment of adult-onset hypogonadism, with a primary debate over whether or not it is a normal physiologic process or abnormal and requiring treatment.
   - a. True
   - b. False

#### 5. What are the two metabolites of testosterone?
   - a. estradiol and DHT
   - b. estradiol and estrone
   - c. DHT and estrone
   - d. none of the above

#### 6. Which metabolite of testosterone has been found to be three to 10 times more potent than testosterone itself?
   - a. estradiol
   - b. DHT
   - c. estrone
   - d. progesterone

#### 7. What laboratory methods are used to measure total testosterone?
   - a. immunnoassay
   - b. mass spectroscopy
   - c. both a and b
   - d. neither a nor b

#### 8. The current recommendation is for blood specimens for total testosterone testing to be drawn upon awakening in the morning.
   - a. True
   - b. False

#### 9. What additional specimen collection measure(s) is/are recommended to ensure accurate diagnosis of androgen deficiency?
   - a. fasting blood specimen
   - b. two or three collections taken on different days
   - c. two collections per day; one in morning and one in evening
   - d. all of the above

#### 10. According to the article, current laboratory diagnostic criteria of androgen deficiency are of concern because of the following factors:
   - a. There is considerable variation in the reference ranges among different reference laboratories.
   - b. There is controversy about the lower end of the limits used to establish the reference range.
   - c. The population used to define the reference range has been poorly defined.
   - d. all of the above

#### 11. A new recommended approach in diagnosing androgen deficiency is to
   - a. establish a whole new reference range.
   - b. use clinical features of the patient.
   - c. use clinical threshold cutoff numerical values.
   - d. all of the above

#### 12. According to Table 2, what clinical symptoms appear to be the most useful indicators of potential androgen deficiency?
   - a. sexual symptoms
   - b. non-sexual symptoms
   - c. other signs/symptoms
   - d. all of the above

#### 13. Besides aging, what are two of the most significant factors in reduced testosterone in men?
   - a. overtraining and diabetes
   - b. chronic opioid use and obesity
   - c. obesity and diabetes
   - d. AIDS and hypertension

#### 14. What factor seems to be both a cause and an effect of low testosterone?
   - a. overtraining
   - b. poor sleep
   - c. hypertension
   - d. diabetes

#### 15. What laboratory test shows promise for future use in the management of testosterone therapy?
   - a. DHT
   - b. estradiol
   - c. free testosterone
d. total/free testosterone ratio
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By John Brunstein, PhD

Cancer has been a scourge of humanity for as long as we know, with written descriptions extending back at least as far as the Ebers and Smith papyri, estimated to have been written around 1600 B.C. and postulated to be derived from earlier sources from circa 2500 B.C. As such, it has been subjected to intensive study, perhaps more so than any other single class of ailment. The pace of progress in battling cancers has steadily accelerated, and a relatively new tool—the oncogene panel—is beginning to prove its value. In this month’s Primer we’ll examine briefly what these MDx tools do, and how they are both changing our understanding of cancer and, in some instances, allowing for effective application of what might otherwise have been unlikely treatment options.

On the surface, cancers are misleadingly simple pathologies. Cells making up the various organs and systems of the body can replicate, and normally only do so when required for development or repair; replication ceases when the cells making up an organ system reach their required size and functions. Simplistically, cancer occurs when replication of a cell becomes uncontrolled and a single cell divides repeatedly to become a tumor, ignoring and overrunning surrounding tissues. This physical disruption of well-behaved cells by tumor tissue leads to disruptions in proper organ function and all of the downstream consequences.

Traditionally a major tool in classifying and directing treatment of cancers has been through identification of the underlying cell type which has become dysregulated. Cancers sharing an origin type such as lymphoma, lung cancer, or colon cancer might reasonably be expected to share commonalities in pathology, disease progression, and best treatment strategies. In reality, however, it is observed that cancers sharing overt similarities in terms of cell type, appearance, and progression stage may respond quite differently to the same drug treatment. We are beginning to appreciate that for some cancer types that have been known under a single name, individual cases can be just that—individual, with regard to the root defects and thus best treatment strategies.

To understand this a bit better and the role of oncogene panels, we should go back to the basic concepts of cell division and its regulation. There are large numbers of highly complex multistep biochemical pathways which either act to turn on cell division or to shut it off. Individual cells are controlled by several such pathways simultaneously, and for progression to cancer generally several of these pathways have to be disrupted in a coordinated fashion. This adds complexity to the underlying cause, but also suggests that effective treatment might be possible through blocking any one of the dysregulated paths. The questions, then, are: “Which path?” and “Where can we block it?” These are the questions that oncogene panels seek to directly answer.

**Pathways to malignancy**

Let’s consider a hypothetical pathway relating to cell division, as sketched out in Figure 1. This consists of an extracellular signal “ligand” (1); a trans-membrane receptor spanning across the membrane of the cancer cell, with extracellular receptor domain (2); an intracellular effector domain (3); an intracellular secondary messenger (4); and a transcription factor (6) with its inhibitory partner (5). This represents a pro-replication signal pathway, then it would function effectively as follows: a positive signal (such as a growth hormone (1), binds (2), causing an activating conformational change in (3); this enzymatically transiently modifies (4), which in its modified state causes inhibitory subunit (5) to release (6), which now translocates to the nucleus, binds specific signal sequences in the DNA upstream of a pro-replication gene, and upregulates or induces transcription of the product RNA, which then is translated to an active protein which functionally proceeds to drive a cell division cycle (providing other required pro-replication factors are present, and anti-replication factors are absent—thus the above statement on need for multiple coordinated errors before cancer occurs). This whole pro-division pathway acts for a finite time, as the ligand at (2) is released or internalized and degraded, the modification of (4) decays off, and the RNA transcript and final protein product both undergo normal turnover processes. Note that we could just as easily postulate this model for an anti-replication pathway, if we called ligand (1) a negative signal such as contact inhibition, and the RNA codes for a replication inhibitory protein; for sake of argument, though, we’ll stick to a pro-replicative model for now.

With this pathway model in mind, let’s ask ourselves what different changes could occur to be cancer-causing (pro-oncogenic). Some immediate possibilities could include:

- Excess or inappropriate expression of ligand (1);
- Alteration of the transmembrane receptor, either in domain (2) or (3), such that it behaves as if ligand is bound even when it’s not;
- Alteration of secondary messenger (4) so it’s constitutively active, thus constantly relaying a signal from (3) that’s not really there; or
- Alteration of (5) such that it loses ability to sequester and inactivate (6).

These are hardly exhaustive or exclusive, and the reader is invited to try to postulate some other possible pro-oncogenic changes to our model path. For instance, consider alteration of the DNA creating a binding site for (6) upstream of a pro-replication gene where it shouldn’t be, such that a signal intended for something unrelated to replication is now “understood” by the cell as a signal for replication. If that sounds far-fetched, it isn’t; essentially that’s the basis of Burkitt’s lymphoma, where the promoter DNA for IgG heavy chain production gets fused in front of a pro-replication gene c-Myc; signals for the cell, which are intended to cause it to make antibodies, now make it go into a cell-division cycle.

**Clinical implications**

The point of this hypothetical pathway and exercise in imagining all the ways in which it can become dysregulated is to begin to appreciate that two cells of the same type, both of which have become cancerous through inappropriate activation of the same pathway, may have done so through very different underlying changes. Both will present, on the continued on page 20
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Sample to Insight
surface (or perhaps we should say, in thin sections below the surface, as seen through the pathologist’s microscope) as very similar, or even identical. Likely both will respond similarly to crude chemotherapies, such as those which generically block DNA replication; however, those chemotherapies are also, for obvious reasons, the ones with the worst side effects. As our knowledge of the mechanisms of cancer has increased, so too have the clinician’s options for highly targeted drug therapies which can block or interfere very specifically with steps on the pathway. For oncogenic pathways similar to our model, drugs exist which can bind and inactivate (2) from binding excess or ectopic ligand (1); others block the activation of secondary messenger (4), or interfere with the binding of (6) to its target DNA sequence.

In the right setting, these drugs can be highly effective. For instance, some types of lung cancer originate through dysregulation of a pathway very similar to our model, through overexpression of ligand—and highly specific drugs have been developed which bind and mask the receptor extracellular domain (2) to stop it from responding to the ligand. These drugs, while expensive, are highly effective, in this case in halting further progression. However, in some cases which present with identical appearance, the defect occurs in (4), (5), or (6)—in the parlance of signal transduction biology, “downstream” from the receptor and point of drug action. In these cases administration of the drug is ineffective and possibly harmful, as valuable time is lost before observing that it’s ineffective.

The key to using these pathway and step-selective drugs in an effective manner is therefore to know, on a highly individual basis, what the exact set of genetic changes in the cancer cell is, so that a drug with appropriate point of action can be selected—something downstream of at least one of the critical mutations. (Remember, usually multiple coordinated mutations must be active to result in full-on cancer; so interfering with even one of these may be enough to stop progression.) Thanks to years of research and the Human Genome Project, cancer researchers now know of literally hundreds of genes whose products play known roles in the multiple pathways promoting or suppressing cell division. They also have detailed libraries of mutations in these genes, known to lead to unwanted activation or inactivation of the gene product.

Oncogene panels

An oncogene panel is a targeted next-generation sequencing (NGS) approach, which can take a patient sample (from tumor tissue, not unaffected tissue) and simultaneously sequence all of these hundreds of understood genes on cell division control pathways. The exact platform and sequencing method is unimportant; from a technical standpoint, however, it is worth noting that the amount of sequence data needed per patient is relatively small on an NGS scale, allowing for multiplexing of many patient samples in a single instrument run and bringing per-patient costs down. The key comes in bioinformatics, where the resulting per-patient data is examined against known sequences and pathogenic sequence variants for each of the genes examined. By doing this, oncologists can obtain a highly detailed picture of each of the points of dysregulation in a specific tumor; with luck, one or more of these may be the target (or immediately upstream of the target) for an available specific drug. Rather than treating all cancers as the same, oncologists now begin to have the ability to select a treatment which is customized to the unique root cause.

Already, the literature is beginning to include reports where use of an oncogene panel has identified that a cancer presenting as one type (based on cell type and appearance) is discovered at a genetic level to share commonalities with another very different cancer type—for which a specific drug is available. Informed by the oncogene panel results, use of a chemotherapeutic agent which would not otherwise have been considered has yielded highly effective treatments in these cases. While this opens complexities related to appropriate drug labeling—whether it should be more related to specific genetic defect, than to cancer class—the increasing use of oncogene panels and the concomitant development of yet more therapeutic agents targeted to specific pathways promise to provide significant advances in the treatment of cancers as highly individual presentations.

John Brunstein, PhD, is a member of the MLO Editorial Advisory Board. He serves as President and Chief Science Officer for British Columbia-based PathoDx, Inc., which provides consulting for development and validation of molecular assays.
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mRNA-based hrHPV assay in cotesting for cervical cancer screening

By Juan Felix, MD

The dramatic decline in cervical cancer in women is attributable first to screening with the Papanicolaou (Pap) test, followed later by the addition of the human papilloma virus (HPV) test, which enhanced screening sensitivity. In keeping with this excellent performance record, the current standard of care for cervical cancer screening for most women (those over 30), as currently recommended by U.S. guidelines, is cotesting with Pap and HPV tests. In 2014, the Food and Drug Administration (FDA) approved an HPV assay to be used alone as a primary screening test, initiating a debate about what is the best way to detect cancer.

Since this FDA decision, a retrospective, cross-sectional analysis performed in 256,648 women demonstrated that HPV-alone testing missed 18.6 percent of 526 cervical cancer cases detected by cotesting. The challenge is to improve screening cost-effectiveness without compromising efficacy, and the notion that screening with one test may be more cost-effective than two tests seems reasonable upon first consideration—but closer examination reveals this assumption to be wrong. Understanding the cost-benefit ratio of screening methods requires a thorough analysis of HPV assay technologies, what they detect, and how these factors influence the cost-effectiveness of cervical cancer screening.

Assays for HPV detection
Not all HPV assays are the same, and the first step in understanding their differences is to review the relationship between HPV and cervical cancer. Cervical cancer is predominantly caused by a small group of 14 genetically related high-risk (hr) HPV species, and more than 70 percent of cervical cancers are caused by the hrHPV 16 and 18 genotypes. The majority of hrHPV infections spontaneously regress; however, persistent hrHPV infection and expression of the E6 and E7 oncogenes are associated with neoplastic transformation. The hurdle that must be overcome to improve cervical cancer screening cost-effectiveness is distinguishing the minority of HPV infections or lesions prone to progression from the vast majority likely to regress. Improving the ability to make this distinction would limit unnecessary follow-up costs.

There are currently five nucleic acid-based hrHPV assays available in the U.S. for cervical cancer screening. Four of the assays analyze HPV DNA; one analyzes HPV messenger RNA (mRNA). By detecting HPV mRNA, as opposed to DNA, this latter test identifies expression of HPV E6 and E7 oncoproteins.

Comparing specificity
Numerous studies have demonstrated that the mRNA-based hrHPV assay has higher clinical specificity for detection of cervical cancer lesions than DNA-based hrHPV assays (Figure 1). The underlying explanation for improved specificity is detection of mRNA encoding E6 and E7 oncogenic proteins indicating lesion progression to invasive cancer. When E6 and E7 proteins are detected, as opposed to HPV DNA detection indicating viral presence only, fewer false positive test results have been reported. A recent study by Reid et al. demonstrated a 24 percent reduction in false positive test results with mRNA-based compared with DNA-based hrHPV assays. Whether mRNA-based hrHPV testing performs comparably to DNA-based hrHPV testing in a cervical cancer screening protocol was also explored in this study.

Comparing sensitivity
The Reid study compared the clinical performance of DNA-based hrHPV assays and an mRNA-based hrHPV assay using a cotest strategy for cervical cancer screening in a cohort of 10,860 women aged 30 years or older. The cumulative three-year absolute risk for CIN3 (cervical intraepithelial neoplasia) or higher was comparably low for either test for women with a negative result, indicating both tests provide a high negative predictive value (Figure 2). In contrast, consistent with current U.S. cervical cancer screening, a similar significantly greater risk of CIN3 or higher with either test was observed for women with positive results. Together these data, and other studies, indicate that cotesting with mRNA-based compared with DNA-based hrHPV assays delivers equivalent clinical sensitivity, but mRNA-based testing was more specific for detection of CIN2 or worse.

Comparing cost-effectiveness
The impact of the improved specificity on cost-effectiveness of cervical cancer screening was investigated in a study by Ting et al. that compared costs and...
health outcomes between mRNA-based and DNA-based hrHPV assays in the context of current U.S. cervical cancer screening guidelines. Screening efficiency was examined using two different screening strategies: cotesting with HPV and liquid-based cytology in women 30 to 65 years; and triage of women with mild cervical cytological abnormalities (ASC-US) in the United States. A Markov model for stochastic cost-effectiveness analysis was constructed using data from the Reid study and another by Monsenego et al., both conducted in population-based settings. The model followed a theoretical cohort of women from age 12 to 100 years, not vaccinated for HPV, and assumed that at the beginning of the simulation that no woman was infected with HPV, or had CIN or cancer.

For both cotesting and ASC-US triage screening protocols, mRNA-based hrHPV testing cost less than DNA-based hrHPV testing; however, differences between the protocols were not statistically significant. To better estimate cost-effectiveness differences, an analysis of willingness-to-pay thresholds was performed. Results indicated a 100 percent probability that DNA-based testing was not cost-effective, relative to mRNA-based testing, at the $100,000 per life-year saved threshold for ASC-US triage, and a 50 percent probability that DNA-based testing was not cost-effective at the $100,000 per life-year saved threshold for cotesting.

Preliminary results from another study comparing cost-effectiveness between cotesting with an mRNA-based hrHPV assay and a DNA-based hrHPV assay alone found that mRNA-based cotesting (combined with follow-up genotyping) provided improved clinical and economic outcomes.

These studies show cervical cancer screening efficiency can be affected by the type of HPV assay used as well as the overall strategy. Results from these studies provide evidence that cotesting with an mRNA-based hrHPV assay is more likely to be cost-effective than DNA-based hrHPV testing, whether DNA-based hrHPV testing was used in cotesting or alone as a primary screening strategy.

It is worth noting that DNA-based primary screening has not been recommended by screening guidelines at this time. The cost-benefit associated with the mRNA-based hrHPV assay observed in these analyses arises from the improved specificity of the mRNA-based assay that detects expression of HPV oncogenic proteins, as opposed to DNA-based testing that reports only presence of the virus. The ability to detect expression of HPV oncogenic proteins favors the distinction between HPV infections that will progress to cervical cancer from those that will regress, leading to fewer cases where HPV nucleic acids are detected but disease is not present. The information provided by an mRNA-based hrHPV assay result gives healthcare providers and patients greater assurance about whether or not there is a need for follow-up procedures. The improved specificity of mRNA-based hrHPV assays, together with improved sensitivity of mRNA-based hrHPV assay cotesting compared with DNA-based hrHPV testing, suggest transitioning to DNA-based hrHPV testing alone as a primary screening would be not only less efficacious, but also more costly.

REFERENCES
Emerging applications in clinical mass spectrometry

By Lisa Thomas, BS, MBA

Mass spectrometry (MS) is being used by an increasing number of clinical laboratories to measure small sample volumes with improved confidence across an expanding range of healthcare applications—from toxicology to personalized medicine. Enhanced assay performance and new laboratory-developed test (LDT) methods offer rapid results at a reduced cost and potentially more clinically relevant information, enticing more clinical core testing laboratories to implement mass spectrometry technology.

Current clinical mass spectrometry applications

With origins in basic research, mass spectrometry emerged as a clinical research tool when it was first applied to fingerprint molecules for drug screening in the fight against drugs of abuse. Since then, the technique has evolved, and with the advent of tandem mass spectrometry (MS/MS) technology to support targeted experimental testing—combined with separation technologies such as gas chromatography (GC), liquid chromatography (LC), and ion mobility spectrometry (IMS)—ever smaller concentrations and metabolites can be targeted. Macromolecule ionization methods, such as electrospray ionization (ESI) and matrix-assisted laser desorption/ionization (MALDI), enable the study of protein structure.

The adoption of liquid chromatography-tandem mass spectrometry (LC-MS/MS) for small molecule targeting and translational clinical applications was driven by a need for higher immunoassay accuracy, a lack of availability in approved immunoassays, and the desire for cost reduction. While sample preparation can be more labor-intensive than immunoassays and an ever-increasing demand for automation integration, in-house mass spectrometry-based assays can be cost-effective, even for smaller labs.1 MS technology is now routinely applied in clinical laboratories to improve the sensitivity and specificity of clinical tests, screen for diseases, monitor drug therapy, analyze peptides and proteins for diagnostic testing, and identify causes of infections for targeted therapies.2-5

Technology drivers of mass spectrometry

The American Association for Clinical Chemistry (AACC) and Mass Spectrometry and Separation Sciences (MS3) carried out a survey of 63 clinical laboratory representatives to determine the outlook for clinical mass spectrometry testing. Results indicate the current demands that are likely to drive the future technology trends in clinical mass spectrometry. The organizations asked: Of the environments where mass spectrometry tools ARE NOT currently in use, in which ones would you like to see the technology take hold by 2020? The most frequent answers are shown in Figure 1, below. Other uses that were specified by the survey respondents include continued immunoglobulin work, protein analysis, and peptide determinations, and large molecule bioanalysis. To support new clinical mass spectrometry applications, laboratories expect to see improved technical functionality to automate sample acquisition and preparation as well as data analysis and reporting.

AACC and MS3 also asked: In 2020, which of the following laboratory processes would you anticipate will be automated on your mass spec testing line? The responses are shown in Figure 2 on page 28.

Advancing technologies and potential applications

Recent advances in clinical research and MS technology promise even more sophisticated development of clinical applications and potential new LDTs. Matrix assisted laser desorption/ionization imaging mass spectrometry (MALDI-IMS) now supports direct tissue analysis with diagnostic potential and reduced analysis time.7 Pathologists are now able to examine biological tissue directly, detecting cancerous tissue in real time during an operation using MS with smart electrosprays.8 Mass spectrometry imaging (MSI) enables histologists to define tissue types by chemical composition rather than structure.7

Able to distinguish and measure the separate contributions of molecules such as the 25-hydroxy vitamins D2 and D3 and thyroid hormones, MS/MS methods have enabled clinical laboratories to overcome the limitations of immunoassays caused by nonspecific antibody binding and cross-reactivity with metabolites.9 Endocrinologists are also now investigating a “lab on a plate” method to more accurately predict risk of heart attack and stroke in diabetes patients. Application of MS technology in clinical and translational research is opening up new lines of discovery in blood-based biomarkers, tumor markers, and even endogenous metabolites as new disease biomarkers.8,10

More sensitive urine screening methods capable of detecting designer drugs are available in the market, and vendor investments assure continued development. Some clinical research and forensic toxicology laboratories already use high-resolution, accurate-mass (HRAM) or time-of-flight (TOF) MS, for multi-analyte drug screens. Wholeas triple quad-based techniques can quantitate targeted analytes, newer HRAM systems can simultaneously detect and deliver...
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One out of 5 cases of cervical cancer were missed with HPV-Alone screening in a recent landmark, retrospective study—the largest ever conducted to evaluate the effectiveness of cervical cancer screening strategies in women ages 30-65. And screening with Pap+HPV Together (co-testing) identified more than 70% of those missed cancers. So is HPV-Alone screening really worth the risk?

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*A positive HPV screening result may need to be further evaluated with cytology and/or coposcopy.

Continued from page 24

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Advanced mass spectrometry methods are producing novel functional assays. Liquid chromatography MS/MS using online solid-phase extraction (XL-C-MS/MS) was used to develop a plasma renin activity (PRA) assay for monitoring mineralocorticoid therapy and screening hypertensive individuals.10 A further LCMS/MS method for quantifying isothalamate in plasma and urine can act between and eliminate candidate isomers.13 Metabolomic methods to distinguish between and eliminate candidate isomers is now used to screen candidate isomers.13

Data Analysis – software

Data reporting – interface

Other (please specify)

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

Figure 2. Results from a survey of 63 clinical laboratory representatives. SOURCE: AACC / MSSS Outlook for Clinical Mass Spec Testing Q9 p10.1

The impact of mass spec in clinical labs

Exponential growth in MS methods in clinical laboratories is expected in high-throughput and quantitative clinical and translational workflows, bacteriological identification, imaging of tissue sections, diagnostic testing, and functional assays. Improvements in automation will support validation and seamless communication with laboratory information systems (LIMS) to bring mass spectrometry-based detection into larger and more complex clinical laboratories. The development of handheld mass spectrometers will enable clinical measurements in remote environments opening up the possibility of point-of-care applications.1

In conclusion, as technology advances and technological challenges such as sample preparation, online extractions, throughput, automation, and system interfacing are overcome, we can expect the impact of MS in clinical laboratories to mature. “Mass spec” will increasingly be relied upon for sensitive, highly reproducible, accurate results.6

REFERENCES


4. Choices A, Vendor I, AACC / MSSS outlook for clinical mass spec testing cl my lab is… aacc / mass outlook for clinical mass spec testing q2 currently, do you view clinical mass spec applications being used as… I select all that apply | 2015:1-17.


This series of courses is designed for anyone in the clinical laboratory field who wants to learn about mass spectrometry and utilize this technology in the clinical laboratory. Medical laboratory scientists with training in mass spectrometry are in demand in the clinical laboratory.

No background knowledge in mass spectrometry is needed as we will cover the fundamentals and build on them throughout the program. Recommended background for participants is a college course in Biochemistry. Those with some mass spectrometry experience will also benefit from these courses as we will cover mass spectrometry theory in detail and apply this knowledge to clinically-based samples. We will also cover instrument maintenance and trouble shooting tips.

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Based in Norfolk, Virginia, the not-for-profit Sentara system operates more than 100 sites of care with more than 2,800 hospital beds, including 12 acute care hospitals in Virginia and North Carolina. The system, which has a 3,800-provider medical staff, includes the area’s only Level I Trauma Center, advanced imaging centers, assisted-living and nursing centers, physical therapy and rehabilitation services, home health and hospice services, and medical transport and air ambulances.

Sentara Laboratory Services (SLS) is a key component of this outstanding, and growing, healthcare system. Sentara laboratories are dedicated to addressing and meeting the clinical diagnostic and monitoring needs of patients throughout Virginia and northeastern North Carolina. System wide, more than 700 Sentara clinical laboratory professionals are vital to the high quality of healthcare provided at Sentara’s 12 hospitals. In addition, SLS’s reference laboratory and consolidated laboratories, based in southeast Virginia, perform more than eight million tests annually, serving providers and patients throughout the region. The reference lab includes clinical diagnostics in hematology, chemistry, coagulation, microbiology, and transfusion as well as anatomic pathology services. Specialty laboratories include Molecular Diagnostics, Flow Cytometry, and Cytogenetics.

MLO asked those submitting nominations for the 2016 Lab of the Year award to discuss their lab in terms of six criteria: Customer Service, Productivity, Teamwork, Education and Training, Strategic Outlook, and Lab Inspections. SLS gave MLO waaaaaaay more interesting information than we have space for in this article, but, to organize the article, we will use those categories as sub-sections—and review some highlights.

**Customer service**
SLS has embraced the concept of consumer-driven healthcare and partnered with the Sentara IT team to educate patients in signing up for MyChart, the Sentara Healthcare app which allows patients to view their health information on their personal electronic devices. The SLS marketing department created a written step-by-step procedure that patients can use to easily check and see if their test results are available.

SLS recently implemented Epic Beaker and Haemonetics SafeTrace as its laboratory information systems (LIS). This provides a common platform across the organization of Epic hospitals and provider practices for a single electronic medical record. Laboratory staff have realized numerous efficiencies as a result. Workflows were adapted to maximize the efficiency provided by the two new LIS systems. The staff, utilizing the expertise from lab super users and IT, worked together to maintain the highest standard of quality healthcare during the transition.

Patients have benefited significantly from the standard platform. Additionally, they may present to any hospital, draw site, or physician practice and have all their medical information available to the healthcare team. Physicians also have access to patient results in Epic.

In recognition of the fact that the time patients spend waiting affects the quality of their healthcare experience, SLS has worked to reduce the amount of time patients spend scheduling procedures and blood draws. SLS partnered with the Transplant, Registration, and IT departments to change the scheduling process so patients can go to any Sentara facility to have draws and other tests performed. SLS also teamed up with the Imaging department to assist with specimen collection in order to expand the service line to patients at multiple points of entry. “Today’s patient has a choice; convenience plays a major role in the selection of laboratory services,” says Kathy Prussock, MT(ASCP), Laboratory Manager.

**Productivity**
SLS has aggressively adopted automation to reduce turnaround times and increase productivity across the benches. The labs have implemented a line of high-volume chemistry and hematology instrumentation. An automated sample handler provides the chemistry lines with a continuous stream of samples. The design and workflow of the department ensure that testing never ceases and that the majority of testing panels are available at all times, thereby eliminating the need to perform batch testing.

SLS’s reference Hematology department implemented the automated Sysmex HST-N cell counting line, incorporating cell counters, slide maker, and slide stainer into the workflow. The new instrumentation and workflow improved the efficiency of the department even as the workload increased. This was followed by the addition of CellaVision’s automated differential reader, which significantly reduced the turnaround time for differential reporting.

*Clostridium difficile* infection (CDI) has been named a top clinical initiative at Sentara. The Microbiology Department, Infectious Disease physician group, and pharmacists work together to provide the right antibiotics to streamline therapy for the patient. In order to enhance detection of CDI, a two-step algorithm utilizing simultaneous detection of *C. difficile* glutamate dehydrogenase with toxin A and B followed by PCR testing, if indicated, is performed. This initiative allows quicker identification of *C. difficile* and control of processes and costs. “Microbiology underwent a renovation, leased the department, brought anaerobe testing back in house, and expanded their hours of culture reading to two shifts. Processes are now more efficient, and there is a decreased turnaround time for antibiotic reporting, which supports our Antibiotic Stewardship Program, DNV-MIR certifications, reduction in CDI, and overall improvement of patient care,” explains Kathy Judge, MT(ASCP), Clinical Specialist of Microbiology.

continued on page 32
You’ve decided to automate your lab, but what’s the next step? How do you find the right partner to meet your growth and productivity needs?

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LAB MANAGEMENT

LAB OF THE YEAR

Losing a specimen is a serious event in any lab, and SLS has introduced an initiative to directly reduce the number of opportunities for losing a specimen and the number of resources required in locating samples. As part of this initiative, the laboratory set out to find a waste receptacle that would fit in its current spaces. The receptacle was to have a solid top and a side opening so no specimens could accidentally fall into the can from counters above.

After a search of available receptacle models on the market, and after several model trials, it was determined that the best approach for the system would be to design and have manufactured a customized receptacle. The design included a single-sized removable lid with two separate openings on opposing sides. The standard lid would fit three different cans of varying heights and a single footprint size so that they could be used in different lab locations. The design was given to a manufacturer and prototypes were created. Once approved, the product was placed into production and several receptacles were put in place across the system of labs.

Teamwork

Laboratory services were critical components in two of the hospitals achieving DNV-MIR (Det Norske Veritas—Managing Infection Risk) certification. The DNV-MIR Standard adopts a structure based on 18 elements covering all areas associated with the design, operation, and management of healthcare facilities. The MIR Standard was developed by DNV to provide a framework to help organizations improve their management of infection risk. This standard is compatible with World Health Organization and U.S. Centers for Disease Control and Prevention (CDC) guidelines.

Two Sentara hospitals were the very first to achieve this certification worldwide. All of the hospital’s ancillary departments were recognized by the accreditation surveyors as providing outstanding support to the clinical nursing units and for their ability to communicate efficiently and consistently. Communication and collaboration were key components in achieving the certification.

One large project embraced in 2015 was the start-up of an Ebola Assessment Center at Sentara Princess Anne Hospital. In response to the Ebola outbreak in Africa and the sudden emergence of patients being treated in the U.S., Sentara was selected as an assessment center. A Task Force was developed to include the collaboration of many disciplines, and the lab was at the center. Much work was done to decide upon test menus, lab equipment, and staffing. Ten lab staff members went through intensive training in order to be able to work in the Center—training that included donning and doffing of personal protective equipment (PPE), specimen handling, equipment training, packing and shipping, waste handling, and test result distribution. Several point-of-care testing (POCT) staff provided training on POCT devices to members of the interdisciplinary team. An on-site assessment was conducted by the Virginia Department of Health and a CDC representative in October. When the Ebola crisis passed, the unit was renamed the Highly Infectious Communicable Disease Unit. “This has enabled Sentara to maintain a laboratory at the ready for any highly communicable disease that may be coming in the future,” notes Dan Scungio, MT(ASCP), SLS, CQA(ASQ), Laboratory Safety Officer.

Groundbreaking discoveries in healthcare have brought personalized medicine to the forefront. The SLS Hematology department partnered with a group of Oncology specialists to provide “targeted medicine” to improve the level of care delivered to hematology oncology patients. Through this collaboration, pathologists have been provided education on utilizing specific algorithms to render...
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a diagnosis. The development of new physician order sets improved the processing or ordering of tests and reduced the number of unnecessary tests being performed. Currently, the Hematology department is reviewing the coagulation order sets to further eliminate duplicate and other unnecessary testing.

Teamwork has also been a key to improvements in the SLS labs’ blood banks. To meet the needs of the community, SLS Transfusion Service has developed sickle cell protocols. One example: as patients develop more antibodies, it becomes increasingly difficult for Transfusion Services to find compatible blood. “Our sickle cell protocol has been very advantageous in preventing allo-immunization to the Rh and Kell blood groups, which makes it easier to find compatible units of blood,” says Noel Janelino, MT(ASCP), Clinical Specialist of Transfusion Services.

Education and training
All new employees complete a thorough onboarding process at Sentara. They attend a standard orientation and then deploy to their lab departments, where they are required to demonstrate competencies prior to reporting test results. This includes the technical tasks, as well as general laboratory and safety competencies. The laboratory competency program is standardized. Sentara has developed tools to meet the needs for the documentation of each method of competency performed. The College of American Pathologists (CAP) reports that competency is the most frequent deficiency cited during its inspections of laboratories. To address this issue, SLS developed a standardized competency process. A PowerPoint presentation was created to provide education on the CLIA regulations relative to competency and the qualifications required to be a competency assessor. The focus was to offer competency for a specific discipline at a specified time during the calendar year to ensure each laboratory is working on the same type of competency at the same time.

To complement the competency initiative, SLS created an Education Department that fulfills the needs of the laboratory staff and students. The initial focus of the new department will be on standardizing and optimizing the orientation process.

Strategic outlook
SLS leaders say the strategic imperative for their system’s operations includes a focus on lab technology and efficiency and the creation of a lab formulary. “Our focus on technology has always been to ensure that we are using the best equipment to perform the job with our large volumes,” says Tabetha Sundin, PhD, MB (ASCP), Laboratory Director. “After making the selection for equipment that is scientifically sound and cost-effective, we strive to standardize the equipment across our health system. This allows us efficiencies such as collective bargaining power, and sharing of resources and best practices. With the ever-rising cost of operating a reference laboratory and impending reimbursement cuts, it has become critical to ensure the right tests are being ordered at the right time. We can control this better with the implementation of a laboratory formulary. This will help us keep cost low, while also providing the necessary results for patient treatment.”

Among the advances that are in SLS’s five-year plan is an increased level of automation in Microbiology, which has already begun with the purchase of an automated streaker and MALDI-TOF for organism identification. SLS is also looking into smart incubators, digital plate reading, and conveyor belts to pull plates to reading stations, as well as an RFID solution for specimen tracking and the implementation of digital pathology. Lab leaders will also be adding next generation sequencing (NGS) to the molecular diagnostics laboratory and bedside barcode collection and labeling this year.

They are also considering technology advancements that will have major workflow impacts. Hematology will move to a diluent system for concentrated reagents, and sed rates will be automated. The Cytogenetics lab will implement an automated cell harvester, an automated FISH dropper, and a cell separator. Anatomic Pathology is presently validating Peloris processors for dual tissue type protocols and anticipates the use of auto-embedders. Molecular testing is already seeing a shift to primary tube-to-answer testing, automating molecular microbiology testing.

Lab inspections
SLS has had many years of successful inspections, and is both AABB and CAP accredited. Its Lab Quality Department has developed a strong quality system manual.

The Lab Quality Team is responsible for the development and maintenance of a safety manual for lab services, internal audits (quality and safety), investigations, compilation of facility-specific and system performance and process monitors (including turn-around times), and involvement with process-improvement and problem-solving teams. They serve as regulatory and accreditation resources and liaisons with accreditation and regulatory agencies.

The team conducts internal audits for every laboratory discipline and follows up on every finding to ensure that all are resolved and that actions are sustained. They develop LIS reports, and administer document control and competency programs. Members are certified auditors through the American Society for Quality (ASQ) and maintain their expertise with CAP, AABB, CLIA, ISO, and COLA requirements.

“This lab quality program has enabled SLS to achieve high scores with our inspection agencies. We consider each finding an opportunity for improvement and work hard to not have a repeat finding,” notes Lou Ann Wyer, MS, MT(ASCP), CQA(ASQ), Laboratory Director. “We track the total number of standards reviewed with each assessment to monitor trends and types of findings.”

Congratulations to all
Sentara Laboratory Services convinced the MLO judges that it was indeed the Lab of the Year for 2016, and we congratulate the lab and its leaders for delivering invaluable healthcare services to its patients. Congratulations, too, to the first runner-up and second runner-up labs (see page 36)—and to all who submitted nominations for their labs. Any lab that puts forth maximum effort to serve the public and the profession is a winner. In times of change for the healthcare delivery system in the United States, outstanding clinical laboratories are islands of excellence and stability in sometimes raging seas. MLO is proud to honor you all, and to be a voice for the profession.
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First runner-up: Le Bonheur Children’s Hospital’s Laboratory

Le Bonheur Children’s Hospital is a 255-bed pediatric hospital located in Memphis, Tennessee. The hospital and pediatric specialty programs care for more than 250,000 patients each year. Le Bonheur’s outstanding laboratory makes a vital and integral contribution to the institution’s success. Here are some marks of particular distinction, in the words of Le Bonheur’s Lab of the Year nomination:

• “Le Bonheur is a Level One Pediatric Trauma Center and phlebotomy is an important part of the trauma team. We respond to all ‘Trauma Stats’ and assist the team by accurately and completely labeling the specimens and personally delivering them to the blood bank and laboratory. This has eliminated unlabeled and mislabeled samples from traumas and ensures that the specimens arrive in the blood bank quickly.”
• “Every year our laboratory hosts a Symposium and invites all CLS and MLTs from the surrounding area to attend. We alternate each year between the Clinical Laboratory Symposium and the Laboratory Management Symposium. The symposium assists the staff with their required continuing education hours to maintain their license and, if desired, to obtain their Supervisor’s license.”
• “Our Blood Bank has accomplished some amazing things over the past few years. The TEGs were relocated into the blood bank to provide increased customer service for both the ECMO [Extracorporeal Membrane Oxygenation] program and for the open heart surgery program, and also in preparation of the cardiac failure/heart transplant program. Since the TEG is mandatory testing for the Berlin Heart protocol, this helped prepare Le Bonheur for these expanded patient programs.”
• “The laboratory integrated outpatient samples from our pediatric specialty clinics into primarily our core services department. These additional specimens increased our testing volume by 45 percent and were initially performed by current staff. As volumes have continued to increase, we did add one FTE to support the OP testing. This additional volume increased our efficiency and stabilized our laboratory productivity. Our turnaround time, quality results, and consolidated EMR (patient results from IP and OP testing are available to the physician) have increased physician satisfaction and patient safety.”
• “The Microbiology Department has implemented the Bruker MALDI TOF. We are now able to identify bacterial pathogens directly from a blood culture bottle within an hour of it becoming positive on the instrument. This enables the physician to prescribe the correct antibiotic versus a broad spectrum or ineffective antibiotic. Starting the correct antibiotic quicker potentially shortens the length of stay and improves outcomes. The MALDI identification also aids the physicians in deciding if a discharged emergency room patient needs to come back to the hospital for IV antibiotics immediately.”
• “Our molecular diagnostics lab is designated one of two “Molecular Centers of Excellence” in the United States. We perform molecular testing primarily for infectious diseases and are in the process of validating next-generation sequencing for cystic fibrosis. We support transplant patients across the city by performing testing for the BK virus, CMV, HCV, etc. Our transplant and GI physicians have been very supportive of the gastric pathogen panel, which tests for 22 targets and results within an hour.”

Second runner-up: Cape Regional Medical Center Laboratory

Cape Regional Medical Center (CRMC) is a 242-bed, acute-care facility located in Cape May Court House, New Jersey. In lab leaders’ own words:

• “The Lab at Cape Regional employs 30 technicians/technologists, a team of 15 in-house Phlebotomists, 10 outreach Phlebotomists, and a professional support staff consisting of three Client Service Representatives, two transcriptionists, and a dedicated courier for all our outreach clients.”
• “Our Lab may seem small, but it is quite a powerhouse! The number of reported tests completed every year is approximately 1.5 million; for example, we perform approximately 340,000 CBCs and more than one million Chemistry tests annually. Our outpatient volume constitutes 60% of our total volume.”
• “All clinical staff is cross-trained to work in at least two sub-sections of the Lab, and flexible scheduling occurs between the shifts to help accommodate staffing needs. During morning phlebotomy rounds, clinical staff work alongside the phlebotomy team to have results available to the physicians during their AM rounds. Phlebotomists assist the technicians/technologists by helping to load specimens on the robotics track systems in Hematology and Chemistry.”
• “The Lab has seen an expansion in patient-focused bedside testing by means of a collaborative and interdisciplinary team approach among several departments and locations. In the Emergency Department, we offer point-of-care glucose, urinalysis, and urine pregnancy testing. For our brain and heart rescue patients, we provide POC troponin and PT IN’s. In our GI Center, POC glucose and CLO testing is performed. The Laboratory, Nursing, Pharmacy, Interventional Radiology, and Wound Care Teams work together to provide a POC program that fits the needs of the department and patients it serves, as well as meeting all regulatory standards.”
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Solving the thrombocytopenia puzzle with immature platelet testing

By Maggie Fischer, RN, BSN, MS, and Krista Curcio, BS, MBA

Thrombocytopenia, or low platelet (PLT) count, is a common hematologic abnormality that may be associated with risk of severe bleeding. Understanding the cause of thrombocytopenia can be a clinical puzzle for clinicians. While the PLT count is the most important parameter to diagnose thrombocytopenia, it doesn’t provide information regarding the underlying cause of low platelet count, which makes the differential diagnosis unclear. It is merely a snapshot in time, reflecting PLT quantity and not the mechanism responsible for the low count.

Possible causes of thrombocytopenia may include decreased platelet production or increased platelet consumption. Clinicians must determine the cause of thrombocytopenia because low platelet counts can be associated with spontaneous bleeding, even without injury. Patients with thrombocytopenia therefore must be carefully monitored and treated based upon the underlying cause.

Rapid assessment of platelet production may aid clinicians in distinguishing between thrombocytopenia due to platelet destruction (such as immune thrombocytopenia [ITP]) and low platelet count due to aplastic disorders or other bone marrow failure syndromes.

Assessing the cause of thrombocytopenia

Determining the cause of thrombocytopenia may require additional laboratory tests and potentially invasive procedures. It is virtually impossible for the clinician to differentially diagnose thrombocytopenia from CBC results alone.

One non-invasive method of understanding the underlying cause of thrombocytopenia is to measure the immature platelet fraction (IPF), which indicates the presence of immature platelets in the peripheral blood.

The IPF is the automated measurement of reticulated, or immature, platelets. It reflects the presence of nucleic acid material in the cell by using a combination of fluorescent stains, flow cytometry, and algorithms to separate immature from mature platelets. The more immature the platelet, the more it fluoresces, thus allowing an accurate immature platelet count without requiring a separate reticulated platelet test performed by traditional flow cytometry.

Using IPF as a screening tool

The value of IPF has been proven as a screening tool for the clinician in the differential diagnosis of thrombocytopenia. IPF is most effective when the measurement is used serially and interpreted in conjunction with the platelet count. IPF can also be used as an early indicator of bone marrow recovery in patients who are undergoing a stem cell transplant or chemotherapy. In fact, IPF has been found to show recovery faster than absolute neutrophil recovery.

Because immature platelets are usually larger in size, some technologies use the MPV, or mean platelet volume, as an indication of platelet immaturity. However, MPV may not be an accurate indication of immaturity because of interference from giant platelets, platelet clumps, microerythrocytes, and cell fragments. Due to these interferences, MPV is not necessarily an accurate indication of platelet immaturity. However, MPV may not be an accurate indication of immaturity because of interference from giant platelets, platelet clumps, microerythrocytes, and cell fragments. Due to these interferences, MPV is not necessarily an accurate indication of immaturity.

In summary, IPF provides an automated, direct measurement of thrombopoietic activity in bone marrow. Used in conjunction with platelet count and other patient information, IPF may help the clinician assess the mechanism of newly identified thrombocytopenias. Therefore, IPF is a valuable laboratory parameter that may provide clinicians with the missing piece to the thrombocytopenia puzzle.

REFERENCES


Maggie Fischer, RN, BSN, MS, has more than 25 years of clinical and technical experience within the healthcare environment. For Sysmex America, Inc., she manages a clinical support team that educates healthcare providers about Sysmex’s novel clinical parameters.

Krista Curcio, BS, MBA, is a hematology product manager at Sysmex, where she manages the XN-Series product line as well as the RU-20 reagent unit system. Krista has been with Sysmex for 10 years. She has 20 years of industry experience including managing a hematology laboratory and working at CAP. Krista holds a BS in Medical Technology from Michigan State University and an MBA from Lake Forest Graduate School.
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June will mark four years since the Centers for Disease Control and Prevention (CDC) halved its reference blood lead level (BLL) for children from 10 micrograms per deciliter (μg/dL) of blood to 5 μg/dL, the agency’s threshold for public health action.1 As the water supply contamination crisis in Flint, Michigan, illustrates, the spread of lead in the environment—as well as the resulting health impacts—has been insidious, perhaps even more so than public health agencies had anticipated just a few years ago. Labs play an increasingly important role in helping to detect higher levels of human exposure. This article will look at the reasons for the revised reference level, the laboratory experience since the policy shift, how labs test and guard against contamination, and why lead will continue to be a public health problem long after the crisis in Flint is resolved.

Genesis of policy change
The shift in policy came on the heels of a two-year investigation by a work group of the Advisory Committee on Childhood Lead Poisoning Prevention, which was chartered to provide guidance to the CDC and the U.S. Department of Health and Human Services. The group’s report cited new research showing that any level of lead exposure can be detrimental to children.2 Even moderate exposure to lead is associated with cognitive development problems and lowered IQ.

“We have not been able to identify a safe blood level for children,” says Mary Jean Brown, PhD, chief of the CDC’s Healthy Homes and Lead Poisoning Prevention Branch. “We only use 5 because it is the top 2.5 percent of the population distribution [for lead exposure], which means something different is going on with that child.”

The report recommended that CDC move from a poison identification-based approach to a strict prevention-based approach. In due course, the CDC lowered the reference level and decided to update it every four years based on the results of two national surveys on lead exposure. The first cycle is about to end.3

A surge in positives

Hashim Othman, PhD, director of Toxicology & Special Chemistry at Bio-Reference Labs in northern New Jersey, says his facility has not done significantly more lead testing since the cutoff change. “But the rate of positives has increased tremendously!” he exclaims. “In August, when kids are tested before school, we see more than double the rate of positives than before. We used to have three, four, maybe five positives a day. Now we have 20, 30, maybe 40.” Most of the year, the lab runs 425 to 475 lead tests daily; during the preschool spike, it runs 550 to 650 tests a day.

His lab’s rate of positives seems to mirror the national trend. Back in June 2012, the CDC predicted the new reference level would increase the number of children affected nationwide from fewer than 100,000 to close to 373,000.1 Now it estimates that approximately 535,000 children ages one to five years have been found with blood lead at or above 5 μg/dL, says Bernadette Burden, a CDC spokeswoman. The estimate is based partly on the CDC’s biannual National Health and Nutrition Examination Survey (NHANES) and partly on the agency’s Childhood Blood Lead Surveillance System, which includes data from 35 state and local health agencies, many of which receive CDC funding.

Picture may be brighter
While the CDC estimate may sound dramatic, the exposure picture for children nationwide might not be as dire as the tragedy in Flint suggests. The percentage of children found with elevated blood levels (under the old reference level) has actually been falling steadily during the past
In fact, under the old reference level, the incidence rate has been below one percent since 2007 (Table I).

One reason for the decline is the Residential Lead-Based Paint Hazard Reduction Act of 1992, which directs the Department of Housing and Urban Development (HUD) and the Environmental Protection Agency (EPA) to require disclosure of known lead-based paint and paint hazards before the sale or lease of houses built prior to 1978. While the EPA and HUD are charged with strict enforcement of the law, CDC tracks BLL exposures, provides technical and financial assistance to state and local childhood lead poisoning prevention programs, and makes policy. Dr. Brown is proud of her agency’s efforts. “Our surveillance data have shown that, in many communities, a small number of houses repeatedly poison children,” she says. “And with that information we’ve been able to work with HUD and EPA to enforce the lead disclosure rule.”

Industry perspective

The Association of Public Health Laboratories (APHL), representing some 800 state and local public labs, has taken a keen interest in efforts to reduce childhood lead exposure. The APHL’s mission is to provide practical and cost-effective tools and methodologies that can detect lead concentrations below the current reference level. But members have heard that the CDC is considering lowering the level again, to 10 µg/dL. With the growing use of point-of-care (POC) BLL testing instruments, the APHL is concerned that federal standards may outpace current POC technology.

“More clinicians are using point-of-care devices because they are quick, cheap, and easy,” says Sanwat Chaudhuri, PhD, chair of the APHL Environmental Health Committee. “But that technique is not as sensitive compared with the other techniques. And when you’re pushing the regulatory limit so low, then you are challenging the instrument, and that may affect the data that you’re getting.”

The most common lead testing methodologies are graphite furnace atomic absorption spectrometry (GFAAS), anodic stripping voltammetry (ASV), and inductively coupled plasma mass spectrometry (ICPMS). A portable device using ASV technology is also available for POC BL testing. According to the World Health Organization (WHO), ICPMS is the most sensitive method for detecting BLL levels as low as ~0.1 µg/dL. That’s followed by GFAAS (lower limit: <1–2 µg/dL); lab-based ASV instruments (lower limit: 2-3 µg/dL); portable ASV instruments (lower limit: 3.5 µg/dL).4

Testing and precautions

To determine lead exposure levels among children, adults, hospitals across the country send public and private labs blood samples each day. They are shipped in either tan-capped or lavender-capped vials—the colors indicate the level of assurance that the sample is untainted and the analyzer has access to quality measures. Those samples are run again on another rack. We do an extra preparatory step must be performed before lavender-topped vial samples are analyzed.

At lab, samples are tested each night on three ICPMS instruments to have results for doctors by morning. Each instrument ionizes the sample, sorts and separates the ions by mass and charge, detects and measures the ions, and displays the result. Labs employ quality measures to ensure that the sample is untainted and the analyzer has accurately read what ends up on a graphic display.

“Here we have samples and quality controls,” Othman says, as a robotic arm inserts a pipette into one of 90 sample tubes nested in a bread loaf-size rack. Because of the ubiquity of environmental lead, he says, labs like his across the nation must take precautions—such as controls, standards, and redundancy—to keep the testing process free of contamination.

First, whole blood controls with concentrations of lead at three known levels—normal (6.1 µg/dL), critical (13.7 µg/dL), and toxic (37.6 µg/dL)—are introduced. (The child reference level is <5 µg/dL and <25 µg/dL for adults). These are freeze-dried samples whose purity and lead concentration have been subjected to rigorous QC. The controls are processed and analyzed at the same time and in the same manner as patient samples. The result is then compared against acceptable variance ranges.

“We dilute every sample and quality control 100 times with 0.5 percent nitric acid. We start the run with three controls, then alternate controls after every 30 samples. If we get five positives, those samples are run again on another rack. We do another dilution, add more controls—the same procedure. Then we compare the results. If they match, we release the original results. If they don’t match, we repeat the process a third time.”

Another critical measure involves the use of independently-validated blood-based NIST standard reference materials.5 The lab also adds a common internal standard for lead, bismuth, to each sample to ensure accuracy of results and instrument performance. Finally, a calibrator blank (0.5% HNO3) is included in each run. The system software uses the blank as a baseline for calculating the concentrations of all unknown samples.

Each sample is run three times, and the software then averages the three readings and provides a mean concentration and standard deviation, which must be less than 10 percent to avoid retesting.

“Any deviation from controls will depend, in large part, on how careful the technologists are and how good the controls and calibrators are,” Othman says, adding that CLIA sets the allowable error for controls: +/- 4 mcg/dL (equal to three standard deviations). “If you fail two controls, you have to do a corrective action. You either repeat a portion of the batch or the entire batch.”

Later the same morning, Othman is at his desk, sifting through a two-inch stack of BLL test reports. “Look at my calibration curve,” he says. “It’s almost perfect: 0.99999. And my calibration blank has only 129 counts of lead in it, which is considered very low compared to my lowest standard and then standards 2, 3, 4 and 5. As you can see, it’s a perfect curve.”

Satisfied, he initials the report.

REFERENCES


Robert Kapler spent nearly a decade as a science writer, editor, and government relations specialist at America’s Blood Centers. He now works as a freelance journalist and as a copywriter and marketing consultant for Bio-Rad Laboratories.
TIPS FROM THE CLINICAL EXPERTS

Pleural and peritoneal fluids

“TIPS” is an exclusive MLO feature that allows readers to ask technical questions and have them answered by our clinical experts. Please email your questions to: editor@mlo-online.com.

Q: We are looking for information regarding reference ranges for Pleural Fluid for Total Protein, LD, Glucose, Amylase, pH, Cholesterol, and Triglyceride, Peritoneal Body Fluids for Albumin, Total Protein, and Amylase. Do you have any published reference ranges for these body fluids?

A: The standard format used in establishing reference ranges for all various serous body fluids has not been well established. And of those references published, the literature shows some variation in what is considered “normal.” Unlike taking a blood sample that is analyzed to see if there is some abnormality, this is not well established. And of those references published, the literature shows some variation in what is considered “normal.”

Pleural effusions

Pleural Fluid (PF) is normally found in the space between the lung and the chest wall (normal amounts are estimated to be between 10 and 20mL) and is similar in biochemical composition to plasma. However, excess PF can accumulate due to a number of different disorders resulting in a pleural effusion (PE) and is obtained through a procedure called thoracentesis. Approximately 1.3 million individuals in the United States are diagnosed with a PE each year.

PEs may be classified as a transudative PE or as an exudative PE. A transudative PE may occur during systemic illnesses such as heart failure, cirrhosis (with ascites), or hypoalbuminemia (due to nephrotic syndrome), whereas exudative PE results from some abnormal local process, such as pneumonia, cancer, pulmonary embolism, and viral infection.

While a reference range for PF is not as clear-cut as that seen with other clinical laboratory tests, in general, normal PF may show the following:

- Appearance: Mostly clear, straw-colored, and odorless
- pH of 7.60 to 7.64
- Protein content of less than 1 to 2 g/dL
- Fewer than 1000 WBC/μL
- Glucose level similar to that of plasma

The presence of biomarkers, such as carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), CA 125, CA 19-9, alpha-fetoprotein (AFP), CYFRA 21-1, and osteopontin, has been shown to differentiate between malignant and benign PE. Pancreatic disease may show elevated amylase level in PE and may reach levels of 100,000 IU/L.

Lymphocytosis (>85 percent of nucleated cells) is seen in tuberculosis, lymphoma, sarcoïdosis, and several other disorders. Eosinophilia (>10 percent of nucleated cells) may be encountered in certain cases of pulmonary exudates.

Visual examination of exudative PEs may show turbidity and may be milky, hemorrhagic, or greenish in color. Evaluation of a PE exudative studies have shown:

- LD levels >0.45 of the upper limit of normal serum values
- Protein level >2.9 g/dL
- Cholesterol level >45 mg/dL
- Triglycerides >110 mg/dL
- Albumin gradient (serum albumin minus PE albumin) <12g/L for exudates and >12g/L for transudates
- WBC >500/μL
- Hematocrit of PE is >50 percent of peripheral blood hematocrit, patient has hemothorax
- pH of 7.44 to 7.30
- PF Amylase: Serum amylase ratio >1
- PF Creatinine: Serum creatinine >1
- Transudate effusions: 6
- Appearance: Tends to be clear yellow in color
- Nucleated cells: Fewer than 500 nucleated cells/μL
- PE LD: Serum LD (upper normal limit) ratio is <0.67
- Glucose: Level similar to serum glucose level
- Cholesterol: Less than 520mg/L
- pH of 7.45 to 7.55

Some additional analyses have also been noted to be of some value in evaluating pleural effusions. N-terminal pro-brain natriuretic peptide (NT-proBNP) has been shown to be elevated in heart failure (>1,300-4,000 ng/L). Effusions with elevated LD levels (>1,000IU/L) have been associated with empyema, malignancies, rheumatoid effusions, paragonimiasis (lung fluke), and Pneumocystis jiroveci (formally P carinii). Decreased glucose levels in PE have been seen in malignancies, tuberculosis, esophageal rupture, and lupus.

Peritoneal fluids

The peritoneum consists of serous membranes that line the peritoneal cavity through a network of mesothelial cells and collagen. Pathologic accumulation of peritoneal fluid results in ascites fluid (obtained through peritoneocentesis) that is generally submitted to the laboratory for evaluation. The amount of peritoneal fluid normally present is 5mL to 20mL, but may be as much as 50mL particularly in women during ovulation.

Similar to PF, reference ranges are generally not published as part of standard clinical laboratory guidelines. However, some cut-off values have been determined as to what one might find in normal fluids.

- Specific gravity: <1.016
- Protein: 3g/dL
- Glucose: similar to blood glucose
- Amylase: similar to blood amylase
- BUN: similar to blood BUN
- WBC: <500/μL
- pH of 7.5 to 8

Peritoneal fluid is often clear and/or slightly yellowish in color. A cloudy, turbid color suggests an infection, while a milky color suggests an inflammatory condition such as peritonitis, pancreatitis, or appendicitis. A red color is consistent with a traumatic tap (specimen has clots) or malignancy (non-traumatic tap has no clots). A greenish color has been associated with a ruptured gall bladder, pancreatitis, or intestinal perforation.

Peritoneal fluids may also be identified...
as an exudate or a transudate. Exudates are most often associated with infections, neoplasms, trauma, pancreatitis, or ruptured gall bladder. Transudates may be caused by congestive heart failure, hepatic cirrhosis, or hypoproteinemia (nephrotic syndrome). Peritoneal fluid resulting from an inflammatory condition generally contains an increased number of WBCs that are predominately neutrophils and reactive mesothelial cells. Transudates often will show more lymphocytes.7,9

The serum-ascites albumin gradient (SAAG) is a reasonably reliable way to differentiate between transudate and exudate fluids (serum albumin minus the ascitic albumen level). Transudates, as found in portal hypertension, exhibit a SAAG level of 1.1 g/dL or greater, whereas values less than 1.1 g/dL are seen in patients with normal portal pressure and with ascitic exudates.7,9

Some additional tests to consider in the evaluation of ascites fluids: 8,9,12

- Ascitic fluid bilirubin-serum bilirubin ratio of 0.6 or greater is consistent with an exudate, generally due to the presence of bile.
- LD is greater than 130 U/L; fluid LD/serum ratio >0.6 suggests a malignant effusion.
- If total protein is greater than 3.0 g/dL (ascitic fluid/serum ratio >0.4-0.5), then an exudate is considered to be the cause.
- Amylase level three times greater than the plasma level suggests a pancreatic ascites.
- Alkaline phosphatase of >100 U/L is seen in hallow visceral injury; >240 U/L is seen in secondary peritonitis.
- BUN and creatinine levels that are greater than blood levels may be a result of intraperitoneal leakage of urine outside of the urinary tract.
- Cholesterol >45-48 mg/dL has been used to differentiate between malignant and non-malignant ascites.
- Triglycerides >199 mg/dL or higher than blood level would be a concern.
- Glucose that is <50 mg/dL is consistent with secondary bacterial peritonitis.

Tumor markers (CEA, CA 19-9, CA 15-3, PSA) may also be of some value when evaluating ascites fluid for the presence of certain malignant cells. CA-125 may be elevated in peritoneal fluid samples from patients with ovarian, fallopian, or endometrial carcinomas. It should be noted that it may also be positive in certain non-malignant disorders such as cardiovascular or chronic liver diseases.9

Each laboratory should carefully review the literature and make individual determinations in developing guidelines in assessing all body fluids. Collaboration with clinicians is often the best approach in establishing these guidelines so that appropriate diagnostic algorithms are developed to include laboratory testing, imaging studies, and the clinical presentation when diagnosing and managing patients with effusions.

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The laboratory’s role in the transformation to patient-centered care

By Donna Beasley, DLM(ASCP)

The “Patient.” The patient has finally re-emerged as the focal point in healthcare, after decades of being shunted aside by other major systemic concerns. It is a heartening development, and it is one in which the clinical laboratory is critical. Laboratories play a crucial role in caring for the patient; over 50 percent of electronic medical record (EMR) information is coming from lab data. In the context of the challenges of healthcare reform and payment changes which will reward value over volume, lab information is vital to providers in the management of their patients. Patient-centered care is the integration of all healthcare and clinical information for a patient, which is then portable to all providers of that patient’s care. The fundamental goal of patient-centered care is a higher quality of care that produces improved patient outcomes.

The challenge for laboratories, then, is how to adapt their business model to accommodate this new patient-centric model when all of their experiences have driven them to focus on volume/accessions. Accountable Care Organizations (ACOs) are structured to focus on the patient and all activities that involve cost management while adding value to patient care. Payment methodology impacts patient-centered care by paying for all services in the patient’s episode of care, which would include lab testing. In some risk-sharing or bundled payment models, this can be dangerous for labs if they do not demonstrate value beyond a reduced cost of the testing. Labs have an opportunity to contribute to improved value for the patient-centered care in many ways.

Patient-centered care: some relevant contexts

This begins with optimized workflow to collect correct patient demographics and insurance information, which is crucial to support health information exchange throughout the continuum of care. Laboratories have the opportunity to play a large role in data exchange with physician offices. The elimination of paper requisitions in favor of electronic connectivity helps in the containment of costs and error reduction. Errors can slow down processes and affect the entire patient encounter, not to mention negatively affect the filing of clean claims.

The communication of clinical information is less valuable if it doesn’t reflect accurate patient information. Errors create cost down the service line and can affect quality as well. For this reason the electronic health records’ (EHRs’) bi-directional connectivity to and from the lab/hospital system is vital to patient-centered care. The data repository of results helps contribute to improved patient outcomes when this data is used as expanded clinical intelligence. Outreach programs help to drive the data exchange with physician offices while aligning physicians to the healthcare system. Without this connectivity, physicians will look elsewhere, to other labs that make ordering simpler and resulting into their EHRs a possibility.

The movement to adopt a unique master patient identifier that is utilized from any service source is another positive industry-wide consideration. Similar to a Social Security number, this patient identifier stays with the patient throughout his or her lifetime, regardless of where the service is performed or what IT system is being utilized. Without it, true data information exchange will not be complete.

However, there are numerous challenges attached to this solution. At the top of that list is assuring patient privacy. In addition, the adoption of the patient identifier must receive Congressional approval before it can be implemented. In the meantime many health systems have adopted an Enterprise Master Patient Index (EMPI), in which the patient has the same identifier regardless of which hospital or service within the health system the patient originates.

The central data repository must be inclusive of clinical information. A longitudinal record for the patient would represent a complete medical history and all clinical data for the patient regardless of place of service. The comprehensive record is achieved via Health Information Exchange (HIE) connectivity which brings together multiple disparate systems. As an example, if a patient has testing as an outpatient, or in an emergency department, has an ambulatory surgery procedure, or was recently hospitalized in another hospital within the system, all of the results associated with those encounters must be available to the practitioner in one longitudinal record. This is value-added in patient-centered care, and the lab plays a role in its contribution. The EMPI is essential to overcome the patient type challenge. With the EMPI, it will be easier to manage and optimize care by tracking all tests in the data repository. The integration of the data from various disparate systems requires connectivity solutions that cross these boundaries. There are challenges with varied terminologies within each system, but solutions to cross-map the translations are possible.

Patient-centered care: the lab’s contribution

Knowing this, what can the laboratory do to contribute to patient-centered care?
• Start by eliminating or significantly reducing paper test ordering requisitions and replacing them with electronic order entry to significantly reduce errors and streamline efficiencies to add value. Evaluate the connectivity that currently exists with ordering provider systems and work to extend connectivity to other providers that currently are still on paper. Consider a middleware provider to connect EHRs to your LIS instead of individual proprietary interfacing. It is faster to deploy and should be a less expensive route.
• Be involved with clinical decision support committees to help further develop the Computerized Physician Order Entry (CPOE) capabilities and maximize right test, right time automated
ordering aids. Often the lab and pathologist are not a part of order set formulation. Explore what committees exist and insert a lab representative where applicable.

• Know that test utilization management is a key component of patient-centered care, and have a formal program in place to aid providers. Improve the testing performed for the patient while reducing costs by utilizing algorithms: clinical pathways based on data. Again, pathologists need to be involved with variation of care solutions.

• Review front-end error processing reports to better understand the type and source of ordering errors. Work with your Information Technology (IT) team to build rules that minimize errors such as duplicate test orders, date-of-birth issues, and demographic issues, or purchase third-party connectivity solutions that have robust rules already built into their software. Additionally, work with your staffed Patient Service Centers (PSCs) to hold them accountable for getting accurate and complete information upfront. Take every advantage of having the patient available, and get the data correct. Tie in an eligibility check to this process as well.

• Be aware of having duplicate patient records and work to minimize and eliminate this. Utilize multiple identifiers that match to confirm a particular patient record to include components other than just name and date of birth.

• Have a mechanism for the PSC staff to view patient balances within the health system, and develop stringent co-pay collection policies, which further extends to patient-centered care to pull in billing capabilities.

• With regard to the actual Lab report, be sure to include all recent issues, or purchase third-party connectivity solutions that have robust rules already built into their software. Additionally, work with your staffed Patient Service Centers (PSCs) to hold them accountable for getting accurate and complete information upfront. Take every advantage of having the patient available, and get the data correct. Tie in an eligibility check to this process as well.

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• With regard to the actual Lab report, be sure to include all recent encounters regardless of patient type for a longitudinal view of the record. Have this data contribute to the central repository of the patient record, which is visible from all operational workflows.

• Utilize the test results in advanced strategies to add value to providers. Focus on alerts to help better predict the potential for readmission. Help providers and case managers determine if any additional testing or abnormal results have occurred post discharge.

• Use technology and data to deliver value:
  o Help your providers by flagging patients at risk.
  o Offer special questionnaires around disease states within your ordering template.
  o Support clinical intelligence dashboards that go beyond the test result itself, which will help to reduce costs and translate into better care.
  o Use your test report formats to educate for appropriate test utilization and new testing.
  o Develop actionable insight data sets to improve quality of care at the patient level.
  o From a global perspective, utilize data to contribute to proactive population health considerations. Key to data sharing for population health is “big data” management; the Lab contributes significantly to that volume of data (Figure 1).

• Know that a patient portal is an excellent resource for patient-centered care that allows patients to access to their results, review and correct their information, and even pay their bills.

• “Lean” processes to eliminate waste and reduce costs by minimizing variation to be better positioned within the ACO environment.

• Have a seat at the table with ACO formation to demonstrate the value of the Lab in the patient-centered care focus.

Patient satisfaction is also an important component of patient-centered care. Patients have more tools today to stay informed and contribute to their care. Labs should look for ways to enhance the patient experience, either online or in person, by providing more information and streamlining processes. Consider… how can the registration process be improved? How does the patient bill look? Is it understandable, accurate, and consolidated? Multiple bills can be confusing to patients and decrease their satisfaction, although the practice today is very prevalent. Patients themselves, and their contribution to their own care, cannot be an overlooked component of patient-centered care.

All of these building blocks will contribute to a developed patient-centered care focus and help any laboratory move in the right direction for the future while ultimately impacting the quality of patient care. The laboratory plays a pivotal role in the creation of meaningful clinical information, impacting the diagnosis and treatment of patients. Labs should help to build upon a solid patient-centered care foundation by decreasing errors, contributing to improving quality outcomes, and operationally modifying workflow processes to reduce costs and improve patient and provider satisfaction. Successful labs will plan and position for the future reimbursement changes, leveraging provider relations and current connectivity to define their value in the shift to patient-centered care model.

Donna Beasley, DLM(ASCP), serves as director of Chicago-based Huron Consulting Group. She is a member of the MLO Editorial Advisory Board.

Population Health Management

Integrated information technology systems share patient care information (dotted lines). PCMH (patient-centered medical homes) IT-powered medical homes emphasize prevention, illness avoidance. Hospitals (e.g. acute care) Nursing homes/Long-term care Pharmacies Home care/Visiting nurses Ambulatory/Specialty clinics Public health resources (e.g. screening) Figure 1
Enhancing the patient experience through a patient-centered approach to care is a growing priority for healthcare organizations. The primary objective of patient-centered care is to ensure a continuing relationship between the patient and his or her healthcare team with a focus on prevention and detection, diagnostic accuracy, and team-based, multi-disciplinary information sharing and collaboration.

Improving health outcomes by providing “the right test for the right patient at the right time” is a popular credo in laboratory medicine that is becoming more achievable every day due to advances in genetic testing and pharmacogenetics, and the systems that support their implementation. A personalized approach to medicine based on a patient’s genetic profile not only accelerates patient diagnosis, but also helps determine response to medications and his or her healthcare team with a focus of patient-centered care is to ensure a continuing relationship between the patient and his or her healthcare team with a focus on prevention and detection, diagnostic accuracy, and team-based, multi-disciplinary information sharing and collaboration.

To date, more than 50 specialty societies have joined the campaign and developed more than 50 evidence-based recommendations to help make the most appropriate care-based decisions at the patient level and provide information on when tests and procedures may be appropriate, as well as the methodology used in their development. The program has begun to spread internationally to Canada, the United Kingdom, Australia, and other countries.

Seven multi-stakeholder alliances were recently formed to focus on the local implementation of Choosing Wisely at health systems, hospitals, and medical groups across the United States to achieve measurable reductions of at least three Choosing Wisely recommendations.

Motivated by the campaign, and to advance both patient-centered and value-based care initiatives, healthcare organizations are developing their own evidence-based best practices for laboratory testing and clinical procedures as a resource to help clinicians better understand and improve their ordering practices to better serve patients.

As laboratory test recommendations are developed and implemented through these types of emerging evidence-based best practices, laboratory professionals will play an important role in educating clinicians and patients and consulting with them on how to improve the diagnostic value of laboratory tests while preventing the overutilization of laboratory resources.

II. Implementing clinical decision support to guide genetic testing

The growth of genetic testing is transforming the standard of care for some diseases, and clinicians will increasingly be able to pursue targeted, patient-specific therapies in the future based on the presence of specific biomarkers and molecular mechanisms causing a disease.

According to the National Center for Biotechnology Information’s Genetic Testing Registry, there are currently more than 32,000 genetic tests for 5,800 medical conditions and 3,900 genes. This vast volume of available genetic diagnostic tests makes it virtually impossible for physicians to keep current and know when to order a specific genetic test, or which one to order based on the patient’s medical history and other factors.

To help clinicians order appropriate genetic tests, interpret test results, and make the best treatment decisions for patient-centered care, labs should take a proactive role in supporting the development and integration of clinical decision support tools and genetic-based knowledge bases into clinical workflow. These tools evaluate and interpret the patient’s personal history, medication list, and genetic profile to analyze and guide clinical decisions about which tests and drugs are most relevant for the patient. Clinicians can review treatment implications and weigh trade-offs among medication alternatives based on known gene-drug interactions.

III. Supporting multi-disciplinary team collaboration

The multi-disciplinary care team is now widely recognized as an essential mechanism to achieve a more patient-centered, coordinated, and effective healthcare delivery system. Healthcare providers collaborate with patients and their families and share information within and across healthcare settings to deliver higher-quality and lower-cost care.

Technology is driving the ability of care teams to coordinate care and communicate through use of web-based healthcare portals, collaborative networking tools, electronic health records, or other hospital-based information and cloud-based systems, many of which can be accessed by the patient as well.

Laboratories and other diagnostic service providers are also leveraging technology to enable specialists such as radiologists, pathologists, and oncologists to access information and expertise from remote locations to facilitate consultation and collaboration on difficult or challenging cases. By having the ability to discuss a patient’s case in real time and share care information and digital images with the patient care team regardless of geographic location, labs support more efficient coordination of care and maximize the interpretation of diagnostics.

Integrated diagnostic reporting between pathology and radiology also provides an opportunity for the multi-disciplinary team to collaborate and bridge the information and diagnostic gap. Technology advancements and platforms are now making it possible to integrate diagnostic findings, results, digital images, and other relevant data into a combined diagnostic report to help determine a more accurate diagnosis and treatment plan.

Labs that are proactive in developing and communicating evidence-based testing algorithms, supporting tools for effective clinical decision making, and ensuring a collaborative care team environment with specialists from both inside and outside the existing network will be better positioned to elevate and cement their role in the patient-centered care model.

Please see references online.

Chrystal Adams is an Associate Vice President with XIFIN, Inc. Chrystal has an extensive background in digital pathology and product strategy for several innovative technology products.

FUTURE BUZZ

PATIENT-CENTERED CARE

In pursuit of patient-centered care

By Chrystal Adams

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48
More than 18,000 clinical laboratory innovators convene in Philadelphia this year. Join them to experience education on the hottest scientific and practice areas in laboratory medicine while evaluating hundreds of new cutting-edge products that are transforming the lab and patient care.

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The article, “Understanding the CDC’s updated HIV test protocol,” identifies the BioPlex 2200 HIV Ag-Ab assay as “the first fifth-generation (HIV) assay.” Clearly, the single most important defining characteristic for each new generation of HIV assays is a reduction in the window period [i.e., the time period between HIV infection and the presence of detectable HIV-RNA or HIV antibodies/antigen (p24)], not the ability to differentiate between HIV-1 and HIV-2 infection in a single assay. Discriminating between HIV-1 and HIV-2 infection is clinically important, despite the fact that the prevalence of HIV-2 infection in the U.S. is low compared to HIV-1 subtype M infection. During the 22-year period, 1987–2009, only 166 cases of HIV-2 infection were reported in the United States by the Centers for Disease Control and Prevention (CDC), while in 2011 alone, the CDC estimated that the number of HIV-infected individuals was 1.2 million.1,2

The reduction in the window period of up to five days by fourth-generation HIV assays has been achieved by the development of an HIV “combo” assay that detects both HIV antibodies and the HIV p24 antigen. The serologic profile of p24 antigen in the time-course of HIV infection demonstrates an earlier rise and peak in plasma concentration than occurs with HIV antibodies (Figure 1).

The principal difference between the BioPlex 2000 HIV Ag-Ab assay and currently available fourth-generation HIV assays is the ability to discriminate between HIV-1 and HIV-2 infection in a single assay. Notably, Mr. Kapler’s article provides information on the window period for first-, second-, third-, and fourth-generation HIV assays, yet no information, data, or reference citations are provided indicating the window period for the BioPlex 2000 HIV assay. In my view, and for reasons indicated above, earlier detection of HIV infection, HIV-1 or HIV-2, is a more important characteristic of an HIV screening assay than the ability to differentiate simultaneously whether a positive HIV test result is due to HIV-1 or HIV-2, especially given the markedly low prevalence of HIV-2 infection in the United States.

I suggest that we reserve the definition of a new and improved HIV assay, deserving of the moniker fifth-generation, for an HIV assay that reduces the window period below that achieved with a fourth-generation assay. If that can be achieved with the ability to simultaneously differentiate in a single assay between HIV-1 and HIV-2, then this is an added bonus of such an assay; otherwise, we need to change the currently prevailing definition of a new “generation” of an HIV assay. However, a change in definition based solely (assuming there are no data indicating a reduction in the window period for the BioPlex 2000 HIV assay versus current fourth-generation HIV assays) on an analytical characteristic of any HIV assay (e.g., the type of instrument, the principle of the method, etc.) is not consistent with our current usage of new “generation” of an HIV assay.

—Frank H. Wians, Jr., PhD, AT(ASCP), MASCP, DABCC, FACB
Professor of Pathology
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Technical Director, Clinical Chemistry,
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Figure 1. Time course of HIV-1 RNA, HIV antibodies, and HIV p24 antigen detection for 1st-, 2nd-, 3rd-, and 4th-generation HIV assays.2

Using HIV Ag/Ab Combo assays closes the window to detect HIV infection up to 5 days.
Author's response

Dr. Wians makes the case that the BioPlex 2200 HIV Ag-Ab assay does not deserve fifth-generation status because it does not significantly reduce the window period of infectivity detection. I appreciate his close reading, but that argument misses the mark. The assay in question deserves next-generation status because it is the first assay that can simultaneously detect and differentiate the p24 antigen and antibodies to HIV-1 and HIV-2—in one set of results. Therefore, the assay can tell a clinician not only the type of HIV infection but also the patient’s stage of infectivity (acute vs. established). This should significantly reduce what I might call the “treatment window”—the time period between overall HIV detection and the initiation of correct treatment. For the record, the assay’s window period is ~12 days. (Disclosure: I work part time for its maker, Bio-Rad, through an outside consulting firm.)

He further suggests that earlier detection of HIV infection of either type “is a more important characteristic of an HIV screening assay” than whether the type of infection is HIV-1 or HIV-2, because of the rarity of HIV-2 in the U.S. He concedes elsewhere, however, that distinguishing between HIV-1 and HIV-2 is “clinically important.” In this regard he is trying to have it both ways. Either it is important or it isn’t, whether the type is revealed during the initial screening phase or the differentiating phase of the algorithm. As he knows, the CDC—like the FDA—takes actions based largely on the precautionary principle, which has been a component of public health policy since the AIDS epidemic began. Two of the CDC’s stated objectives in changing the algorithm were to identify infections earlier and to more accurately diagnose HIV-2 because it had been misdiagnosed under the former testing paradigm. Certainly, there were only 166 cases of HIV-2 in 22 years. That doesn’t mean much statistically. It only matters to the person infected with HIV-2 who is desperately seeking the right medicine.

More generally, his argument sits atop two faulty premises: that some official entity confers generational status on HIV assays, and that such status is based solely on the criteria used to determine a new generation, filters confers generational status on new HIV assays. That status, classification of the infection-detection window. I have found no evidence that the CDC, or any other agency, body, or authority, confers generational status on new HIV assays. That status, like the criteria used to determine a new generation, filters up from the laboratory/research/manufacturing community itself. And filter it has. None other than Bernard Branson, MD, former Associate Director for Laboratory Diagnostics in the CDC’s Division of HIV/AIDS Prevention, has in at least one public presentation referred to the assay in question as a fifth-generation assay. —Robert Kapler

INDEX OF ADVERTISERS

<table>
<thead>
<tr>
<th>ADVERTISER</th>
<th>WEB</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AACC</td>
<td><a href="http://www.aacc.org/2016am">www.aacc.org/2016am</a></td>
<td>49</td>
</tr>
<tr>
<td>Arkray</td>
<td><a href="http://www.arkrayusa.com">www.arkrayusa.com</a></td>
<td>33</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td><a href="http://www.TAGRISSHcp.com">www.TAGRISSHcp.com</a></td>
<td>8</td>
</tr>
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<td>25</td>
</tr>
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</tr>
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<td>37</td>
</tr>
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<td>Compact Group Medical</td>
<td><a href="http://www.compactgroup.com">www.compactgroup.com</a></td>
<td>15</td>
</tr>
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<td>21</td>
</tr>
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<table>
<thead>
<tr>
<th>ADVERTISER</th>
<th>WEB</th>
<th>PAGE</th>
</tr>
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<tbody>
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<td>26-27</td>
</tr>
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<td>39</td>
</tr>
<tr>
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<td>3</td>
</tr>
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<td>45</td>
</tr>
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<td>Verbatim Americas, LLC</td>
<td><a href="http://www.pathfast.com">www.pathfast.com</a></td>
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NEW PRODUCTS

Inverted microscope

The OXX53 is a next-generation inverted microscope designed for fast, efficient cell culture checking and documentation. Its imaging capabilities and user-friendly design reduce operator fatigue and improve cell culture throughput. The microscope provides excellent clarity and resolution, with a newly developed integrated phase contrast system that enables the operator to view samples at 4x, 10x, 20x, and 40x, without exchanging or re-centering the ring slit. Brightfield imaging is improved with an energy-efficient, long-life LED light source. In addition, the color temperature of the LEDs is optimized for cell culture observation to enhance color reproducibility when raising or lowering the brightness level. The microscope is 29 percent lighter than previous models so it can be moved as needed and placed on a sterile bench when aseptic conditions are required.

Olympus
www.rslead/604ml-157

Micromanipulator with joystick

The TransferMan 4m micromanipulator features a Dual-Speed joystick and functions to help speed up and facilitate the handling of sensitive samples. The micromanipulator therefore helps minimize exposure of sensitive cells to trauma or adverse conditions like room temperature or removal from CO2 atmosphere. The micromanipulator is a tool for applications, such as ICSI, PGD, and related techniques. In conjunction with the manual microinjection of the Eppendorf CellTram family, it forms an ideal system for demanding cell manipulation procedures. The TransferMan 4m is classified in the United States as an assisted reproduction micromanipulator and microinjector medical device under 1 CFR 884.6150.

Eppendorf
www.rslead/604ml-158

X-well slide cell culture system

A new lumox x-well cell culture chamber with a 50μm ultra-thin, gas-permeable film base that combines imaging with superior cell growth. Compared to plastic or glass bases, the gas-permeable lumox film provides more effective gas exchange and homogeneous cell growth. It offers virtually no autofluorescence and higher light transmission for consistently high assay sensitivity and excellent microscopy and fluorescence-based imaging. The film is chemically resistant to a multitude of fixatives and stains and can be easily cut for cell isolation or storage after fixation and staining.

Sarstedt
www.rslead/604ml-159

Portable all-in-one printer

This device is a small, lightweight and portable all-in-one printer. It’s perfect for people who need to print, scan, and copy while on-the-go. Its functionality to print, scan, and copy matches any full-size all-in-one printer. At just 2.6 lbs. (1.2kg) and about the size of a hardcover book, Primera Trio fits just about anywhere.

Primera
www.rslead/604ml-160
Developing blood biomarker tests for the detection of cancer

If you were explaining Oncimmune to someone who is not familiar with the organization, how would you characterize its areas of expertise? What major categories of solutions does Oncimmune provide for its customers? Oncimmune is a biotech company specializing in blood biomarker tests for the early detection of various cancers. The first major focus has been on the early detection of lung cancer. More specifically, Oncimmune specializes in detection of autoantibodies against cancer antigens in order to build a panel of autoantibodies that serve as a blood biomarker test for early detection of specific cancers. Its first autoantibody biomarker panel is for the detection of lung cancer before it becomes symptomatic, and it is called EarlyCDT-Lung. This test is a panel of seven autoantibodies to cancer antigens. If one or more of the autoantibody levels is elevated, then the test is considered positive.

You became Chief Medical Officer for Oncimmune in January. What will be your primary responsibilities and challenges in your new position? My major focus will be to assist in the further development and refinement of the EarlyCDT-Lung biomarker test for use in screening of high-risk individuals for lung cancer, and for assessing the risk of malignancy in non-calcified or indeterminate pulmonary nodules. The challenge of any biomarker is to make sure that it is sensitive and specific enough that it aids practicing physicians in their decision-making over and above the clinical risk profiles. Equally challenging will be the education of practicing physicians as to how the biomarker test can optimally assist them in the decision-making process.

Prior to your appointment as Oncimmune CMO, you worked on a clinical trial offered at National Jewish Health utilizing the EarlyCDT-Lung test. Can you tell us about this trial? I was the principal investigator on a clinical trial that was assessing the utility of adding the EarlyCDT-Lung blood test to low-dose CT scan screening of high-risk individuals. That trial is ongoing and has more than 1,000 individuals enrolled to date. The plan is to enroll a total of 1,600 participants.

What were the results of the trials? What insights were gained that may enhance their value to oncologists and to the clinical laboratory? The results to date are preliminary but suggest that the risk of lung cancer is elevated approximately fivefold if the blood test is positive. This is in a cohort of individuals who are already at high risk for lung cancer due to their age and smoking history. These early results support the results of a previously published clinical use audit which showed a fivefold increased risk of lung cancer in individuals with a positive test.

The autoantibodies in the EarlyCDT-Lung blood test have been shown to be positive in all stages of lung cancer including the earliest, Stage I. Preliminary data has shown the blood test to be positive one to two years before the clinical diagnosis of lung cancer in some cases. Two ongoing prospective clinical trials are in progress to further clarify the ability of the test to detect lung cancer before individuals develop signs and symptoms of disease.

Will the approach be applicable to other kinds of solid-tumor cancers as well? Is Oncimmune developing blood autoantibodies assays for other cancers? The EarlyCDT-Lung autoantibody biomarker approach is theoretically applicable to most cancers. However, the cancer antigens expressed on different cancers can vary greatly. Also, the extent of their expression for developing an autoantibody response will vary. Additional autoantibody blood tests for early detection of other cancers are in development. Oncimmune is in the process of developing a blood autoantibodies test for hepatocellular carcinoma (liver cancer), and preliminary work is underway for ovarian cancer.

You spent many years serving at the Mayo Clinic (Rochester) before moving on to National Jewish Health and now Oncimmune. How does your career as a top clinician and researcher help you function more effectively in your industry capacity? For more than 30 years the focus of my career has been on early detection, diagnosis, and treatment of lung cancer as well as other malignancies of the chest. During this time period I have been privileged to interact and collaborate with top physicians in the lung cancer field. Through this exposure to critical thinkers and my own clinical practice, I have become aware of the high bar set for biomarkers to be of clinical usefulness. Additionally, I have credibility and contacts within the lung cancer field. This will allow Oncimmune to develop a registry study for indeterminate pulmonary nodules and other potentially necessary prospective clinical trials. The acquired knowledge gained from these lung cancer clinical trials will translate to other malignancies.
It’s Your Sample

Biological samples stored in standard vessels can lose up to 90% material within 24 hours due to adsorption to the plastic surface. Eppendorf LoBind Tubes and Plates maximize sample recovery by significantly reducing sample to surface binding.

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Learn more about the FilmArray Meningitis/Encephalitis (ME) Panel and BioFire’s leading syndromic panels at FilmArray.com