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On Death and Dying revisited

In recent weeks I have been re-reading On Death and Dying, the groundbreaking work about managing the terminally ill, written by the brilliant psychiatrist Elizabeth Kübler-Ross (1926-2004). Few works of scientific research have been as widely read by the general public, and deservedly so.

In the mid-1960s, Kübler-Ross, then working at the University of Chicago School of Medicine (and its hospitals), along with hospital chaplains and graduate students, began a project in which they interviewed terminally ill patients, mostly cancer patients, with the goal of better understanding the problems they faced and the ways they responded to the approaching end of their life. The project turned into student seminars, and transcripts from the seminars eventually formed the backbone of On Death and Dying, which was published in 1969.

The book made an immediate impression. Time magazine’s reviewer wrote: “The Chicago seminar has vanquished the conspiracy of silence that once shrouded the hospital’s terminal wards. It has brought death out of the darkness.” Life magazine called the book “a profound lesson for the living.”

Part of the book’s thesis is that death, always a fearful prospect for human beings, had become even more frightening in modern times, because it was often slower (due to cancer or other progressive disorders rather than infectious diseases, which had been mostly conquered by antibiotics) and more impersonal. People used to die among the comforts of home, Kübler-Ross argues; now, more often they died in the stressful environments of hospitals, tended more by technicians than loved ones, connected to ventilators and other machinery, and dehumanized in many ways. Dying in the twentieth century (it is only more true today) was emotionally harder, and the psychological burden on patients was greater.

Another part of Kübler-Ross’s thesis, and one that inspired howls of protest from some clinicians, was that doctors, nurses, and others who come into contact with the terminally ill unconsciously bring their own fears of death and unresolved conflicts into those interactions, to the detriment of good practice. Being in the presence of dying people reminds us that we are going to die, too—so the unempathetic doctor, and the cold nurse who focuses more on the machines than the patients, are actually engaged in self-protective psychological strategies, defending themselves through denial or detachment. The patient whom they are there to serve becomes secondary.

The most famous part of On Death and Dying, which has become part of American popular culture, is Kübler-Ross’s division of the stages of dying into Denial, Anger, Bargaining, Depression, and Acceptance. Some critics have complained that the progression is too schematic, and Kübler-Ross herself later acknowledged that she wished her book had made clearer that not all patients go through all five stages, or in that order, or finish one and then enter the next without sometimes going back. But the thrust of her generalizations remains valid and extremely useful for healthcare workers, who can better serve the dying if they understand what the dying person is going through from his or her own perspective and recognize that a dying person does not surrender his human dignity. Is the “difficult” or “hostile” patient, for instance, really being difficult or hostile, or is he working through his Anger or Depression?

On Death and Dying should be required reading for physicians and nurses; for social workers and psychologists and other hospital personnel; for phlebotomists. I think laborators should read it too, even though they rarely see the patients whose imminent deaths they sometimes view through the microscope.

In my experience with readers of MLO, I am struck by how aware most of the human stories that lie beyond those slides. It is to your credit that you are not hardened or cynical. But On Death and Dying is a good refresher course on how important and valuable your work is.

Alan Lenhoff
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The Toll of Tuberculosis

Tuberculosis (TB) remains a global scourge. Every day, as many people die of TB as would die in 15 jetliner crashes.

- 33% is the proportion of the people in the world infected with the TB bacterium; only a small number become sick with the disease.
- 10.4 million is the estimated number of new cases of TB that occurred worldwide in 2016.
- 6.3 million is the number of 2016 new cases who were detected and notified.
- 7 is the number of countries that account for nearly two-thirds of total TB cases: India, Indonesia, China, the Philippines, Nigeria, Pakistan, and South Africa.
- 61% is the proportion of total TB cases that occur in Asia.
- 26% is the proportion of total TB cases that occur in Africa.
- 1.7 million is the number of people who died of TB in 2016.
- 1 million is the number of children who became ill with TB in 2016.
- 210,000 is the number of children who died of the disease in 2016.
- 400,000 is the number of people with HIV who died of TB in 2016.
- 490,000 is the number of people who developed multidrug-resistant TB in 2016.
- 37% is the decrease in TB deaths between 2000 and 2016; WHO efforts to diagnose and treat TB are having an effect.
- 53 million is the number of lives saved by TB treatment between 2000 and 2016.
- 83% is the treatment success rate achieved in 2016.


Infectious Diseases

New research suggests immune system can protect against MRSA.

Researchers at Johns Hopkins, the University of California, Davis, and NIAID have discovered how the immune system might protect a person from recurrent bacterial skin infections caused by staph. The findings, published online in The Journal of Clinical Investigation, open new doors to developing vaccines to prevent staph skin infections, which account for 14 million outpatient visits, nearly 500,000 hospital admissions, and $3 to $4 billion in inpatient healthcare costs in the U.S. annually.

Multidrug-resistant strains, such as MRSA, are causing severe skin infections in healthy people outside of hospitals. And subsequent to infection, the recurrence rate is 50 percent within six months.

Using mice with defective immune systems, a research team found that after an initial exposure of the skin to staph, they were protected against a second skin exposure with the same bacteria. After testing for antibodies and other “usual suspects” of the immune system against this infection, it was not clear what immune response was protecting the mice.

The researchers then tested a drug that is FDA-approved for treatment of multiple sclerosis, which acts by preventing certain immune cells from leaving lymph nodes for sites of inflammation.

Genetic sequencing data revealed that specific cells substan- tially multiplied after the initial infection, then moved to the infection site and provided protection against the second infection. These so-called gamma delta T cells account for less than one percent of all the cells in the lymph node prior to infection. After infection, they accounted for more than 20 percent.

To see whether the findings were applicable to people, researchers tested blood from healthy individuals and people with a rare immune disorder that makes them highly susceptible to staph skin infections. Patient blood samples presented an increase in percentage of gamma delta T cells, similar to what they observed in mice, which remained stable over years. Researchers hope gamma delta T cells may be targeted for developing new therapies or even a vaccine against staph skin infections. This, they say, could alleviate the burden of staph skin infections, prevent invasive complications, and reduce healthcare costs.

Rapid Testing

A roadside test for marijuana intoxication? It isn’t as easy as it sounds. As the movement to legalize marijuana in the U.S. gains momentum, researchers worry about public safety, particularly on the roads. Recent studies in which marijuana users took controlled doses of cannabis in the lab have identified new biomarkers that can be used to estimate a person’s recent cannabinoid intake. But using those markers to judge cognitive and behavioral impairment is complex, say toxicologists in a commentary published in the journal Trends in Molecular Medicine on biomarkers of substance abuse.

“There is no one blood or oral fluid concentration that can differentiate impaired and not impaired,” says Marilyn Huestis, who spent over 20 years leading cannabinoid-related research projects at the National Institute on Drug Abuse.

Alcohol can impair a user more than cannabis, and the risk of an accident while driving increases in proportion with blood alcohol concentrations. But marijuana is different: many variables can affect how impaired someone is at any given concentration of THC, the primary psychoactive agent in cannabinoids. Whether it is inhaled or consumed, and whether the user titrates the dose, can affect the level of impairment.

Another problem is that THC quickly leaves the bloodstream. Previous research by Huestis has shown that blood THC concentrations can be effectively zero after 2.5 hours. And on average in the U.S., it takes 1.4 to four hours after a crash or traffic stop to administer a blood test.

Long-term users, such as those who use marijuana for medical reasons, also present a challenge for developing roadside protocols. THC accumulates in body tissues and then slowly releases over time, so chronic users can test positive for cannabis even after 30 days of abstinence. Psychomotor
impairment can be observed three weeks after the last dose.

Huestis advocates for well-trained police officers who can identify the behavioral signs of impairment and less invasive biological marker tests, which could be immediately performed at the roadside to confirm the presence of a cannabinoid. To that end, recent research has identified new blood and urine markers, and tests using breath and saliva markers are being developed. These new markers and tests could also be used to assist in treating drug dependence, in determining appropriate therapeutic levels of medicinal marijuana, and in monitoring women who want to stop using cannabinoids during pregnancy.

**Phlebotomy**

**Study demonstrates reduction in blood culture contamination rates.** A Medical University of South Carolina (MUSC) research study found that use of a mechanical initial specimen diversion device (ISDD) and staff education led to a four-fold decrease in contaminated blood cultures that was sustained over 20 months.

Results of the Emergency Department (ED) research were presented at the Institute for Healthcare Improvement (IHI) National Forum by lead study author Lisa Steed, PhD, MUSC Department of Pathology and Laboratory Medicine professor.

Blood cultures help physicians determine whether patients have serious and potentially life-threatening blood infections such as sepsis. These blood draws may become contaminated with bacteria-containing fragments of a patient’s skin that enter the needle during the blood collection process. Studies have shown that conventional techniques can lead to false positives, which in turn may lead to patients receiving more blood draws, extended length of stay, increased exposure to HAIs, and unnecessary antibiotic treatment.

The mechanical ISDD used in the study, called Steripath (Magnolia Medical Technologies), is a sterile, closed blood culture collection system that diverts, sequesters, and isolates the first 1.5 to 2 milliliters of blood—the portion that is known to contain contaminants—during the blood draw.

The study also showed that use of the mechanical ISDD could reduce costs and use staff time more efficiently. Researchers suggested that MUSC would have saved $744,955 if the ISDD had been used for every blood draw in the ED during the study, based on an estimate of $4,850 for the cost of a contaminated culture.

**Molecular Diagnostics**

**Medical organizations update guideline for molecular testing and targeted therapies in lung cancer.** Rapid advancements in the molecular diagnostic testing of lung cancer have led to new treatments for patients battling the disease, the most common cause of cancer death worldwide. To ensure that clinicians stay apace and provide optimal patient care, three leading medical societies—the College of American Pathologists (CAP), Association for Molecular Pathology (AMP), and International Association for the Study of Lung Cancer (IASLC)—have updated their 2013 evidence-based guideline.

Published online, the “Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment with Targeted Tyrosine Kinase Inhibitors” continues to set standards for the molecular analysis of lung cancers for test results that effectively guide targeted therapy and treatment.

Targeted cancer therapies are drugs or other treatments that block the spread of cancer by interfering with specific molecules that spur that specific cancer’s growth and progression. Patients whose tumors harbor certain, specific molecular alterations may be candidates for targeted tyrosine kinase inhibitor (TKI) therapy, which may improve survival and quality of life.

The updated guideline strengthens the majority of the 2013 recommendations for patients with lung adenocarcinoma, and also recommends testing for some new genes.

The complete guideline is available online at the Archives of Pathology & Laboratory Medicine, Journal of Thoracic Oncology, and Journal of Molecular Diagnostics. Additionally, the three societies developed resources to help pathologists and oncologists review and implement the guideline, including a summary of recommendations, a teaching presentation, and frequently asked questions.

**Industry News**

**FDA extends comment period to March 30, 2018, for two draft guidances.** The U.S. Food and Drug Administration (FDA) is extending the comment period to March 30, 2018, for these two draft guidances:

- Select Updates for Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices – Draft Guidance for Industry and Food and Drug Administration Staff
- Recommendations for Dual 510(k) and CLIA Waiver by Application Studies – Draft Guidance for Industry and Food and Drug Administration Staff

Instructions for submitting comments are available in the Federal Register under docket numbers FDA-2017-D-5570 and FDA-2017-D-5625.

The FDA published these two draft guidance documents on November 29, 2017, to help manufacturers of IVD devices apply for and receive CLIA waivers. “Select Updates...” is issued in accordance with section 3057 of the 21st Century Cures Act (PL. 114-255). When finalized, this will represent FDA’s thinking regarding the appropriate use of comparable performance between a user in a waived facility and a user in a moderately complex laboratory to demonstrate accuracy. When final, this content will revise “Section V. Demonstrating Insignificant Risk of an Erroneous Result — Accuracy” of the guidance Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices (2008).

“Recommendations for Dual 510(k)...” when finalized, will describe the agency’s expectations regarding study designs for generating data that supports both 510(k) clearance and CLIA Waiver by Application. The FDA believes that increased use of this pathway will speed up the process of bringing simple and accurate IVD devices to CLIA waived settings, which will better serve patients and providers.
Finding the truth in laboratory testing

Commutability, traceability, and uncertainty of measurement

By Greg Cooper, CLS, CQA, MHA

Truth, trueness, true value: these terms have become part of the clinical laboratory lexicon over the past decade. We seek to know the “true” value of an analyte (measurand) in a patient sample. We strive to determine the “trueness” of our measurement systems by participating in PT/EQA. We test control materials alongside patient samples to verify that the test system is “truly” operating within specification. This leads to the question of whether the processed materials we use, such as control materials, PT/EQA samples, reference materials, and so on, “truly” reflect what is happening with patient samples. Part of the answer to this question lies in the topics of commutability, traceability, and measurement uncertainty.

The three topics are especially relevant at the moment, as there are national and international committees working to provide direction and guidance to clinical laboratories. At the same time, laboratory professionals may not understand when commutability of quality control materials should be evaluated, whether control material needs to be traceable for daily operations, or how uncertainty of measurement is relevant to reporting patient results. This article provides an overview of the importance of each of these topics in the clinical laboratory. “Truth” in laboratory testing is central to contemporary discussions concerning commutability, traceability, and measurement uncertainty.

COMMUTABILITY

The question of what is the appropriate relationship between control performance and patient test results has been around since the introduction of antigen-antibody diagnostic methods in the 1990s. Laboratories have been perplexed by changes in control performance when implementing a new method or when one sample is examined by two different measurement procedures for a stated quantity in a given material and the relation obtained among the measurement results for a stated quantity in other specified materials” (ISO 15194); and “closeness of agreement between the mathematical relationship of the measurement results obtained by two measurement procedures for a stated quantity in a given material and the mathematical relationship obtained for the quantity in routine samples” (ISO 17511).

When two “different” samples are examined by the same method or when one sample is examined by two different methods and the results are the same within a specified uncertainty, the samples are commutable. But, is this a problem?

The Clinical and Laboratory Standards Institute (CLSI) defines a processed sample as “a sample that is prepared to be used to mimic one obtained from a patient. It is considered a processed sample if it has been modified in any way that causes it to be different from one obtained from a patient—for example, freezing, lyophilization, adding non-endogenous substances or stabilizers.” Therefore, processed samples include control materials, EQA/PT samples, calibrators, certified reference materials, trueness controls, and altered patient samples.

These processes may include spiking measured to achieve desired concentrations, using measurands not of human origin due to cost or a unique molecular structure, using recombinant measurands, adding preservatives and stabilizers to assure expected performance, or undergoing extreme heat and pressure to create lyophilized materials. Furthermore, some matrices are not human, but instead are contrived, albumin-based, or occasionally bovine.

Each of these processes can cause some degree of unwanted effects during testing; these are called matrix effects. When matrix effects are of a magnitude that is not seen in the patient samples, the material is considered to be “non-commutable.” But, is this a problem?

The general definition of commutability is “equivalence.” There are two similar definitions found in ISO standards ISO 15194 and ISO 17511: “property of a given reference material, demonstrated by the closeness of agreement between the measurement results for a stated quantity in this material, obtained according to two measurement procedures, and the relation obtained among the measurement results for other specified materials” (ISO 15194); and “closeness of agreement between the mathematical relationship of the measurement results obtained by two measurement procedures for a stated quantity in a given material and the mathematical relationship obtained for the quantity in routine samples” (ISO 17511).

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LEARNING OBJECTIVES

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

1. Explain why it is important to identify the trueness of analytical results.
2. Define and discuss commutability, as it relates to measurement results.
3. Define and discuss traceability, as it relates to measurement error.
4. Define and discuss measurement uncertainty, as it relates to test performance.

continued on page 10...
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tolerance, the materials are considered equivalent or commut-utable. Establishing equivalency or commutability (that is, identifying non-commutability) is a mathematical/statistical exercise and has value for determining whether control materials may be used to verify performance after a reagent lot change or whether patient samples are required. But there is one other facet of commutability relevant to control materials that must not be overlooked.

The primary purpose of control materials is to verify that the test system is performing within established specifications based on past performance of the control material. Control materials are not and never have been intended to verify the “trueness” of patient test results—only whether the test system is working within specification or not. The quality control process (regardless of whether the control material is quantitative or qualitative) is basically a pass/fail system. In this respect, commutability should only be an issue of whether to recalculate the performance specifications or focus on test system failure when a change in test system performance is verified; that is, control materials do not have to be statistically commutable to perform their intended purpose.

So, when do laboratory leaders suggest testing processed samples for commutability? Common instances when commutability experiments need to be performed on processed samples may include (but are not limited to) the following:

• verifying that control materials can be used to verify the presence (or absence) of reagent lot-to-lot performance changes
• determining when statistical process control ranges need to be adjusted after a reagent lot change
• developing assurance by providers that EQA/PT samples are equivalent in performance to patient samples, particularly when results of testing EQA/PT samples are used to determine outlier performance or to de-certify the use of a method
• verifying claims of “trueness” for manufactured materials (e.g., control materials).

Consider the following example: The laboratory has a new reagent kit lot. Before putting the kit into use, the laboratory needs to verify that the test system performs within specification after the new kit is put into use as it did before. Historically, laboratories have used control materials to verify performance before and after a kit or reagent lot change. Current laboratory best practices dictate that the laboratory should first run experiments before any need arises to verify whether the control materials are suitable for this purpose or exhibit matrix effects to the extent that would invalidate their use for such verifications: that is, a commutability study. If control materials are found to be fit for this purpose (com-utable), they can be used to verify performance subsequent to a reagent lot change; if not, then patient samples must be used. CLSI EP14 examines the topic of commutability and explains the evaluation process with worked examples.

TRACEABILITY
For years, leaders in the laboratory profession have sought to achieve harmonization of diagnostic testing. The goal has been to achieve equivalent results for a single test among varying testing methods. The first approach was to create and implement an international regulatory standard (ISO) that would require calibrations of diagnostic devices to trace back to a recognized international reference measurement procedure. The standard for diagnostic tests is ISO 17511, and a companion standard for enzyme calibration is ISO 18153.4 Essentially, these two standards are based on a series of cali-brator manufacturing steps called a “calibration cascade.” Briefly, the cascade is represented in Figure 1. (Please refer to ISO 17511 for more detailed versions of the cascade.)

There are three things that are important to know about ISO 17511 and ISO 18153.
• First, the standard is intended for manufacturers or labora-tories developing their own tests (LDTs) and applies only to the manufacture of calibrators and control materials that are intended for “trueness” determinations.
• Second, the manufacturing of daily use control materi-als, such as those commonly in use in most laboratories, are exempt from the requirements of these two standards. It is recognized that these precision controls are not required to meet the requirements for traceability because they have no

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**Figure 1. Representation of a manufacturer’s calibration cascade**
Once-a-day QC works just fine, until it doesn’t.

How much of a risk is your lab taking?

Just because you’re meeting the regulatory minimum of once-a-day QC, doesn’t mean you sleep well at night, or are confident that your laboratory has patient risk under control. Daily QC may be adequate for some tests, but using the same approach for higher risk tests could put some patients at risk for inappropriate treatment due to undetected instrument failure. Can your lab afford that risk - or the delay and costs of repeating patient samples? Bio-Rad Mission: Control is the first tool a laboratory can utilize to help assess and manage those risks objectively: calculate your current risks, and help select the right QC rules and frequency for your lab.

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MEASUREMENT UNCERTAINTY

One might say that measurement uncertainty is the new kid on the block. It first gained the attention of clinical laboratories and accreditors with the 2003 publication of the first international laboratory practice standard, ISO 15189. This standard, and later versions in 2007 and 2012, require laboratories accredited to the standard to calculate their own measurement uncertainties and have this data available for each quantitative test performed in the laboratory. Attribute tests (for example: positive, negative) must also have measurement uncertainty calculated if the method has a quantitation step, such as an absorbance value for determining a cutoff. Unfortunately, there is no companion standard from ISO that describes for laboratories the process and formulae to calculate the measurement uncertainty statistic, nor is there a publication of measurement uncertainty benchmarks for comparison purposes. As a quality initiative, laboratories do maintain a record of calculated uncertainties should review those calculations at regular intervals to assure their continued relevance.

So, what value does measurement uncertainty provide? Measurement uncertainty is a range expressed by a percent (and sometimes a unit of measure) within which the “true value” of the measurand is expected to be. It can be helpful to a clinician when a laboratory test result is at or near an actionable value. The statistic can be useful in making decisions about health status (normal/abnormal), physiology (treatment effective/not effective), or comparison of results on the same patient (Is the difference due to physiology, treatment, or an artifact of the test performance?). Measurement uncertainty can also be useful when a result is questioned and a repeat test is ordered and performed: Is the repeat value within or outside expectation?

A repeat within the measurement uncertainty would go far in validating the original result reported.

One approach for calculating uncertainty originates within the science of metrology and is referred to as the GUM (Guide to Uncertainty of Measurement) approach. It is extremely detailed, uses advanced statistical tools, and requires examination of every possible contributor to variability—for example, the uncertainty associated with the fill of anticoagulant in collection tubes. Many in the industry regard this approach as onerous and unwarranted for medical laboratory testing, and the approach has been met with stiff resistance. However, if a laboratory develops tests or modifies a test, the GUM must be followed.

An alternate approach has been suggested and is being developed under the auspices of the ISO organization in Technical Committee 212. This standard is still in development as of this writing, and is expected to be based on information and statistics easily developed or obtained by the laboratory. Laboratories should also be aware that CLSI has published a guidance, C51, that examines a modified GUM procedure and an alternate approach using laboratory data to calculate uncertainty.

“To thine own self be true”

So said Polonius in Shakespeare’s Hamlet, and that advice might have relevance to this brief discussion of truth in laboratory testing. The laboratory must first and foremost be “true” to its stated goals and objectives by protecting its credibility with appropriate quality systems, using materials and devices with proven quality, and having a rigorous program of self-assessment and self-awareness. Only then can the laboratory assure the well-being of the patients it serves.
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CONTINUING EDUCATION TEST
FINDING THE TRUTH IN LABORATORY TESTING: COMMUTABILITY, TRACEABILITY, AND UNCERTAINTY OF MEASUREMENT

March 2018 (This form may be photocopied. It is no longer valid for CEUs after September 30, 2018.)

TEST QUESTIONS

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

1. According to the author, truth in laboratory testing results depends on
   ○ a. commutability and traceability.
   ○ b. traceability and measurement uncertainty.
   ○ c. commutability, measurement uncertainty, and traceability.
   ○ d. none of the above

2. The matrix effect must be addressed when there is a change in control material performance of a new reagent lot, but patient sample performance remains the same.
   ○ a. True
   ○ b. False

3. What type of material is not affected by the matrix effect?
   ○ a. a frozen material
   ○ b. a raw material
   ○ c. a material with added stabilizers
   ○ d. a lyophilized material

4. Commutability in lab testing is generally referring to
   ○ a. traceability
   ○ b. precision
   ○ c. accuracy
   ○ d. equivalence

5. When is a material considered non-commutable?
   ○ a. when a matrix effect is not observed, but a high variance of non-commutability is observed in patient samples
   ○ b. when a matrix effect is observed of a magnitude that is not observed in patient samples
   ○ c. when both a matrix effect and a variance of non-commutability are observed in patient samples
   ○ d. none of the above

6. Patient samples must be used for reagent lot changes when
   ○ a. non-commutability is identified.
   ○ b. commutability is identified.
   ○ c. traceability is identified.
   ○ d. measurement uncertainty is identified.

7. Control materials are intended to verify the “trueness” of patient test results.
   ○ a. True
   ○ b. False

8. What two approaches were originally created by the International Organization for Standardization (ISO) that require calibrations to trace back to a recognized international reference measurement procedure, called a calibration cascade?
   ○ a. ISO 15194 and 17511
   ○ b. ISO 15189 and 18153
   ○ c. ISO 17511 and 15189
   ○ d. ISO 17511 and 18153

9. What type of material is exempt from the two ISO standards developed for traceability?
   ○ a. controls used for daily use
   ○ b. enzyme calibrators
   ○ c. proficiency testing samples
   ○ d. all of the above

10. The introduction of analytical variables contributes to error along the calibration cascade, which is produced as the measurement uncertainty of the calibrator
   ○ a. decreases.
   ○ b. increases.
   ○ c. stays constant.
   ○ d. all of the above

11. In what instance should laboratories be concerned when it comes to assessing traceability?
   ○ a. when calibrating a new lot of analyte
   ○ b. when performing testing on proficiency material
   ○ c. when selecting a new commercial test or test method
   ○ d. when performing daily QC

12. Which test of trueness gained attention with the publication of ISO 15189?
   ○ a. accuracy
   ○ b. commutability
   ○ c. measurement uncertainty
   ○ d. traceability

13. ISO 15189 has created a specific formula to calculate measurement uncertainty characteristics for laboratorians.
   ○ a. True
   ○ b. False

14. The measurement uncertainty statistic is helpful in making decisions about
   ○ a. health status.
   ○ b. physiology.
   ○ c. comparison of two results.
   ○ d. all of the above

15. This organization has published this guidance, which uses a modified GUM procedure to help laboratorians calculate uncertainty:
   ○ a. ISO, Technical Committee 21
   ○ b. ISO, Technical Committee 12
   ○ c. GUM: ISO 15189
   ○ d. CLSI: C51

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Diabetes is not so much being cured as it is being surrounded. Researchers are coming at this common disorder from a number of different perspectives, and some of their discoveries are finding their way, or soon might find their way, into clinical practice. Here’s a roundup of some recent scientific approaches regarding type 1, type 2, and gestational diabetes mellitus (GDM), as well as an exciting recent FDA approval of a needle-free glucose testing device that may make life easier for people with diabetes.

**Biosensor to monitor glucose in tears/sweat**

We may be one step closer to providing people with diabetes with an improved monitoring tool that continuously tracks their glucose levels through their tears or sweat. Researchers report in the journal *ACS Nano* the development of an ultra-thin, flexible sensor that could be incorporated into contact lenses or on the backs of watches for real-time glucose tracking.

Wearable sensors are part of an increasingly digitized world. But those that are commercially available typically monitor physical activities by measuring steps taken, for example, or heart rate. Creating ways to measure health markers on a molecular level has been far more challenging, but the benefits could be life-changing for some patients. Diagnosing and tracking conditions are often done by analyzing a sample of someone’s blood. The pain of pricking fingers or drawing blood, however, can deter people from vigilant monitoring conditions such as diabetes that require regular checks. To take the sting out of the process, wearable glucose sensors are in development but have been hampered by several factors. Some devices can’t detect the low levels of glucose that are in sweat and tears, or they stop working when they are bent.

The researchers created a biosensor using nanoribbons of indium oxide, an enzyme glucose oxidase, a natural chitosan film, and single-walled carbon nanotubes. When glucose is present in a test sample, it interacts with the enzyme, setting off a short chain of reactions and ultimately creating an electrical signal. Testing showed that the device could detect a range of glucose concentrations from 10 nanomolar to one millimolar, which is sensitive enough to cover typical glucose levels in sweat, saliva, and tears in people with and without diabetes. Bending the film 100 times didn’t noticeably affect its performance.

**Women who have GDM risk future health issues**

Women who have gestational diabetes mellitus during pregnancy have a higher risk than other women of developing type 2 diabetes, hypertension, and ischemic heart disease in the future, according to new research led by the University of Birmingham (UK). The retrospective cohort study was published in *PLOS Medicine*.

The researchers studied the incidence of type 2 diabetes, hypertension, and ischemic heart and cerebrovascular diseases in a UK primary care database that included more than 9,000 women diagnosed with GDM between 1990 and 2016.

The study found that women diagnosed with GDM were more than 20 times more likely to be diagnosed with type 2 diabetes later in life, more than two-and-a-half times more likely to develop ischemic heart disease, and almost twice as likely to develop hypertension.

Dr. Krish Nirantharakumar, of the University of Birmingham’s Institute of Applied Health Research, says: “Results showed women diagnosed with GDM were significantly more likely to develop hypertension and ischemic heart disease at a relatively young age compared with women without a previous diagnosis of GDM in addition to the established risk of developing diabetes. The risk was greatest for type 2 diabetes in the first year following diagnosis of GDM and persisted throughout the follow-up period.”

The findings add an important insight into the trajectory of the development of type 2 diabetes, hypertension, and cardiovascular disease in the early and latter post-partum periods.

“Furthermore, the findings are the first to report on a large UK population and identify an at-risk group of relatively young women ideally suited for targeting risk factor management to improve long-term metabolic and cardiovascular outcomes,” says Nirantharakumar.

The study also found that follow-up screening in women diagnosed with GDM for diabetes as well as cardiovascular risk factors was low. With the exception of blood pressure, less than 60 percent of women were screened in the first year after giving birth, and that decreased to less than 40 percent by the second year after having their baby.

Barbara Daly, of the Faculty of Medical and Health Sciences at the University of Auckland (New Zealand), continued on page 18
An accurate HbA1c diagnosis requires the detection of hemoglobin variants
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DIFFERENT VOLUMES
SAME GOLD STANDARD
New findings in early-stage islet autoimmunity
Type 1 diabetes is the most common metabolic disease in childhood and adolescence. In this disease, the body's immune system attacks and destroys the insulin-producing cells of the pancreas. Regulatory T cells (Tregs) play an important role in this process: in healthy people, they suppress excessive immune reactions and thus prevent autoimmune diseases.

Dr. Carolin Daniel's team is investigating why Tregs fail to protect the islet cells in type 1 diabetes. She is a group leader at the Institute for Diabetes Research (IDF) of Helmholtz Zentrum München (Germany). In the current study, her team elucidated a mechanism that causes fewer Tregs to be produced during islet autoimmunity onset and therefore allows the immune system to get out of control and attack.

According to study findings miRNA181a and NFAT5 molecules play a key role. Says Daniel: “We showed that miRNA181a leads to the activation of the transcription factor NFAT5 during islet autoimmunity onset. The consequence is an inhibition of Treg induction and thus increased immune activation.”

To test the suitability of this new finding for possible therapeutic approaches, the scientists investigated a preclinical model with early-stage islet autoimmunity. When they interrupted the miRNA181a/NFAT5-axis, they observed a significantly lower activation of the immune system and an increased formation of Tregs. This was achieved by the pharmacological inhibition of both miRNA181a and NFAT5.

“The targeted inhibition of miRNA181a or NFAT5 could open up new approaches to reduce the activity of the immune system against its own islet cells,” says Professor Anette-Gabriele Ziegler, director of the IDF. “The combination with other immune-modulating therapeutic approaches would also be conceivable as an intervention.”

In the future, the researchers want to further investigate these findings in preclinical tests. To this end, humanized models will be used to test whether the combination of insulin vaccination and inhibition of the miRNA181a/NFAT5 axis leads to an immune system that is more tolerant toward insulin-producing cells.


Gene causes low and high blood sugar in family

A study of families with rare blood sugar conditions has revealed a new gene thought to be critical in the regulation of insulin. The research, carried out at Queen Mary University of London, University of Exeter, and Vanderbilt University and published in the journal PNAS, could lead to the development of novel treatments for both rare and common forms of diabetes.

In addition to the more common forms of diabetes (type 1 or type 2), in about one to two percent of cases diabetes is due to a genetic disorder. A defective gene typically affects the function of insulin-producing cells in the pancreas, known as beta cells.

The research team studied the unique case of a family in which several individuals suffer from diabetes, while other family members have developed insulin-producing tumors in their pancreas. These tumors, which are known as insulinomas, typically cause low blood sugar levels, in contrast to diabetes, which leads to high blood sugar levels.

Lead author Professor Márta Korbonits says: “We were initially surprised about the association of two apparently contrasting conditions within the same families—diabetes, which is associated with high blood sugar, and insulinomas, associated with low blood sugar. Our research shows that, surprisingly, the same gene defect can impact the insulin-producing beta cells of the pancreas to lead to these two opposing medical conditions.” The team also observed that males were more prone to developing diabetes, while insulinomas were more commonly found in females.

“One exciting avenue to explore will be seeing if we can use this finding to uncover new ways to help regenerate beta cells and treat the more common forms of diabetes,” Professor Korbonits adds.

The researchers identified a genetic disorder in a gene called MAFA, which controls the production of insulin in beta cells. Unexpectedly, this gene defect was present in both the family members with diabetes and those with insulinomas, and was also identified in a second, unrelated family with the same unusual dual picture.


Immune system could regulate insulin

Inflammation processes are responsible for the failure of insulin production in diabetes patients, but patients’ own immune systems could contribute to treatment of this disease. Researchers at the University of Basel and University Hospital Basel (Switzerland) have found a feedback mechanism that could help maintain insulin production in overweight sufferers, they report in the journal Immunity.

In their study, the researchers focused specifically on recently discovered ILC2 immune cells in the pancreas, where, under diabetic conditions, the protein IL33 is activated, among others. This protein stimulates the ILC2 cells, which trigger the release of insulin in overweight individuals using retinoic acid and could therefore be used to inhibit the failure of insulin production.

The research gives an insight into an inflammatory network that could contribute to the maintenance of insulin production in diabetics. The complex interactions between endocrine cells and immune cells are clearly significant for the maintenance of insulin release.

It is already known that obesity and diabetes lead to an excessive, pathological activation of the immune system in which the messenger substance IL1-beta plays a central role. This results in the death of insulin-producing cells. However, if IL1-beta is blocked, diabetes and its complications—in particular cardiovascular diseases—can be inhibited. Diabetic inflammatory reactions are already finding use in clinical applications.


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According to the FDA/MAUDE database:

**Nova StatStrip® Reduces Glucose Meter Related Patient Deaths and Adverse Events by 98%**

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<thead>
<tr>
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<th>StatStrip</th>
<th>Roche Accu-Chek® Inform II</th>
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<tr>
<td>Per 6,500 StatStrip meters</td>
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<td>Per 6,500 Inform II meters</td>
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The FDA requires manufacturers and users to report all hospital adverse events, including patient deaths that are caused by their glucose meters. These reports are then summarized on the FDA’s MAUDE database. The most recent 2015-2017 MAUDE data shows a dramatic improvement in patient care when advanced technology Nova StatStrip glucose meters are used in place of other meters. This FDA data shows that hospitals using Nova’s advanced technology have an adverse event rate 40x lower than others. This remarkable reduction in Nova adverse events, including no patient deaths, comes from using the more accurate (no known clinical interferences) Nova StatStrip meter. These dramatic improvements in patient outcomes are obtained despite the fact StatStrip is the only meter cleared by the FDA for use on critically ill patients who have the most analytically challenging samples.

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3. StatStrip market share of 57% and Inform II market share of 30% from 2017 market share survey. Data available on request.
Potential enzyme as therapeutic target

Abnormalities in glucose uptake by the liver (or hepatic glucose uptake, HGU) cause elevations in blood glucose levels following meals, a state that is known as postprandial hyperglycemia. Such abnormalities are observed in obesity and type 2 diabetes and result in an increased risk of cardiovascular complications. Although the exact mechanism of HGU impairment is unknown, there is evidence that it is mediated by abnormal regulation of the enzyme hepatic glucokinase and the glucokinase regulatory protein (GKRP).

Now, a team of Japanese researchers has identified a sirtuin enzyme (Sirt2) as a key player in regulating hepatic glucokinase through modifying GKRP, suggesting that this mechanism offers a potential therapeutic target for type 2 diabetes.

Previous reports show that the signaling molecule nicotinamide adenine dinucleotide (NAD+) governs glucose metabolism. In this paper, the researchers used in vitro experiments to identify Sirt2 as a mediator of NAD+-dependent HGU. However, Sirt2 did not influence the gene expression levels of glucokinase and glucose-6-phosphatase. This implies that Sirt2 affected HGU through post-translational modifications.

In normal cells, glucokinase binds to GKRP in low glucose conditions, while the two proteins dissociate in response to elevation of glucose levels. In cells derived from diabetic mice, however, this does not take place even under high glucose concentrations. In the current study, researchers were able to reverse this perturbation by overexpressing Sirt2 and showed that Sirt2 can regulate the dissociation by directly binding to GKRP and deacetylating it (at residue K126) in a NAD+-dependent manner.

The researchers also performed experiments in mice and found that expressing a form of GKRP that could not be acetylated perturbs HGU, suggesting that acetylation of GKRP is involved in HGU and the maintenance of normal glucose levels. They also found that a decrease in NAD+-dependent Sirt2 activity and defective Sirt2-dependent deacetylation of GKRP were responsible, at least in part, for the HGU abnormality observed in obese diabetic mice.

Overall, the results indicate that NAD+ and Sirt2 regulate HGU and that Sirt2 acts through deacetylating GKRP.

The authors conclude that “these findings suggest that NAD+ /Sirt2-dependent GKRP deacetylation regulation plays an important role in HGU control and that this regulation is a novel therapeutic target in type 2 diabetes and obesity and is responsible for HGU impairment.”

Source: https://www.eurekalert.org/pub_releases/2018-01/ku-pea012518.php

FDA clears first continuous glucose monitoring system

The U.S. Food and Drug Administration has approved the FreeStyle Libre Flash Glucose Monitoring System, the first continuous glucose monitoring system that can be used by adult patients to make diabetes treatment decisions without calibration using a blood sample from the fingertip.

The system reduces the need for fingerstick testing by using a small sensor wire inserted below the skin’s surface that continuously measures and monitors glucose levels. Users can determine glucose levels by waving a dedicated, mobile reader above the sensor wire to determine if glucose levels are too high (hyperglycemia) or too low (hypoglycemia), and how glucose levels are changing. It is intended for use in people 18 years of age and older with diabetes; after a 12-hour start-up period, it can be worn for up to 10 days.

“The FDA is always interested in new technologies that can help make the care of people living with chronic conditions, such as diabetes, easier and more manageable,” says Donald St. Pierre, acting director of the Office of In Vitro Diagnostics and Radiological Health and deputy director of new product evaluation in the FDA’s Center for Devices and Radiological Health. “This system allows people with diabetes to avoid the additional step of fingerstick calibration, which can sometimes be painful, but still provides necessary information for treating their diabetes—with a wave of the mobile reader.”

People with diabetes must regularly test and monitor their blood sugar to make sure it is at an appropriate level, which is often done multiple times per day by taking a fingerstick sample and testing it with a blood glucose meter. Typically patients use results of a traditional fingerstick test to make diabetes treatment decisions; however, fingerstick testing is not needed to inform appropriate care choices or to calibrate glucose levels with this system.

The FDA evaluated data from a clinical study of individuals aged 18 and older with diabetes, and reviewed the device’s performance by comparing readings obtained by the FreeStyle Libre Glucose Monitoring System to those obtained by an established laboratory method used for analysis of blood glucose.

Risks associated with use of the system may include hypoglycemia or hyperglycemia in cases where information provided by the device is inaccurate and used to make treatment decisions, as well as mild skin irritations around the insertion site. It does not provide real-time alerts or alarms in the absence of a user-initiated action; for example, it cannot alert users to low blood glucose levels while they are asleep.

The FreeStyle Libre Flash Glucose Monitoring System is manufactured by Abbott Diabetes Care Inc.

Source: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm577890.htm
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MLO's 2018 Annual Salary Survey of laboratory professionals

By MLO staff

The United States Department of Labor, Bureau of Labor Statistics (BLS) states that employment in “Healthcare Occupations” is projected to grow 18 percent from 2016 to 2026, much faster than the average for all occupations. Healthcare occupations will add about 2.4 million new jobs to the workforce. In fact, healthcare is projected to add more jobs than any of the other occupational groups. This projected growth is mainly due to an aging population which leads to greater demand for healthcare services. According to BLS, the 2016 median pay was $50,930 per year, or $24.48 per hour, for medical and clinical laboratory technologists and technicians.

The median annual wage for healthcare practitioners and technical occupations was $63,420, which was higher than the median annual wage for all occupations in the economy of $37,040. Healthcare support occupations had a median annual wage of $27,910, lower than the median annual wage for all occupations in the economy.

Medical laboratory technologists and technicians both fall under the Bureau’s “Healthcare Practitioners” category. Most worked in hospitals in 2016, while others worked in medical and diagnostic laboratories or doctors’ offices. The median annual wage for technologists was $61,070, while the median annual wage for technicians was $38,950.

As we know, medical laboratory technologists typically need a bachelor’s degree. Technicians usually need an associate degree or a postsecondary certificate. Some states require technologists and technicians to be licensed.

Phlebotomists typically enter the occupation with a postsecondary non-degree award from a phlebotomy program. However, almost all employers look for phlebotomists who have earned professional certification. The median annual wage for phlebotomists was $32,710 per year, or $15.72 per hour.

All of which provides context for the 2018 MLO Annual Salary Survey. As in every March issue, we are pleased to report the results!

This year we had 21 percent more respondents than last year. However, we had less Lab Directors/Managers/Administrators/Supervisors respond, all of whom tend to be higher-paid employees. We had more responses from MLTs/MTs and phlebotomists, who tend to be lower-paid employees. Additionally, 76.8 percent reported they did not receive a bonus in 2018, compared to 71.5 percent last year; indicating 5.3 percent less received bonus monies. These factors likely lowered the overall average salary in 2018.

In terms of education, we captured six percent fewer post-graduate degree holders this year compared to last, and the survey showed a four percent increase in AA degrees. Both of these factors may have also contributed to the salary wage gap between the 2017 and the 2018 surveys.

In a nutshell
- Only 33.8 percent of survey respondents are Lab Managers/Administrators/Supervisors, compared to 53.6 percent last year.
- 7.9 percent of survey respondents are Lab Directors, whereas 16.8 percent identified as such last year.
- MLS/MLTs made up 18.5 percent of respondents this year, compared to 6.8 percent in 2017.
- More than 55 percent have worked in the industry for more than 30 years.
- Almost 40 percent have worked with their current employer for 20 years or more.
- Just over 60 percent have worked with their current employer for less than 20 years.
- About three-quarters work in a hospital-affiliated lab.
- About seven in ten respondents are female.

Salary basics
The average salary as reported by the MLO 2018 survey is $79,006; that is a significant decrease from the 2017 average salary of $84,654. However, interestingly, 68 percent of survey respondents reported an increase in salary during 2018.

The discrepancy seems to be a result of a distinction that can be drawn between survey respondents who work in a facility other than a hospital lab (26 percent) and those who work in a hospital lab (74 percent). Hospital lab workers reported an average salary of $81,757, while “other” workers reported an average salary of $71,127.

Another factor to consider is an influx of lab newbies in the workforce. In 2018, 2.6 percent of respondents had been employed for three to five years in the lab industry, whereas only 1.6 percent had been employed for that span in 2017.
Also, in 2018, 14.1 percent of respondents have been employed for six to nine years; the corresponding number was 12.1 percent in the 2017 survey. An additional factor contributing to the lower average salary may be that there were more respondents who were paid hourly in 2018 (45 percent) versus in 2017 (31 percent).

New government data released offered some good news about salary discrepancies among men and women: 2017 was the largest recorded narrowing of the gender wage gap in the U.S. in a decade. Women in 2016 made 80.5 percent of what men did on average—up from about 80 percent in 2015, and from less than 60 percent in the 1970s.2

Overall, reported 2018 salaries were lower by most measures as compared to 2017. The average salary for a female laboratorian was $75,629 ($83,199 last year). The average salary for a male was $89,084; believe it or not, the same number as last year.

As has been the case most years, there were significant differences in average salary among the regions of the U.S. (see Salary by Region and Gender map). Nearly three out of four respondents (74.1 percent) work in hospital-affiliated labs, as opposed to a slightly larger percentage last year (78.2 percent). The largest number of respondents this year (26.7 percent) work in labs with one to 10 employees. Labs with 21 to 50 employees came in a close second at 21.1 percent. In last year’s survey, just under 23 percent worked in labs with one to 10 employees, and just under 25 percent worked in labs with 21 to 50 employees.

**Salary and education**

With regard to highest academic degree, 62.9 percent hold a bachelor’s degree, up slightly from last year’s 61.6 percent. The average salary for these laboratorians is $75,145, lower than last year’s $79,616. Just over 25 percent hold post-graduate degrees, down from 30.8 percent last year, and their salaries averaged $101,375, compared with $100,896 the year prior. 10.5 percent hold associate degrees, compared to 6.6 percent who held two-year degrees in last year’s survey. Associate degree holders’ 2018 salary averaged $52,162—substantially lower than last year’s figure of $62,206.

**Age distribution**

The highest number of respondents in the 2018 survey are in the 56-to-65 age group; 43.9 percent. This is in the same range as the 2017 survey, when the corresponding number was 42.3 percent.

This year, 24.4 percent of respondents are in the 46-to-55 age group, compared to 28.3 percent last year.

There was a downturn in the number in the 36-to-45 age group, from 13.3 percent last year to 11.4 percent this year. The number in the 26-to-35 age group increased, from 5.8 percent a year ago to 7.7 percent this year.

**Salary by geographic region**

Geographically, the salary breakdown is as follows:

- In the Pacific Coastal region, the average is the highest-paying, with an average salary of $112,327 ($117,911 for women and $106,620 for men).
- In the Mountain region, the average salary is lower this year: $72,200 ($72,871 for women and $67,500 for men).
- In the Central region, the average salary is lower this year: $70,695 (a decrease to $68,644 for women, and an increase to $82,210 for men).
- In the Northeast, the average is lower this year: $82,504 (a significant decrease to $77,901 for women, $94,730 for men).
- In the Southeast, the average is lower this year: $70,462 ($69,662 for women, $72,433 for men).

The historical trend in the survey has been that salaries seem to drop from west to east, with some recovery in the Northeast; this is probably at least in part a reflection of the cost of living in the different regions of the nation. Also repeating last year’s pattern, women’s salaries were higher than men’s in the Pacific and the Mountain regions, but men’s were higher in the other three regions.

**Increases and benefits**

Nearly seven in ten respondents (68 percent) reported a salary increase in 2018, while 28.9 percent said their pay remained the same, and 3.1 percent saw their salaries decrease. These numbers are comparable to last year’s, except more than twice as many laboratorians saw a decrease than last year (when the number was 1.4 percent).

Seventeen percent of survey respondents say they expect no pay increase in 2018. Last year, the corresponding number was 14.2 percent. 42.8 percent expect a raise of two to four percent; 26 percent predict a raise of less than two percent; and 3.2 percent think they will receive a raise of five percent or higher.

In terms of benefits, 97.9 percent of survey respondents received health insurance through their employer. 92.9 percent have dental; just over 90 percent have a 401(k) or pension plan; 83.4 percent have life insurance; and 87 percent have vision insurance. Seven in nine respondents (78.5 percent) have disability insurance.

With regard to holidays, 66.7 percent have paid holiday time, and 44.5 percent received overtime pay. Only 23.3 percent of our survey respondents received bonuses last year, as opposed to 28.5 percent the year prior.

Instead of and/or in addition to offering monetary compensation, labs often provide their employees other incentives, such as travel to and from conferences, department awards, and other employee recognition programs.

**Service and staffing**

Overall, Bureau of Labor Statistics figures say that employment of medical laboratory technologists and technicians is projected to grow 13 percent from 2016 to 2026, faster than the average for all occupations. Employment of phlebotomists is projected to grow 25 percent during the same period—much faster than the average for all occupations. An increase in the aging population is expected to lead to a greater need to diagnose medical conditions through laboratory procedures.3

55.8 percent of survey respondents have been in the lab workforce for 30 years or more, and another 24.9 percent have had between 20 and 30 years of service. This totals more than 80 percent of our survey respondents! What we are seeing is a lot of workers in the later stage of their careers; concerns within the industry about an aging workforce and a future shortage of laboratorians seem to be justified.

The number of laboratorians who have been in the industry between 10 and 20 years is 11.7 percent; nine years or less came in at 7.6 percent, and only four percent of respondents indicated they have been in the industry for less than five years.

Just under 40 percent of survey respondents have worked for their current employer for 20 years or more—loyal, to say the least. On the other side of the spectrum, 14 percent have been with their current employer three years or less; that is up from 10.9 percent a year ago.
Survey participants who have been in the clinical lab 30 years or more make the most money on average: $82,728, vs. $90,529, last year. The newest employees—three years or less in the industry—averaged $58,944 in 2018 versus $67,929 in 2017. That’s considerably less—$8,985, to be exact. Those in the industry three-to-five-years are averaging $60,156; while the six-to-nine folks make a shade more, averaging $61,614.

According to the survey, 64.4 percent work a standard eight-hour shift, but about 28 percent work nine-, ten-, or twelve-hour shifts.

Certification and continuing education
As in the past, the large majority of our 2018 survey participants (77 percent) received their accreditation through the American Society for Clinical Pathology (ASCP). State certification came in a distant second at 15.8 percent, and the National Credentialing Agency for Laboratory Personnel (NCALP) placed third with 11.7 percent. Of course, many respondents had multiple certifications.

Almost 50 percent (46.6 percent) of certifications are medical technologists (MT). MT was followed by clinical laboratory scientists (CLS) at 17.2 percent, medical laboratory technicians (MLT) at 13.8 percent, and medical laboratory scientists (MLS) at 11.1 percent. Specialists in blood banking (SBB) made up 4.3 percent of our survey respondents.

Continuing education remains very important to laboratorians. The survey reports that just over half of respondents took ten or more CE classes (53.7 percent), while only 8.2 percent took no CE classes.

Test volume and automation
It is difficult to summarize the volume of tests performed annually by all laboratories in the U.S. Moreover, it is even more difficult to obtain stratification of this test volume by specialty and subspecialty of clinical or anatomic pathology. However, when we asked, “What is the annual volume of testing performed at your lab?” the results were as follows:

- 15.3 percent run more than two million tests per year.
- 20.7 percent run one to two million tests.
- 16.4 percent run between 500,000 and a million tests.
- 7.6 percent run less than 25,000 tests annually.

Automation in the lab saves time and money. Just over half (51.6 percent) of survey respondents indicated that their lab had automated or further automated processes during the last year. This is up slightly from 50.3 percent last year.

Personnel shortages continue to affect the lab, but not to the point of most labs deciding to outsource as a response to that problem. 18.3 percent of laboratories were outsourcing as a result of personnel shortages last year. That is higher than last year, when 13.1 percent outsourced. Although outsourcing lab services can save money, it can also mean longer turnaround times for lab results and a hospital’s loss of control over lab services. There are sound arguments that can be made that outsourcing limits profit in the long run.

Molecular diagnostics (MDx) has certainly made its mark in the microbiology laboratory: 65.8 percent of survey respondents stated MDx has been embraced in their lab. However, it has been slower to make progress in Chemistry (11.7 percent), Hematology (6.1 percent), and Blood Bank (4.7 percent).

Job security and satisfaction
The number of survey respondents who reported they are either very or somewhat secure in their work is 92.4 percent. Only 7.6 percent said they are somewhat or very
insecure in their job. 86.5 percent reported themselves as either very or somewhat satisfied with their job, while 13.5 percent indicated they were somewhat or very unsatisfied. These numbers are comparable to last year.

According to Clinical Laboratory Management Association (CLMA), medical laboratory students said the following influenced them the most in terms of accepting employment offers: competitive salary, tuition reimbursement, sign-on bonus, health benefits, certification and/or licensure reimbursement, flexible hours, and vacation time.

Something less tangible, but no less important, was how they were treated if/when they were in the lab for a clinical rotation. In addition, some students expressed discomfort in settings where staff did not comply with safety regulations or there was unprofessional treatment of co-workers.

The quality of medical laboratory operations is driven by technical skills, quality management systems, and the motivation provided by lab leaders. But the bottom line is the people; the employees. The 2018 MLO Salary Survey gives us a snapshot of the lab workforce in real time.

See additional 2018 salary survey charts and graphs online at www.mlo-online.com.

**REFERENCES**
Big Data may not always be better in the clinical lab

By Don Barton, MS, MT(ASCP)

The last few years we’ve been listening to the trumpeting of the efficacy of Big Data1,2 and the role it will play in the healthcare industry and the clinical laboratory from now on. Just this morning I received an email from a vendor, and I quote “…I’ve seen how many customers struggle with data—or the lack of data, causing the inability to make good decisions in the laboratory.” If we only had enough data and proper analysis, the mantra goes, we could become more effective and practice better healthcare. The mad rush to connect all our data sources and feed them into a common well seems unstoppable. And data analytics businesses are popping up all around us, promising to give meaning to our reams of untapped data, as if a vast gold field has been recently discovered and is waiting to be mined.

There is unquestionable merit in this view, and indeed, sophisticated use of informatics will be part of the future of healthcare. But as we run cables, connecting us like a well-groomed spider’s web, the old adage still applies: “garbage in, garbage out.” Ultimately, the quality of the data is far more important than the quantity. At a certain threshold, having more data only adds marginally to its meaning, while every data point must be scrutinized for the integrity of its value. Regarding laboratories, every lab director needs to be able to unhesitatingly testify to the integrity of his or her test results. No lab wants to be questioned regarding the quality of his or her test results. No lab wants to have its product be questioned regarding the quality of his or her test results. No lab wants to hesitate in giving meaning to its results, causing the inability to make good decisions in the laboratory.

If we only had enough data and proper analysis, the mantra goes, we could become more effective and practice better healthcare. The mad rush to connect all our data sources and feed them into a common well seems unstoppable. And data analytics businesses are popping up all around us, promising to give meaning to our reams of untapped data, as if a vast gold field has been recently discovered and is waiting to be mined.

Knowing your processes

The most telling irregularity was the large standard deviations in our dataset. This finding definitely raised our suspicion that something wasn’t right. Upon closer examination of the data, we discovered three outlier groups—data that shouldn’t have been included in the study:

1. specimens that had troponins added on at a later time (add-on test),
2. specimens reviewed for quality assurance reasons, and
3. specimens with delayed receive times.

It was not uncommon for an ER provider to add on a troponin after running other laboratory tests. These add-on troponins were ordered and performed anywhere from a few minutes to hours later, and because they were run on an existing specimen, the receive time of the specimen was not changed—resulting in an inaccurately longer TAT.

We do quality assurance on all our troponins and have found they are not always correctly documented. We edit these records, and while we don’t change the troponin result, when re-filing the test the verified time is reset and updated in the EMR. In addition, the quality assurance review may not be done until a few days later, thus greatly affecting the standard deviation and the average TAT.

The largest factor that influenced our study involved delayed receive times. Often, after a patient is drawn, the specimen is taken directly to the chemistry area and spun in a stat centrifuge. The phlebotomist then enters the specimen/receive time information in the LIS computer—that is, if he or she doesn’t have other stat draws to finish first. By the time the troponin specimen is received into the LIS, several minutes may have gone by and the specimen is already running on the analyzer. The minimum amount of time a troponin specimen can be “spun and run” in our laboratory is 24 minutes: five minutes to spin and 19 minutes to put on the analyzer and then run and file. We found that in several cases (eight percent) specimens were being verified in less than 24 minutes. While our process still

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Case study: troponin testing in ER versus laboratory

We are a small independent hospital in rural Colorado. Our ER providers decided they wanted to do point-of-care troponins instead of having our laboratory perform the test. The fact that the laboratory was literally across the hall from the ER didn’t seem to dissuade them from that idea. A feasibility analysis was done. Part of this analysis, and one of the most important aspects of the study, was to determine accurately the laboratory turnaround times (TAT) for troponin testing. If this were a study being done involving a large hospital system, the laboratory data would be aggregated from the various hospitals, a statistical analysis would be performed, and a decision would be made.

Being a small hospital, we dug through a year’s worth of our data repository and our laboratory information systems (LIS) databases for the various parameters needed to determine our TAT. The primary parameters used were the specimens’ receive times in the laboratory to the times they were verified in the EMR. This would seem to be a very straightforward and uncomplicated study. Yet, after viewing the data, we noticed some significant problems.

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Don Barton, MS, MT(ASCP), is a laboratory informaticist at Delta County Memorial Hospital in Delta, Colorado. He says his work is like teaching a kindergarten class, except with analyzers and computers, making sure they always talk nicely to each other, and never tell lies.

Getting to the point
If a large hospital corporation, data analytics group, or accountable care organization were to extract this data from various laboratories, it could come to a very different conclusion that would not represent the true TAT. In our study, eight percent would not be considered a huge number, but the effect of not excluding this data in calculating the average TAT was significant; 31 vs. 23 minutes, or about a 26 percent difference. This value doesn’t take into consideration the inaccuracies introduced with the other outlier groups. A data analyst, even one with prior laboratory experience, could not be expected to be familiar with the intricacy of each laboratory’s processes in order to take these and any other variables into consideration. Indeed, why would an analyst even suspect there might be any issues with the data?

While Big Data will offer many significant and cost-saving insights into the practice of healthcare in the coming years, there are some decisions that still need to be made at the local level by those who understand best the details, and the strengths and weaknesses, of their internal processes. Determining which processes best benefit from Big Data analysis, and which do not, is critical to making valued decisions that benefit the patients who come to us for their healthcare. Failure to do so will lead to undesirable outcomes in terms of efficiency, economy, and patient well-being. When this happens, we do a disservice to the very processes designed to improve healthcare and ultimately the health of the patients we serve.

Big Data may not always be better. As one observer aptly stated, “It isn’t too much to ask sometimes for data-based decisions about data-based decisionmaking.”

REFERENCES
Digital imaging/morphology is the next chapter in hematology

By Jurgen Riedl, PhD

Digital imaging/morphology makes use of digital images and software algorithms to classify hematological cells, such as leukocytes and red blood cells. For a subset of leukocytes, digital system classification correlates well with the manual microscope method, the gold standard. Digital imaging thereby leads to a faster, more efficient, and more standardized way of performing a morphological analysis of a peripheral blood smear. Future possible applications include the morphological analysis of other cell categories such as red blood cells and thrombocytes and digital analysis of other materials such as bone marrow samples. Furthermore, digital imaging can be used as an excellent learning tool. Independently organized quality surveys should be implemented by manufacturers of digital microscopy systems to ensure quality requirements. Integration of digital imaging with basic cell counter results could lead to a faster detection and higher sensitivity and specificity in the detection of hematological malignancies.

Morphological analysis of the peripheral blood smear (PBS) is an essential element of hematological diagnostics.1 Traditionally, the analysis of a PBS has been performed by using the manual microscope method. This method, however, is labor-intensive, requires continuous training of personnel, and is subject to relatively large inter-observer variability.2-4 The development of digital microscopy systems, capable of using digital images of leukocytes, erythrocytes, and thrombocytes for classification, has been ongoing for more than a decade.4,5

For reasons of clarity, this review will discuss digital imaging by use of a digital microscope developed by the company Cellavision. Sysmex Corporation has generated a similar digital microscope, integrated in a hematology track incorporating both a cell-counter and a slide-maker stainer.6 Other companies have generated digital microscopy systems,6,7,27 especially in the field of pathology.1 However, these systems are still in the experimental phase with regard to implementation in routine (hematological) diagnostics and are currently more used for diagnostic remote and scholar use. In essence, they are not now used as pathology filters in the diagnostic work-up. Some systems have, however, found a central place in the routine hematological peripheral blood smear screening.

The digital workflow in detail

The digital microscope (DM) makes use of a digital camera, which is capable of generating high-resolution images of leukocytes, red blood cells, and thrombocytes. The systems are equipped with software capable of not only detecting these cells, but also subsequently classifying them in the correct cell class. This software application was developed using an artificial neural network, and it considers a large number of features, such as size, roundness, and size and shape of the nucleus for the morphological classification of leukocytes. The number of cells counted by the system can be set by the operator, and the DM will present the results in both absolute numbers and percentages. The classification results can then be judged by an experienced morphological research technician. The expert will validate the results and send them to the laboratory information system (LIS) and hospital information system (HIS). The classification by the system will be defined as pre-classification throughout this article. The subsequent possible re-classification by a trained morphological expert will be defined as post-classification.

Before digital microscopy systems can be implemented in daily hematological routine with regard to PBS analysis, these systems should be validated thoroughly. Currently, the manual microscope method is considered the standard. To date, various papers have described accuracy- and precision-studies of digital imaging when compared to manual assessment. It has been shown that digital microscopy shows good correlation with the standard with regard to the five-part differential: segmented, eosinophilic, and basophilic granulocytes; lymphocytes; and monocytes. Nucleated red blood cells (NRBC) also displayed a good correlation.9-11

Moreover, digital imaging leads to reproducible results when comparing the results of independently operated digital microscope systems of the same type and brand.12 Pre-classification of immature granulocytes and myeloid progenitor cells showed inadequate correlation with the manual method, requiring manual supervision to ensure proper results. Therefore the mathematical algorithm to classify these classes should be further improved. However, one could argue that in a clinical situation the sole description of left-shift is sufficient for diagnostics and does not necessarily need specific subclassification of individual myeloid progenitor cells. Combining this with state-of-the-art immature granulocyte functions on cell counters could help with this issue.

Lymphocyte pathology

Correct subclassification of specific lineage subset pathology, e.g., follicular lymphoma (FLC) or mantle cell lymphoma (MCL) in the case of abnormal malignant lymphocyte classes present, is currently also still lacking. However, recent advances have been made in this specific area. Alferrez et al have developed algorithms to discriminate hairy cells and chronic lymphocytic leukemia (CLL) cells from normal lymphocytes using digital imaging analysis.13 It seems likely that further improvement of these algorithms will facilitate the detection and classification of pathological cells in the nearby future.

Blast cells

Several studies showed high sensitivity scores for the detection of blast cells in the PBS using digital imaging.10,11 Unfortunately this was accompanied by relatively low specificity scores in the pre-classification, rendering the definitive result still subject to experienced manual observer validation.11 However, the high sensitivity makes digital imaging extremely suitable as a screening tool for the presence of blast cells in a PBS. This is, for instance, very useful in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) patient follow-up during therapy treatment, and our

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**Thrombocytes**
With regard to thrombocyte count, digital imaging has been shown to correlate well with both manual and cell counter results. The analysis of platelet morphology (e.g. granularity) using digital imaging is, however, still a work in progress. This development might prove clinically relevant. For example, we know that essential thrombocytosis (ET, MPN) patients can display morphological aberrant thrombocytes in the absence of an absolute elevated thrombocyte count (currently the cut-off point for the diagnosis ET is >450 x 10⁹/L as one of the major criteria).

**Red blood cell morphology**
Recent advances have also been made in the field of red blood cell morphology using digital imaging. The advanced RBC module generates between 2,000 and 4,000 individual images of red blood cells. The systems subsequently classify the cells on the basis of various morphological algorithms, comparable to the method for five-part leukocyte classification.

The first steps toward standardization of the morphological analysis of the RBC lineage by use of digital imaging have recently been made. Recent studies using a morphological red blood cell module show lower within-run, between-run, and between-observer coefficients of variation when counting schistocytes compared to the coefficients observed for manual assessment. Both the study of Hervent et al and Egele et al show that digital imaging overestimates the percentage of schistocytes in the pre-classification, resulting in a high sensitivity. The subsequent low specificity, however, underlines the need for post-classification/manual supervision.

Overestimation is also seen in the pre-classification of teardrop cells, for instance seen in myeloproliferative diseases (i.e. myelofibrosis). Detection of inclusions has also been shown to be possible with digital imaging. A study by Racsa et al demonstrates that digital imaging has the potential to detect intracellular parasites in routine screening of blood smears for RBC morphology. Howell-Jolly bodies can also be detected by the systems, and Revol et al recently even used digital imaging machines to quantify Howell-Jolly body-like inclusions in neutrophils as a possible predictor in ganciclovir toxicity. Moreover, digital microscopy of red blood cells has been successfully used as a screening tool for the diagnosis of hereditary hemolytic anemia.

These latter, specific applications of digital imaging, however, are currently not FDA-approved, and the underlying detection and decision algorithms need further improvement before these modules can be implemented safely in routine diagnostics.

**Integration in daily practice**
The introduction of digital microscopes implemented in total lab automation tracks (i.e., coupled with cell-counter and slide-maker stainers) paves the way for the implementation of clinical decision modules by coupling cell counter results with digital imaging results. This will undoubtedly lead to a higher sensitivity and specificity in the detection and classification of hematological diseases. Several requirements will have to be met, however, before we reach this state of development. One of these requirements is continuous 24/7 proper sample preparation.

Good quality slide/sample preparation plays a pivotal role in good detection and subsequent classification of both leukocytes and red blood cells using digital imaging. For instance, the digital imaging systems have difficulty separating neutrophilic granulocytes from basophilic granulocytes when the staining is of insufficient quality and gets too dark. Manual prepared slides are of insufficient quality to allow for a good and reproducible classification. Semi-automated and fully-automated slide preparation and staining systems (either May Grünwald Giemsa or Wright staining) are the preferred methods of choice.

To summarize, digital imaging seems to work for several cell classes in classifying both leukocytes and red blood cells in peripheral blood smears. The automated analysis of body fluids has also been investigated. Results from both cerebrospinal fluids and other body fluids (including abdominal fluids/asbestos and CAPD) show good and clinically acceptable accuracy when comparing automated morphological analysis using digital imaging with the manual method. Even the pre-classification is good for most body fluid categories. A big drawback for the automated digital analysis of body fluids, however, is the lack of recognition of certain defined categories. For instance, the system is currently incapable of detecting and classifying mesothelial cells, and possible tumor cells present are frequently found in the category “other” (subcategory present in body fluid module). Another disadvantage is the analysis time; automated digital analysis of body fluids still requires significant manual correction and therefore takes longer than a full classification done manually. Improvement of the current digital body fluid applications is needed before this module can be fully integrated in the routine body fluid diagnostic process.

Digital images were already being used for scholarly purposes long before the introduction of digital microscopy systems. With the introduction of such systems, the application of digital imaging in educational settings has grown tremendously. Cell atlases and even mobile apps have been generated to teach students the various normal and pathological cell classes that can be found in both PBS and body fluids. Pictures of classified or pre-classified cells can be sent to colleagues all over the world for a second opinion or to share rarely seen diseases. One can even imagine that imaging modules that are capable of pre-classification could send their pre-classification results to a central location for post-classification. This would be very helpful for hospital locations with low-volume PBS amounts which struggle to maintain morphological expertise.

**Quality survey issues in digital imaging**
Whether it is manual microscopy or digital imaging, good-quality slide preparation and staining is and will remain essential. Digital images already raised the possibility for quality surveys a long time before digital imaging systems capable of pre-classifying cells classes were generated, implemented, and commercialized. Also, commercial use of such quality surveys has become apparent. The quality module usually makes use of a digitalized slide that can be uploaded via the internet. Technicians can subsequently classify the leukocytes, RBCs, and thrombocytes. Next the results are compared to a gold standard, which is usually the clinical chemist or pathologist. Scores can then be used to identify potential training possibilities for individual laboratorians. The hemato-morphology field would greatly benefit from an independent, quality-controlled digital slide institution to fully implement digital quality surveys as a standard routine
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pathology. Digital imaging systems will undoubtedly do the bust and reliable diagnostic tools in detecting hematological g/dl in a 35-year old female with a thrombocyte count of 25 cut-off values could be used to warn laboratory personnel in fragmentocytes by digital imaging. Current pre-classification red blood cells, a slide would be generated. This could then be automatically analyzed for the presence of schistocytes/fragmentocytes by digital imaging. Current pre-classification cut-off values could be used to warn laboratory personnel in case of exceedance. So, for instance, a hemoglobin value of 9 g/dl in a 35-year old female with a thrombocyte count of 25 x 10^11/L in combination with a pre-classification result of 10 percent schistocytes should be presented by the system as a high-priority differential.

This is only one example of the many possibilities these systems could provide. The detection of most hematological malignancies, whether MDS/AML or MPN, would benefit from structural integration of cell counter results with digital imaging. Diagnostic machines such as hematological cell counters and digital microscopes should be used as pathology filters to filter out diseases and discriminate patients from non-patients. Subsequent additional diagnostics, such as flow cytometry, molecular, and cytogenetic testing (on peripheral blood or bone-marrow samples) can then be used to finalize the diagnosis. Interestingly some companies are already trying to perform automated digital analysis of bone marrow samples using digital imaging.27

Routine cell counters have proved themselves to be robust and reliable diagnostic tools in detecting hematological pathology. Digital imaging systems will undoubtedly do the same in the upcoming years. 4

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The DNA ligase: the tie that binds

First let’s review what DNA ligase is and what reaction it catalyzes. Recall that DNA is double-stranded, with each strand having an intrinsic polarity defined by the 3’ and 5’ ends of the sugar segments which alternate with phosphate groups to make up the backbone of each strand. The paired strands are “anti-parallel,” meaning their polarities face opposite directions; if viewed from the side, one strand of the helix would have its 3’ end to the right, and the other strand would have its 3’ end to the left.

A nick in a strand is any place where there’s a missing covalent bond between a sugar and the next adjacent phosphate. Nicks can arise from DNA damage, during normal DNA replication, or from the action of nuclease enzymes. Since a nick breaks the continuity of the backbone of one strand, it must be repaired by re-forming the missing covalent bond in order to make the DNA molecule intact again. This job of sealing nicks (specifically, nicks that occur between a sugar 3’-OH group and the adjacent phosphate attached to the preceding sugar’s 5’-OH group) is the function of DNA ligase. Using a molecular energy source (which differs depending on the enzyme source organism), DNA ligase reforms the missing covalent bond and the strand is whole again. Two aspects of this are critical:

- The nick to be repaired occurs on a single strand but in the context of a double-stranded molecule.
- The bases of the nicked strand, and particularly those directly flanking the nick site, must be properly base-paired to the opposite (un-nicked) strand.

It’s not hard to imagine why this is: the base pairing is required to hold the two parts (sugar 3’-OH and the next phosphate) in place for the ligase enzyme active site to catalyze joining them. If either one of these isn’t base-paired down and is flopping about with thermal motion, the reaction geometry doesn’t occur, and no new bond can be made.

Now imagine that the nick in question isn’t one which arose naturally, but instead exists between two synthetic single-stranded DNA pieces which are complementary to a single-stranded target region. If we have an assay where those two fragments must be joined into a single longer fragment to create a signal, then we can use a preliminary ligase-mediated step to test for the existence of their complement. That is, if we want to know whether strand “A” with a defined sequence exists in our sample, we can mix in the two short, adjacent, theoretically complement strands “B” and “C” with their “nick” being next to the base of interest. They will hybridize next to each other and form a substrate for DNA ligase activity only when a perfect match occurs, and are particularly sensitive to disruption from any mismatch near the nick—like a single nucleotide polymorphism (SNP). If and only if a perfect match occurs, B and C get ligated into a single longer molecule “B+C.”

In the nick of time: detecting ligation

How do we detect that B+C was formed? One way is to imagine that, if together, B+C form one primer of a traditional PCR primer set (call the other “D,” with it being of similar length and annealing temperature to B+C). If we now run a PCR with a primer annealing temperature designed for the full-length B+C/D product, we’ll only get a product if B+C was formed and thereby created the B+C composite primer. (Primers B and C on their own will have much lower annealing temperatures than B+C, so if they have not ligated, they’re relegated to being inactive bystanders in the PCR). By adding on this pre-PCR ligation test step, we’re able to test very specifically for any nucleotide changes in the template at the B+C ligation region.

Why not just skip the ligation fuss, and use a premade B+C primer sequence? In theory it should show less hybridization affinity to a sequence with any mismatch than to a perfect complement target. In reality, however, if it’s a single nucleotide in the middle of a primer, mismatches don’t always destabilize priming enough to disrupt a small number of amplicons being formed. Of course, once formed, by nature of the PCR process, these serve as perfect templates for the subsequent round, and your hopefully SNP-specific longer B+C primer probably doesn’t end up in reality as SNP-specific as you’d hoped.

Why doesn’t the ligase in the reaction tube go about randomly ligating products every cycle and just make a huge mess? There’s a good answer for that, too. We use a non-thermostable ligase enzyme, such that it’s permanently denatured and its function is destroyed by the first high-temperature opening denaturation of the classical PCR phase of the test. Conveniently, most ligases are not thermostable, and most ligation reactions have optimal reaction temperatures well below any of the thermal steps in a PCR, so no fancy enzyme engineering is required for this.
There are other ways to detect that B+C was formed. We can just run the ligation portion of the above, then denature the material and use a method such as capillary electrophoresis or mass spectrometry to look for the B+C product, particularly if either B or C, or both, carry appropriate mass or fluorophore tags. Regardless of the method used to detect that B+C was formed, these types of assays are probably the most common example of ligation-mediated PCR the average laboratorian will encounter and are known more specifically as oligonucleotide ligation assays.

Amplified fragment length polymorphism

A completely different type of ligation-mediated PCR is one which readers may have encountered if they had a need to do microorganism genetic typing or “fingerprinting,” such as for tracking epidemiology. An approach called amplified fragment length polymorphism (AFLP) can be used here. In this assay type, purified test organism DNA is collected from a culture and it’s subjected to digestion with a restriction enzyme (or sometimes more than one, but for sake of argument we’ll only consider one). Restriction enzymes are ones which recognize specific, usually 4, 6, or 8 base palindromic sequences in DNA, and create a pair of nicks at the site—one in each strand. This creates a full double-stranded break, usually offset by a few bases between strands to create a staggered or “sticky” end. This restriction digest is run for a significant excess of time, to ensure that practically all cut sites are indeed cut. The result is that the originally intact organism DNA sample is now cut into a huge number of smaller pieces. Different strains of an organism will have at least some sequence differences such as insertions or deletions (which will change the size of some of the end product fragments) or may have nucleotide substitutions which create or destroy restriction enzyme recognition sites relative to the reference strain. Thus, the pool of fragments created from the complete restriction digestion of the genome of two strain variants will have a finite number of differences.

How can these be detected? If we just run the full digest out on an agarose gel, it will look like a big smear in either case and the few differences will be hidden under the literally millions of fragments of different sizes present (and in most cases, identical between the strains). To get around this, we take our restriction digest product—with known sticky ends—and we add in large quantities of a short double-stranded oligonucleotide adapter molecule with a matching sticky end. When we now add DNA ligase, these adapters can anneal to and then ligate to put known, defined sequence “caps” on all of the fragment types present.

Now what can we do is use this as a template to PCR from, using PCR primers which match the end caps, since we now know these flank all of the target genome fragments. Just doing that would be kind of pointless, though, as it would just replicate all of what’s already a far too jumbled mess. We want to find a way to select out and amplify just a very few representative fragments. To do this, we add a few nucleotides on the 3’ end (inside) of the cap-matching section of the primer. This PCR primer will then only productively anneal to those genomic fragments which have ligated on caps, and whose few terminal nucleotides just happen to be the complement of the primer 3’ addition. Each addition of one 3’ direction nucleotide to the defined cap sequence primer pair causes a roughly 16-fold decrease in the number of molecules it can match (there are four choices per nucleotide, so a ¼ chance it fits; since it happens at both ends, 1/16). A three-nucleotide addition means only roughly one out of 4,096 fragments is now amplified by PCR—a small enough fraction that the PCR now generates a visually distinctive banding pattern or “fingerprint” when analyzed by gel electrophoresis. Changes to the size of any of these selected fragments constitutes a differentiable genetic marker allowing for samples (strains) to be distinguished—all without having to know anything about the actual DNA sequence of the organisms to be separated, and requiring only the most basic molecular lab equipment.

The two above examples certainly aren’t it for the forms in which ligation-mediated PCR can be found; they are, however, probably the two most common forms the reader is likely to encounter, and provide a useful framework from which to understand most of the other variations on linking PCR to the outcome of a ligation reaction.
Quantifying the value of LIS, analytics, and data sharing in today’s value-based healthcare environment

By Linda Newman, MT(ASCP)

Historically healthcare systems have used financial methods to compare spending requests that were in competition for the same dollars. Most of these techniques did not contain a component of quality or improved patient care. Data was not available to associate dollars with these components in order to represent a true picture of the proposal. Most, if not all, spending requests came from individual departments. The result was often that funding was granted, say, to a parking garage project because the cash return was easy to demonstrate, but not to, say, the automation of the chemistry lab, because return on investment was less clear-cut in the eyes of decision makers.

Since 2011 the government and payers have pushed to reduce cost throughout the healthcare delivery system, while at the same time improving the quality of care and patient outcomes. In the current environment, to effectively manage patient outcomes, the provider, patient, and many hospital departments must coordinate the patient care.

Along with the government push for cheaper, better patient care has come the push to establish systems of computerized health records. Information that had primarily been on paper has begun moving to electronic form.

As overall healthcare evolves, the laboratory must also evolve to maintain its value in the healthcare organization. Laboratories can keep a seat at the decision maker’s table by rigorously analyzing laboratory data to detect clinical patterns that can be used to accelerate diagnosis or close care gaps.

The first step in justifying a new laboratory project or system should be evaluating its usefulness and alignment with other organizational priorities. Many different tools exist that can be used for this purpose. Two of these tools, the Purpose-based Alignment Model and the Business Model Canvas, can be used to identify projects, processes, and systems that support the organization’s business objectives and contribute to the laboratory value within the organization.

Innovative tools to identify projects and systems

The Purpose Alignment Model, created by business/technology expert Niel Nickolaisen, is a method for aligning business decisions, processes, and feature designs around purpose. The purpose of some decisions and designs is to differentiate the organization in the market; the purpose of most other decisions is to achieve and maintain parity with the market. Those activities that do not require operational excellence either necessitate finding a partner to achieve differentiation or do not deserve much attention.

The PAM ranks systems or projects by market differentiation and criticality for the organization (termed “mission critical”). Items falling in the top right-hand box are items that should be prioritized. Historically, lab projects and purchases would fall in the parity box, which is high on the mission critical scale, but lower on the differentiation scale.

When should the PAM be used? Purpose alignment works well when you need to do these things:

- define business and IT strategic and tactical plans
- align IT with business priorities
- evaluate, plan, and implement large system projects
- filter and design features and functionality
- manage project scope
- reduce resistance to process improvements
- reduce waste by improving focus and resource allocation.

The PAM provides a simple way to determine what activities to concentrate on, and how to deliver them. Ranking items by criticality and market differentiation removes factors that merely act as distractions to decision making and helps the team focus.

Differentiation items create a competitive advantage and link directly to the core business. In healthcare, the business value (differentiation) is often derived from improving care outcomes and reducing costs. This requires the lab to consider costs outside its responsibility and consider how lab results can reduce the cost of care or improve the quality of care. (The best differentiators will do both.) What can the laboratory do to meet goals such...
as improving quality of care? Reducing length of stay? Closing gaps in chronic disease management?

The Business Model Canvas, or BMC² (Figure 2) is a strategic management and Lean startup template for developing new or documenting existing business models. It is a visual chart with elements describing a firm’s or product’s value proposition, infrastructure, customers, and finances.

The BMC is designed to work with cross-functional teams to understand their organization’s existing business model and test out potential new business models. Once leaders of the organization have the current business model mapped out, they develop assumptions for the future. These are business assumptions on which to build. For example, here are assumptions for the laboratory:

- Decreasing reimbursement schedules will have a significant negative impact on lab test profitability.
- Test volume from chronic diseases will rise due to an aging population.

Here are assumptions for the health system:

- MACRA will incentivize healthcare providers to provide greater value to government-insured patients, driving the demand for analytics tools.
- The percent of doctors employed by the health system will remain stable or rise.

Examples of front-line innovation

The first two examples of innovation given below started as laboratory initiatives. The third was a CEO-initiated strategic direction to encourage innovation throughout the entire organization.

**Example one:** Promoting improved utilization of laboratory testing. This case study⁴ describes five years of experience with interventions to improve laboratory test utilization at an academic medical center (University of Iowa). Results included interventions to tackle overutilization of automated tests, which included limits on repetitive ordering by placing messages in the EHR system regarding when the test was last performed and a link to the last results. These interventions proved to be effective in reducing repetitive ordering. The high-frequency laboratory tests showing the biggest declines in order volume post intervention were serum albumin (36 percent) and erythrocyte sedimentation rate (17 percent). Targeted alerts reduced duplicate orders of germline genetic testing and orders of hepatitis B surface antigen within two weeks of hepatitis B vaccination.

Another category of laboratory testing that was targeted to improve laboratory utilization was low-volume but high-cost tests such as panels for genetic testing or autoantibodies. In some cases, these panels may have direct costs of thousands of dollars (sometimes paid directly to external reference laboratories by hospitals, clinics, or laboratories) yet have poor reimbursement by payers. Lab leaders developed “laboratory test formulations” that place tiered restrictions on ordering of certain tests. Restrictions for specific testing included need for pre-approval by pathology or another designated group prior to ordering or limitation of ordering of certain tests to specific specialties (e.g., esoteric coagulation tests by hematologist/oncology specialists). Introduction of restrictions for 170 high-cost send-out tests resulted in a 23 percent decline in order volume.

Two quality improvement projects within the Pathology department focused on misorders of laboratory tests with similar-looking names. Targeted interventions reduced misorders involving several “look-alike” tests: 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D; manganese, magnesium; beta-2-glycoprotein, beta-2-microglobulin.

**Example two:** Early detection of acute kidney injury (AKI).⁵,⁶ AKI is an under-recognized and under-diagnosed disease. Diagnosis delay can result in a six-
Sick Children (Sick Kids) in Toronto, Ontario, elevates 30-fold increase in in-hospital mortality, and hospitalization costs increased by $4,000 to $10,000/day/patient. This was the issue that Northwell Health Laboratories set out to address by monitoring inpatient creatinine results. Delta creatinine detects 99.8 percent of all AKI patients. That means a 50 percent rise in creatinine, according to the relative criteria, or an absolute 0.3 mg/dl increase from the prior baseline minimum value. This has better sensitivity and specificity than other clinical criteria and can be applied in routine hospital practice.

The project involved issuing an alert within the health system’s electronic records to doctors when creatinine levels surpass the benchmarks that could be indicators of AKI. When the alert was first implemented in 2014, the actual identification of AKI within Northwell was around five percent of hospital inpatients. By 2016, after the early warning system alert was implemented, the number of patients identified with AKI had risen to 13 percent.

This early-warning system for AKI helped physicians intervene earlier, improving outcomes and reducing length of stay. Using literature estimates of a two-day drop in length of stay per case for patients treated quickly for AKI, the imputed annual savings at the pilot site, Forest Hills Hospital, alone were $875,000 based on 2,190 avoided hospital days.

In addition to better outcomes and reduced length of stay, the secondary inpatient diagnosis of acute kidney injury can be added to the bills the hospital sends to payers, and adds an average of $700 in hospital revenue per patient. The new lab-driven system increased monthly secondary diagnoses of AKI from an average of 615 in 2014 to 930 in 2015. That adds up to an estimated $220,500 monthly jump in revenue for Northwell Health, a nearly $2.65 million annual increase.

Several data challenges were encountered during this project, which highlights the importance of interoperability throughout the system:

- lack of access to administrative data which can be readily linked to laboratory data
- difficulty in calculating total cost of care and therefore the effect of laboratory intervention
- laboratory data not being linked to other data sets such as pharmacy and claims data
- lack of EMPI preventing linking of inpatient laboratory data to outpatient laboratory data and longitudinal follow-up of patients.

Example three: Overcoming bureaucracy and breaking down silos via strategic innovation. These objectives are perhaps especially critical in healthcare. To address these challenges, leaders at the Hospital for Sick Children (Sick Kids) in Toronto, Ontario, elevated innovation to a strategic direction and engaged a business consulting company to help devise a full system needed to spur innovation. The resulting system has three major components:

1. An innovation blueprint that detailed the types of innovations the organization wants to encourage. SickKids prioritized encouraging doctors, nurses, and clinicians to look for unmet needs they could address, rather than wait for solutions from IT or top management. That required creating a focus group with 25 front-line healthcare workers to discover and catalog key “jobs to be done” (such as reducing the length of hospital visits), surveying all 5,000 employees, and training most of them on how to integrate the innovation system into their daily practices.

2. An innovation pipeline that brought ideas from concept to reality. This involved establishing a new 18-member Central Innovation Group of leaders from different areas of the hospital, a team that was tasked with prioritizing and advancing ideas and projects through various stages. The team helped innovators test prototypes, make adjustments, and then scale to a wider population.

3. An innovation culture that features the right people, in the right roles, speaking a common language of innovation. A key enabler of this culture was the establishment of a $250,000 Innovation Fund to provide seed money for promising ideas. Now, instead of being stalled by permission hurdles that suppress initiative, promising new ideas can be funded, fast-tracked, and prototyped.

Following are two of many innovations that grew out of this strategy:

- A pain reporting application, Pain Squad, encourages pediatric cancer patients to record pain levels. Whereas pain reporting with paper diaries yielded compliance rates below 50 percent and Web-based diaries yielded 70 percent, Pain Squad has boosted rates to more than 90 percent.
- A simple one-screen billing app for the iPad has improved billing procedures. Canada has a single-payer system, but hospitals still must track all procedures so that the hospital and its doctors are properly paid. At SickKids, only 30 percent of procedures were being filed accurately and on time. With a $10,000 grant from the Innovation Fund, the app went from idea to pilot in three months. It is now used throughout several departments in the hospital. In urology, for example, billing compliance rates went from below 50 percent to higher than 99 percent.

### Evaluating functionality

After identifying potential projects using the PAM and BMC tools, lab leaders will have a better understanding of the functionality required for the project. It is a given that Lab IT systems should provide management data that can boost lab productivity, workflow, and accuracy. In more recent years, additional expectations such as analytics for turnaround time, physician utilization, staffing workload, auto-validation percentages, and other quality measures have been added to the list of expectations. The Association for Pathology Informatics has created an LIS Functionality Assessment Toolkit that contains a comprehensive list of available LIS features. Appendix III of the toolkit is a list of the elements that should be included in the total cost of ownership. The toolkit is continued on page 40
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available to the public and can be accessed at https://www.pathologyinformatics.org/lis_toolkit.php.

In addition to traditional IT functionality, data analytics and interoperability will be required for the laboratory to make a greater positive impact on patient care and cost savings. To effectively measure total quality of care and the total cost to provide that care, data silos must be combined into one master data base or, alternatively, communicate with one another to exchange data (interoperability) that can track all aspects of the patients care and the associated cost.

Molecular and genetic advances are emerging that require advanced algorithms, interpretations, and big data technology that older technology cannot handle. Because these tests produce large quantities of data, new technologies will require a “Big Data” component that allows for mining and evaluation of large quantities of unstructured data. Even if an institution doesn’t perform these assays now, that doesn’t rule out that it might perform them in the future.

Financial measurements
Once lab leaders have developed the concept and evaluated the functionality required, they can use traditional financial tools to prioritize the projects. The most common financial methods used for analyzing the purchase of equipment and services are: 1) payback (or break even) analysis; 2) return on investment (ROI); and 3) net present value (NPV).

Payback analysis refers to the period of time required to recoup the funds expended in an investment, or to reach the break-even point. Payback period is usually expressed in years. In the example given in Table 1, the payback year would be Year 3.

Net cash flow doesn’t have to be just revenue. It could be savings, for example:

• labor savings if implementing a system that performs auto-verification.
• cost-of-testing savings if the system can monitor and reduce inappropriate test utilization.
• cost-of-patient-care savings if the system can perform algorithms that detect care gaps that, when identified, lead to more efficient and effective patient care.

ROI is a simple calculation that is used by organizations to compare capital expenses or projects that are competing for the same investment dollars. The simplest ROI calculation would be the manufacture of a laboratory instrument. If the instrument sold for $100,000 and cost $90,000 to manufacture, the ROI would be 11 percent: return on investment = (revenue − cost of goods sold) / cost of goods sold; ($100,000 - $90,000) / $90,000 = .11 or 11 percent.

Unfortunately, ROI in healthcare organizations are not as straightforward as revenue and cost. Gain from the investment is normally substituted for revenue, or it could be a combination of both. Gain from the investment could be revenue, labor savings, reduced length of stay, or fewer Emergency Department visits. Whatever the gain, it must be converted to a dollar value: return on investment = (gain from investment − cost of investment) / cost of investment.

The Total Cost of Ownership (TCO), not just purchase price, should always be used for the above calculations. TCO will include the licensing fees for the system, the installation fees, training fees, yearly maintenance fees, and the cost of hardware and software upgrades. Lab leaders should not forget the costs to migrate data from existing systems, or ongoing maintenance of existing systems for data access. Some institutions also include the labor costs of their employees for training and implementations. These resources should be understood, even if not included in the TCO calculation.

NPV is a financial assessment tool that considers that the value of a dollar today and the value of a dollar in the future are not equal. If a project has income over a long period of time, for example 30 years, the future dollars are discounted at a notional rate determined by the project stakeholders. This calculation is used for capital projects such as buildings that have paybacks of many years. It can also be used to compare contractor bids with long payment schedules.

Internal Rate of Return (IRR) is the rate at which the project breaks even. It’s commonly used by financial analysts in conjunction with
NPV. That’s because the two methods are similar but use different variables. NPV assumes a particular discount rate for a company, then calculates the present value of the investment. IRR calculates the actual return provided by the project’s cash flows, then compares that rate of return with the company’s hurdle rate (how much it mandates that investments return). If the IRR is higher, it’s a worthwhile investment.

Get started
We have discussed innovative tools that can be used to identify projects and systems that are in alignment with a healthcare organization’s business model and goals. The two laboratory examples of innovation proved that being able to recognize patterns in clinical data can be used to make more informed decisions which resulted in:
• reduced lab volume from proper test utilization; and
• improved patient outcomes and a reduced length of stay.

Functionality checklists for information technology projects are included as well as formulas for the financial analysis of projects and systems.

Don’t wait to put these techniques to work in your organization! Remember to:
• link laboratory strategy with the total health system strategies
• work with departments throughout the health system to identify opportunities
• share and analyze data to identify opportunities and build lab value.

REFERENCES
A culture of lab quality begins with data integrity

By Megan Schmidt

It is the responsibility of all healthcare providers, and developers of healthcare information technology systems, to strive for data integrity. As an industry, we make all possible efforts to ensure the accuracy and consistency of the data we produce, maintain, and present. This data, from the point of order through result delivery, can affect patient care. Given the critical role of data integrity in healthcare decision-making, it must be an important consideration during the design, implementation, and usage of any system that stores, processes, retrieves, or presents health data.

A laboratory information system (LIS) is a central part of the healthcare information continuum. A detailed study by the Lewin Group for the U.S. Centers for Disease Control and Prevention (CDC) concluded that "laboratory medicine is an essential element of the healthcare system. It is integral to many clinical decisions, providing physicians, nurses, and other healthcare providers with often pivotal information for the prevention, diagnosis, treatment and management of disease."

With an LIS, the strength of the underlying database is a fundamental element of data integrity. For example, use of foreign key integrity constraints will prevent orphaned data from entering into the database tables. You can define integrity constraints to enforce vital business rules that are associated with the information in a database. The developers of the LIS can leverage database functionality to design the system in a manner that will protect the user from data entry mistakes at its very core. For instance, the database can be designed to disallow spaces at the beginning and ending of a patient ID, thus protecting the data from accepting invalid data entered by the user.

Backing it up

Another important feature of the database is the ability to restore data to a specific point in time. Many databases, for example, will write logs throughout the day, as laboratory data is entered. These incremental log files contain a complete history of database transactions. In a disaster recovery situation, it is possible to recover the data to the moment of failure with no loss of data by using a recent physical backup and rolling it forward in time by applying these logs.

Furthermore, it is critically important to perform regular backups to another device or system such as an external hard drive or to cloud storage. Backup utilities should be run at least daily to ensure a successful recovery, should a disaster occur. The IT staff could configure an external operating system partition to facilitate recovery of the system, if needed. These external backups should be stored in a secure location, and provisions should be made to rotate a copy of the data off-site on a regular basis to cover the possibility of a major catastrophe at the main site.

Interface issues

Data integrity also includes protections that prevent unintentional changes to information when interfacing data from one system to another. One way to do this in healthcare technology is to reduce unintentional manual transcription errors through use of electronic demographic and orders interfacing. Since Meaningful Use, it is most common for a lab order to be triggered from an electronic medical records (EMR) system. Interfaces with EMRs, practice management systems, and reference lab systems enable up-to-date and accurate insertion and updating of demographic and result information into the LIS as accurately as it was entered in the originating system. When the order is received at the LIS, a label is printed with demographic information from the EMR. The use of barcode printed labels reduces errors during the specimen tracking process from analyzer to storage.

Furthermore, data integrity must be insured between the LIS and medical devices such as interfaces. The LIS must be flexible enough to support instrument interfacing in a large variety of formats such as Excel, ASCII, CSV, ASTM, and HL7. It also must support the many transfer protocols such as TCP/IP, USB, file folder, and serial ports. Data imported from the instrument to the LIS must be evaluated for quality before posting to patient-facing systems through business logic and checksums, as the LIS will need to store values, graphs, corrective actions, and proof of review. The LIS must document QC failures and corrected reports so the documentation is readily available for inspections. The LIS must also assist with ensuring QC is acceptable and can disable release of results if certain criteria fail.

Laboratories conducting molecular diagnostic testing often employ a secondary review of results prior to releasing the patient results. Given the technical nature of these results, users need the ability to verify results and correct any invalid data. This may involve sequential documentation, where one laboratorian enters or accepts results and a second or a supervisor completes a final review before distributing the report. Since the specific review process will vary from lab to lab, users need the ability to customize the technical review workflow to accommodate their organization’s specific best practices.

Data mining

Laboratory data must be stored and maintained for long periods and must be easily retrievable for various purposes. Access to data over its lifecycle can be enabled through mining tools that provide insight from a population level to the patient level. For example, labs can drill down into specific diagnoses or abnormal test results to help their providers better understand how to manage chronically ill populations. These analytical capabilities make the lab a valuable partner for payers and providers that are seeking to improve care and reduce costs through value-based care efforts.

Data is protected from malicious processing through user control and security. Administrators of the laboratory need accessibility and auditing of system changes such as modifications to tests, panels, reference ranges, patient demographics, and results. The management of user access and permissions should be logical and easy to maintain. Granular security measures include strong password settings, user permission settings, and audit trails that record details of systems and are accessed at the user level.

Working with an LIS that helps protect data and data integrity has a direct impact on quality and patient safety. This reduces potential liabilities and allows labs to make informed business decisions and protection for their most valuable asset, their laboratory data.

REFERENCES

Megan Schmidt serves as Vice President of Product Management for CompuGroup Medical Lab Division.
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A closer look at the recent FDA safety communication about biotin interference

By Ramani Wonderling, PhD

On November 28, 2017, the U.S. Food and Drug Administration (FDA) issued a safety communication titled, “The FDA Warns that Biotin May Interfere with Laboratory Tests,” which stated: “The FDA is alerting the public, health care providers and laboratory personnel that biotin can interfere with certain lab tests and cause incorrect lab test results. Some supplements, particularly those labeled for hair, skin, and nail benefits, may have high doses of biotin, which may not be clear from the label. Biotin in patient samples can cause falsely high or falsely low results, depending on the test. Clinical decisions made based on incorrect laboratory test results may lead to patient harm due to inappropriate patient treatment and diagnosis.”

Biotin has always been a part of multivitamins at very low levels (at 30 microgram dose). However, in the past several years, people have been taking biotin at higher levels as over-the-counter supplements (up to 20 mg dose) and prescription dosages (up to 300 mg dose) due to the multifaceted health benefits it offers. With biotin usage increasing and now an FDA safety communication warning about the potential for incorrect lab results, it is critical for the public, healthcare providers and laboratory personnel to understand more about the issue and know the steps that they need to take.

Biotin recommended for various health conditions
Biotin, also known as vitamin B7, is part of the vitamin B complex group, which are nutrients that support the digestive, cardiovascular, and nervous systems. Biotin acts as a coenzyme in the metabolism of fatty acids, amino acids, and glucose. It has been recommended for the overall health of hair, skin, and nails as well as fetal development. Doctors are also prescribing biotin for several health conditions such as multiple sclerosis, diabetes, hyperlipidemia, dermatitis, depression, Parkinsonism, metabolic acidosis, mitochondrial disease, peripheral neuropathy, and muscle cramps in dialysis patients. In addition to supplements and prescriptions, biotin is also being administered as vitamin therapy via injections or intravenous (IV) drips by itself or as part of other vitamin cocktails.

Biotin dosage and consumption have increased. One in three people in the United States takes supplements.1 Biotin supplements, particularly at larger doses, have become increasingly popular. It is estimated that as many as 20 percent of people consume biotin-containing supplements.2 Retail sales of biotin supplements grew more than 260 percent between 2013 and 2016.3 Figure 1 shows only the retail sales volume of biotin. The total sales are probably much higher since these sales figures do not include sales from wholesale warehouses, vitamin and beauty product retail stores, or any online sales from sites where biotin is a top-selling supplement at doses as high as 5 to 10 mg per day.

Why some lab tests are vulnerable to biotin interference
Some lab test developers have designed tests that use the interaction between biotin and streptavidin to capture the analyte in the patient sample; this is usually referred to as the biotin-streptavidin format. This method employs biotinylated antibodies to capture the target analyte in the patient sample. Then, streptavidin-coated microparticles are used to bind these biotinylated components attached to the target analyte, yielding a result based upon the amount of analyte captured. If patients are taking biotin supplements, the free biotin in the blood sample might interfere with this “free capture method” and lead to incorrect lab results and misdiagnosis of patients.

Biotin interference can produce either a falsely lowered or a falsely elevated test result depending on the assay format. In the case of a sandwich assay, where the analyte is “sandwiched” between two antibodies, the results may be falsely lowered due to biotin interference. On the other hand, in the case of a competitive assay format, where the analyte “competes” with the labeled analyte for binding, the results may be falsely elevated due to biotin interference.

Impact of biotin interference on patient results
Although patients taking biotin at levels ranging from 5 mg to 600 mg per day have not experienced adverse effects,4 lab tests that use the biotin-streptavidin “free capture” technique have been documented to produce falsely low or falsely elevated results. Biotin interference has been shown to occur with various thyroid assays;5,6 parathyroid hormone (PTH) assays;7 fertility hormone assays such as testosterone, progesterone, estradiol, luteinizing hormone (LH), and follicle stimulating hormone (FSH) assays; cancer assays such as PSA; and other assays such as ferritin, folate, cortisol, and vitamin B12.8,9,10 It was in the context of growing concerns that the FDA issued its November safety communication, which was directed to consumers, healthcare providers, lab personnel and lab test developers. The FDA communication also specified that there has been an increase in the number of reported adverse events, including one death, related to biotin interference with lab tests.

Due to the multiple health benefits that biotin offers, people will continue to take these supplements. Therefore, physicians, lab personnel, and lab test developers need to evaluate practical ways to prevent the interference from biotin. One idea is to make patients wait for hours or days for the biotin to clear from the patient’s body before running lab tests. But the current data suggests that the length of time required to clear biotin from patient samples varies from a few days to a few weeks.5,6,11 The amount of biotin taken by the patient, how long the patient has been taking biotin (chronicity), and the vulnerability level of each test to biotin interference may add to this challenge. Even on the same diagnostic platform, some tests are more vulnerable to biotin interference than others. As stated in the FDA safety communication, “Currently available data is insufficient to support recommendations for safe testing using affected tests in patients taking high levels of biotin, including about the length of time for biotin clearance from the blood.”12

When waiting-to-clear is clearly contraindicated
This “wait and test” approach certainly will not work in acute care settings, as waiting for biotin to clear from the patient’s system before running critical lab tests is not a feasible option. In the case of patients admitted to the emergency department with chest pain and suspected heart attack, it is important to determine whether they need immediate transfer to the emergency department before running critical lab tests. In the case of patients admitted to the hospital with chest pain and suspected heart attack, it is important to determine whether they need immediate transfer to the emergency department before running critical lab tests.
Biotin Market includes any product that has Biotin as an ingredient.

Volume sold represents # of capsules sold in the market. It equalizes different sizes/forms to make comparisons easier.

Source: Nielsen FDM Data ending 03/26/16

Figure 1

Coronary care unit (CCU) or catheterization lab for further care, so it is critical to test troponin levels as soon as possible to help with the diagnosis. While some suspected heart attacks are diagnosed with ECG and clinical findings, in most cases, clinicians rely on a troponin result to help guide patient management. A falsely low troponin result due to biotin interference could lead to grave consequences, including delays in follow-up testing, misdiagnosis, and death.

In cases where patients are suspected of sepsis, measuring procalcitonin (PCT) levels may be extremely useful in patient care and management. But if the PCT test used is vulnerable to biotin interference, it may generate erroneous results that could cause some confusion and possible delays in appropriate treatment initiation. In the case of sepsis patients, every hour of delay in diagnosis increases their mortality by 7.6 percent.14

In pregnant women, tests that are impacted by biotin interference may produce falsely low beta hCG results, which could lead to the erroneous ruling out of early pregnancy, and the pregnant woman could inadvertently be exposed to x-rays and CT scans that may harm the developing fetus. In women who are undergoing in-vitro fertilization (IVF) procedures, determining fertility, timing of ovulation, extraction of eggs, implantation of the embryos, and confirming pregnancy are all precisely scheduled and orchestrated based on the levels of various reproductive hormones such as estradiol, FSH, LH, and beta hCG. If the hormone levels are measured using tests vulnerable to biotin interference, the timing of the various steps in the IVF procedure may not be accurate, which could result in failure of the IVF procedure, and the patient may lose the opportunity to become pregnant.

Education is part of the answer

Will education and awareness efforts about biotin interference solve the problem? Both are critical; however, such efforts cannot provide a complete solution. Patients may not know that the supplements they are taking contains biotin if it is not clearly stated on the label. Since biotin is a supplement, it may not be included in the list of medications taken by the patient. Some patients may know that they are taking biotin, but they may not know that it can interfere with lab tests. As a practical matter, it is not possible for healthcare systems, including hospitals, labs, and doctor’s offices, to know for sure which of their patients are taking biotin and how much.

It is difficult for the lab to identify which patient samples they receive might contain biotin. Patients may take over-the-counter biotin supplements as high as 20 mg per day. Physicians may also prescribe biotin as high as 300 mg per day for conditions such as multiple sclerosis. Therefore, specimens collected from patients taking such high levels of biotin may contain 100 ng/mL to 1,200 ng/mL of biotin, which is why the FDA is recommending that all lab test developers investigate every single assay that uses the biotin-streptavidin technology up to 1,200 ng/mL for biotin interference and communicate the interference they see to the clinical lab community.

Alternative laboratory test options

In this current environment, in which many people are taking biotin and use continues to increase at a steady rate, it is critical for clinical laboratories to have access to alternate testing methods that are not vulnerable to biotin interference. The good news is that not all platforms and not all lab tests are subject to this issue. Only tests that use the biotin-streptavidin “free capture” format are impacted by biotin interference. Assays that use biotin in a “preformed complex” are very unlikely to have biotin interference. There are also alternative methodologies such as magnetic separation technology that are used in some platforms. In this method, magnetic microparticles coated with antigen or antibody are used to capture the targeted analyte, and then they are separated using the magnet. No biotin and streptavidin are used in this method, so biotin in the patient sample does not interfere with the test results.

As noted earlier, the FDA safety communication stated that the data currently available is “insufficient to support recommendations for safe testing using affected tests in patients taking such high levels of biotin, which is why the FDA is recommending that all lab test developers investigate every single assay that uses the biotin-streptavidin technology up to 1,200 ng/mL for biotin interference and communicate the interference they see to the clinical lab community.

Please visit mlo-online.com for references.

Ramani Wonderling, PhD, serves as Associate Director of Scientific Relations for Abbott’s Diagnostics Division.
Single-sample micro-osmometer

The Osmo1 Single-Sample Micro-Osmometer from Advanced Instruments (AI) is ideally suited for clinical laboratories that prefer to test small sample volumes. Osmo1 utilizes the industry-preferred freezing point depression method to accurately and precisely determine osmolality measurements throughout a wide analytical range. Osmo1 features one-step draw sampling and a 90-second test time. Its integrated 2D barcode scanner reduces transcription errors and links sample ID and user ID to test results for greater traceability. With an intuitive color-coded touchscreen, the system includes built-in quality control, easy data export capabilities, and data security.

AI, www.rsleads.com/803ml-150

ESR analyzer

The iSED Sedimentation Rate (ESR) Analyzer from Alcor Scientific is a fully automated ESR analyzer that samples directly from the primary tube, requires only 100μL of sample, and generates results in 20 seconds. The iSED can run up to 180 samples per hour. It has a 20-tube capacity and requires no preliminary mixing and no additional sample tubes.


Women’s health panel

The new AMPiPROBE Women’s Health Panel is a molecular diagnostic test that allows for the detection of 13 pathogens associated with women’s health and STDs on a single collection device. The Panel is a highly sensitive and specific multiplex nucleic acid amplification test developed with Enzo’s proprietary technology. It allows for the detection of bacterial vaginosis (BV), trichomoniasis (TV), vulvovaginal candidiasis (VVC), and STIs such as chlamydia trachomatis (CT) and neisseria gonorrhoeae (NG).

Enzo, www.rsleads.com/803ml-152

3-screen ELISA

KRONUS offers a commercially available 3-Screen ELISA which allows for the simultaneous detection and measurement of autoantibodies to GAD, and/or IA-2 and/or ZnT8 in a simple, highly robust, user-friendly assay format. For research use only. Not for use in diagnostic procedures.

KRONUS, www.rsleads.com/803ml-154

Chemistry analyzer

Available thru MedTest, the BA-800M Chemistry Analyzer has a throughput of 800 photometric test results per hour with an overall throughput of 1,200 tests per hour with ISE. The Sample Delivery Module provides a sample capacity of 440 positions, providing large-volume labs hours of unmanned operational time. The reagent consumption design minimizes reagent usage, resulting in the lowest consumption cost per test. Advanced features of the BA-800M Analyzer include: continuous reagent loading, reagent bubble detection, water quality monitor, one-key STAT touch button, probe liquid level detection, and sample probe clot and collision recovery, which provides the lab with smooth operational and enhanced workflow efficiencies.


Blood gas analyzer

Nova’s Stat Profile Prime features ZERØ maintenance cartridges and MicroSensor technology for exceptional value in a critical care whole blood analyzer. This design optimizes the life of each cartridge, improves uptime, and eliminates waste, downtime, and costs of older cartridge-based systems. The 10-test menu includes pH, PCO2, PO2, Na, K, iCa, Cl, glucose, lactate, and hematocrit.

NOVA Biomedical, www.rsleads.com/803ml-157

continued on page 48
AMPIPROBE®
Women’s Health Panel
Nucleic Acid Detection of Women’s Health-Related Pathogens

A Single Swab for 13 Pathogens

At Enzo, we are committed to improving women’s health by offering comprehensive, reliable, and cost-effective solutions for clinical laboratories. Our AMPIPROBE Women’s Health Panel is a multiplex nucleic acid amplification test that can detect 13 common pathogens associated with women’s health and sexually transmitted diseases including Candida, Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis, and Bacterial Vaginosis on a single swab.

For more information: salesinfo@enzo.com  enzoclinicallabs.com/ampiprobe-whp
HPV test

The cobas HPV test provides specific genotyping information for HPV 16 and HPV 18, the highest-risk types, while simultaneously reporting the 12 other high-risk HPV types as a pooled result, all in one test and from one patient sample. The cobas HPV test is performed on the cobas 4800 System, which offers walk-away automation of nucleic acid purification, PCR (polymerase chain reaction) set-up, and real-time PCR amplification and detection to help labs achieve maximum efficiency. The system also runs Roche tests for CT/NG (chlamydia/gonorrhea), HSV 1 and 2 (herpes simplex virus), MRSA/SA (methicillin-resistant Staphylococcus aureus and Staphylococcus aureus) and C. difficile, as well as BRAF, EGFR, and KRAS mutations.

Roche, www.rsleads.com/803ml-158

Fully automated analyzer

The ARKRAY ADAMS A1c HA-8180V is a fully automated analyzer that utilizes HPLC technology to perform HbA1C testing. The analyzer eliminates interference from most common hemoglobin variants and generates accurate, precise results. The HA-8180V has low precision claims (CV ≤1%), and provides clinicians confidence in results at critical decision-making levels to diagnose and treat diabetes. The analyzer is simple to operate; continuous sampling enables users to load racks and walk away. Automatic on-board sample mixing ensures that each sample is thoroughly mixed. Results are generated in ninety seconds. Intelligent result review eliminates routine chromatogram review.

ARKRAY, www.rsleads.com/803ml-160

CE-IVD BCR-ABL kit

Chronic myeloid leukemia (CML) is characterized by the “Philadelphia chromosome,” a translocation that results in BCR-ABL gene fusion. Tyrosine kinase inhibitors have transformed CML into a manageable chronic disease, but the standard of care for monitoring response, measuring BCR-ABL mRNA, falls short of clinicians’ needs. Current methods are not sensitive enough to determine whether a patient can discontinue therapy without risking disease recurrence. There also remains significant measurement variation between and within laboratories. The QXDx BCR-ABL % IS kit is a sensitive diagnostic that enable researchers to accurately measure deep molecular responses from the blood of CML patients, so it can better help clinicians in disease management decisions.

Bio-Rad, www.rsleads.com/803ml-161

Immunoassay and clinical chemistry solution

The Atellica Solution is a highly flexible immunoassay and clinical chemistry solution featuring patented bi-directional magnetic sample transport technology that is 10 times faster than conventional conveyors. The transport technology, together with a multi-camera vision system, intelligent sample routing, and automatic QC and calibration capabilities, gives laboratories independent control over every sample to speed patient results to clinicians. Atellica Solution can handle more than 30 sample container types including pediatric and tube top sample cups that can be aspirated from the primary tube. Using the same reagents and consumables across different analyzer configurations, labs can streamline inventory control and deliver consistent patient results. Product availability varies by country.

Siemens, www.rsleads.com/803ml-162
K-ASSAY®. High-Quality, Low-Cost Reagents

Immunoassay Reagents for chemistry analyzers™

Over 35 different assays available

- Lipid Assessment
  - Apo AI
  - Apo AI
  - Apo B
  - Apo CII
  - Apo CIII
  - Apo E
  - Lp(a)
  - Remnant Lipoprotein Cholesterol
- Serum Proteins
  - α-1 Acid Glycoprotein
  - α-1 Anti-Trypsin
  - α-1 Microglobulin
  - Haptoglobin
  - IgA
  - IgG
  - IgM
- Nutrition
  - Ferritin
  - Prealbumin
  - Transferrin
- Allergy
  - Total IgE
- Stomach
  - H. pylori
- Diabetes
  - Cystatin C
  - Fructosamine
  - Hemoglobin A1c
  - Insulin
  - Microalbumin
- Coagulation
  - D-Dimer
  - Fibrinogen
  - Factor XIII
  - Plasma FDP
  - Serum/Urine FDP
- Inflammation/Cardiac
  - Anti-Streptolysin O
  - Complement C3
  - Complement C4
  - CRP
  - RF
- Lung
  - KL-6

New Products Now Available!!

- *H. pylori* Test Reagent* for chemistry analyzers
- Remnant Lipoprotein Cholesterol* reagent for chemistry analyzers
- KL-6 (Krebs von den Lungen-6)* reagent for chemistry analyzers

KAMIYA BIOMEDICAL COMPANY
diagnostics@k-assay.com | 800-KAMIYA-5
www.k-assay.com/MLO.php
### iSED® ESR Analyzer from ALCOR Scientific

ALCOR Scientific is proud to offer the only USA made fully-automated ESR analyzer. The iSED uses 100μl of blood, sampled directly from the primary EDTA tube and produces results in 20 seconds after automatic mixing.

**ALCOR Scientific**
www.rsleads.com/803ml-400

### Experience the power of the Atellica Solution

Atellica® Solution: *Flexible, scalable, automation-ready immunoassay and chemistry analyzers engineered to deliver control and simplicity so you can drive better outcomes. Now available!*  

*Product availability will vary by country.

**Siemens Healthineers**
www.rsleads.com/803ml-407

### Optilite® – The Future of Special Protein Testing

Optilite is the perfect solution for your modern protein laboratory. It’s fully optimized, creating simplicity from complex analytical processes. The analyzer and assays work together, giving you the freedom to allocate your time more effectively.

**Binding Site**
www.rsleads.com/803ml-401

### A Single Swab for 13 Pathogens

The AMPIPROBE® Women’s Health Panel is a PCR test that allows for the detection of **Bacterial Vaginosis**, **Trichomoniasis**, **Vulvovaginal Candidiasis** and STIs such as **Chlamydia trachomatis** and **Neisseria gonorrhoeae** with a single swab.

**Enzo Life Sciences**
www.rsleads.com/803ml-409

### Remnant Lipoprotein Cholesterol Assay

KAMIYA BIOMEDICAL is introducing a new automated colorimetric assay for the quantitative measurement of remnant lipoprotein cholesterol (RLP-C) in serum samples on chemistry analyzers. Research studies have reported that RLP-C may be an important risk factor for coronary artery disease, myocardial infarction, and arteriosclerosis. The assay uses a specific enzymic method to directly detect RLP-C. Applications are available for most chemistry analyzers. For research use only in the U.S.

**KAMIYA Biomedical**
www.rsleads.com/803ml-404

### Affordable Safe Solutions to Decap / Recap

Repetitive manual Decapping and/or Recapping of tubes exposes your staff to potential repetitive stress injuries. We offer a variety of models to fit any volume needs. Our Pluggo Decappers and KapSafe Recappers will eliminate potential injuries.

**LGP Consulting**
www.rsleads.com/803ml-410

### Randox Adiponectin

Clinical diagnostic biomarker for metabolic risk assessment. Applications available for a wide range of biochemistry analyzers.

*Randox Adiponectin is for research use only and not for use in diagnostic procedures in USA.

**Randox Laboratories**
www.rsleads.com/803ml-406

### New HemosIL® HIT-Ab(PF4-H) Assay from IL

Provides detection of Heparin-Induced Thrombocytopenia (HIT) antibodies, optimizing therapeutic decisions and patient care. Simple to use, fast results. Fully automated, liquid, ready-to-use with results in minutes. It’s available on-demand, 24/7.

**Instrumentation Laboratory**
www.rsleads.com/803ml-413
CGM LABDAQ from CompuGroup Medical

CGM LABDAQ®, from CompuGroup Medical (CGM), is a laboratory information system that empowers labs of all sizes to optimize revenue and improve customer satisfaction.

CompuGroup Medical
www.rsleads.com/803ml-414

Stat Profile Prime® Critical Care Blood Gas Analyzer

Nova’s Stat Profile Prime® features ZERØ™ maintenance cartridges and MicroSensor technology for exceptional value in a critical care whole blood analyzer. This design optimizes the life of each cartridge; improves uptime; and eliminates waste, downtime, and higher costs of older cartridge-based systems. The 10-test menu includes pH, PCO2, PO2, Na, K, iCa, Cl, Glucose, and Lactate.

Nova Biomedical
www.rsleads.com/803ml-416

D-100™ System for Hemoglobin A1c testing

The D-100™ System is the future of HbA1c testing. With innovative solutions to maximize workflow efficiency, the D-100 System allows high volume laboratories to quickly and easily report HbA1c results while also detecting hemoglobin variants.

Bio-Rad Laboratories
www.rsleads.com/803ml-402

Molecular Control for Sexually Transmitted Infections

Bio-Rad’s liquid, ready-to-use Amplichek STI is a multi-analyte, unassayed molecular quality control designed to monitor the performance of nucleic acid testing for detection of commonly tested pathogens responsible for sexually transmitted infections.

Bio-Rad Laboratories
www.rsleads.com/803ml-411

Quantimetrix New Urinalysis Controls

Dipper®POCT Liquid UA Control is a single-use, 2-level control with exceptional stability. Also introducing CHROMASCOPICS Liquid UA Control with Microscopics, designed for the Clinitek Novus, & Atellica UAS 800.

Quantimetrix
www.rsleads.com/803ml-405

CAPILLARYS 3 – Next Generation of CAPILLARYS

CAPILLARYS 3 TERA* provides high-resolution separation of proteins, hemoglobins, and HbA1c in high-volume laboratories. With 12 capillaries, CAPILLARYS 3 TERA offers our proven technology with increased efficiency and flexibility for your lab.

*Sed pending FDA clearance.

Sebia, Inc.
www.rsleads.com/803ml-419

ELLKAY is Making Interoperability Happen

As a nationwide leader in healthcare connectivity, ELLKAY builds the data pipeline for laboratories, hospitals, health systems, EMR/PM systems, payers, HIEs, ACOs and other healthcare organizations. Specializing in extracting and converting clinical data from virtually any source EMR system, we are the healthcare industry’s “Data Plumbers.”

Ellkay
www.rsleads.com/803ml-415

ELLKAY Healthcare Data Plumbers
What originally motivated you to solve the problem of repetitive stress injuries? I worked as a clinical laboratory scientist for five years while I was pursuing graduate studies in biomedical engineering. My tenure as an MT helped me recognize the burden of the repetitive stress tasks that technicians and technologists face daily in the laboratory. It also helped me realize that there is a huge need for benchtop pre- and post-analytical automated equipment that is efficient, simple, and smart. Meeting those criteria is always Laboratory Growth & Productivity Consulting’s aim when we design products.

If you were explaining Laboratory Growth & Productivity (LGP) to someone who is not familiar with the organization, how would you characterize its primary areas of expertise? LGP is an innovative company that excels in providing automation solutions that are simple, savvy, and affordable, driven to eliminate exposure to repetitive stress motion in order to avoid potential injury. Our efforts in this direction are realized in our Pluggo Decappers, KapSafe Recappers, and soon-to-be-released benchtop Archiver. LGP also provides consulting services to assess laboratory workflow and assist labs in doing more work at higher quality and with greater efficiency.

What major categories of solutions does the company provide for the clinical lab? LGP has brought to the market our Pluggo Decappers in four models, from decapping a single tube on the Pluggo Solo, to decapping up to 2,400 tubes per hour on our Pluggo RH (rack handler) model. In 2012, LGP was listed by the CDC in one of its Morbidity and Mortality Weekly Reports as one of several manufacturers that market safety devices to help remove caps from tubes. Since recapping is as much a cause of repetitive stress motion as decapping, we also provide our KapSafe Recapper systems, which we also offer in four models. Our latest innovation will be the benchtop Archiver. It will accept analyzer (personality) racks and archive the tubes into 5 x 10 trays for storage.

Tell us about how LGP started. Did it begin with the consulting side or the manufacturing/distribution side? In 2000, LGP started solely as a consulting firm. Back in 1993, when Beckman Coulter was the first company outside of Japan to distribute and support Total Lab Automation, I was fortunate to be the Coulter engineer selected to live and learn in Japan in order to transfer lab automation knowledge and know-how to all countries in which Coulter sold lab automation. Fast forward to the year 2000, when a good friend in the industry suggested that I start a consulting firm to assist labs in understanding and selecting the appropriate lab automation systems. Laboratory Growth & Productivity was created in January 2000.

What has been the most rewarding aspect of your LGP endeavor? What is your greatest challenge? As hard as the road is from idea to a working product, it is still most rewarding to see our products succeed in the real world of the laboratory. Also, it’s great to hear how our customers simply “fall in love” with our products. As for challenges, we are constantly challenged to come up with innovative ideas to keep the systems benchtop and pneumatics-free, yet as fast, if not faster, than large automation systems in pre- and post-analytical processing.

What is some of the most useful feedback that you’ve received from customers? Here is some feedback we received from a customer in December: “We received the decapper at the beginning of the week and we are very happy with the results. The decapper was quick and easy to set up, decaps just as described, and is very clean when removing the caps. And most important, the fatigue we feel on our hands every day has been completely eliminated for this task.” That kind of positive feedback is useful because it reminds us here at LGP of why we do what we do. It also helps keep our eye on our goal of continuing to design products that are effective as well as easy to use.

How have the company’s solutions evolved throughout the years? We have the engineering itch, and this naturally leads to advancements in technology. In 2003, LGP started its own distribution/ manufacturing endeavor. We began to distribute the Pluggo Standard Decapper, decapping from a 24-position Pluggo carousel, a Swedish product. Very quickly we realized that some modifications were needed. CLINICON AB, the Swedish manufacturer, awarded LGP the right to develop and implement the necessary changes to handle the higher volumes in the U.S. market.

In 2006, LGP started development on the Pluggo RH Decapper, which decaps multiple analyzer (personality) racks. The Pluggo RH Decapper was launched in mid-2007. In 2009, we realized the need for the Pluggo RHs (rack handler single) Decapper to handle a single analyzer (personality) rack at a time, for some hospital markets that desire the convenience of decapping straight from an analyzer rack without the need for a multi-rack handler. The Pluggo RH is now pretty flexible, and we effectively use it to decap “long” racks like those manufactured by Hamilton, ImmucorNEO, Tecan, and others.

In 2013, LGP released our KapSafe Recapper instruments, for the automated benchtop recapping of sample tubes. KapSafe is a 2 foot x 2 foot benchtop instrument that does not utilize pneumatics, is very quiet, and is a workhorse, recapping for up to 1,200 tubes per hour.
SAFE SOLUTIONS

Even with minimal tube volumes, the potential for injury from manual decapping or manual recapping is a real possibility.

You have known about our Pluggo™ decappers. Now available; KapSafe™ Recappers in several models to fit any volume needs.

Make your goal ZERO repetitive stress injuries.

From the leader in bench-top solutions for automated decapping and recapping.

Visit our website for additional information www.lgpconsulting.com

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Accommodates all major tube sizes and a variety of analyzer racks.

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Atellica® Solution: Flexible, scalable, automation-ready immunoassay and chemistry analyzers engineered to deliver control and simplicity so you can drive better outcomes.

A bi-directional magnetic sample transport that is 10 times faster than conventional sample conveyors

The new standard in sample management—revolutionary technology that gives independent control over every sample

An immunoassay analyzer that runs up to 440 tests per hour,† the industry’s highest productivity per square meter‡

Unprecedented flexibility with more than 300 customizable configurations including L and U shapes

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†Product availability will vary by country.
‡Dependent on test mix.
†Versus leading IVD companies.

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