Automation advances clinical microbiology

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Innovative PT solutions?
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Epigenetic inheritance and smoking moms

FROM THE EDITOR

By Alan Lenhoff, Editor

Epigenetic inheritance flies in the face of textbook genetics, which holds that genes contained in DNA are the only means for the transfer of biological information from generation to generation. And yet, Gregor Mendel did not know about the presence of genetic tags, and scientists today are only beginning to understand the biology of these genetic influences. Further research may in fact cause geneticists to rewrite the textbook and complicate further the age-old controversy of “nature versus nurture” as well.

Because the research keeps on coming. Recent studies indicate that chronic pain changes the immune system; that there is an epigenetic switch for obesity; and, in research published March 31 in the American Journal of Genetics, that maternal smoking alters fetal DNA.

That’s right. A study of more than 6,000 mothers and their newborn children has solidified earlier evidence that smoking cigarettes while pregnant chemically modifies a fetus’ DNA—mirroring patterns seen in adult smokers. The researchers also identified new development-related genes affected by smoking. Their work suggests a potential explanation for the link between smoking during pregnancy and health complications in children. “I find it kind of amazing when we see these epigenetic signals in newborns, from in utero exposure, lighting up [no pun intended?] the same genes as an adult’s own cigarette smoking,” says co-senior author Stephanie London, an epidemiologist and physician at the National Institute of Environmental Health Sciences (NIEHS), part of the National Institutes of Health. There’s a lot of overlap. This is a blood-borne exposure to smoking—the fetus isn’t breathing it, but many of the same things are going to be passing through the placenta.

Links between smoking and chemical modifications to DNA, or methylation, have been found for developing fetuses in smaller studies, but the larger analysis gives scientists more power to uncover patterns. An international team of researchers pooled results from 6,685 newborns and their mothers around the world. Based on questionnaires, mothers were labeled as “sustained smokers” who smoked cigarettes daily throughout most of pregnancy (13 percent), “non-smokers” (62 percent), or those with “any smoking” during pregnancy (25 percent), which captured mothers who were occasional smokers or who quit smoking early on.

To analyze methylation in the newborns’ DNA, researchers collected samples mainly from blood in the umbilical cord after delivery. For the newborns whose mothers pooled results from 6,685 newborns and their mothers around the world. Based on questionnaires, mothers were labeled as “sustained smokers” who smoked cigarettes daily throughout most of pregnancy (13 percent), “non-smokers” (62 percent), or those with “any smoking” during pregnancy (25 percent), which captured mothers who were occasional smokers or who quit smoking early on.

To analyze methylation in the newborns’ DNA, researchers collected samples mainly from blood in the umbilical cord after delivery. For the newborns whose mothers fell into the “sustained smoker” category, the research teams identified 6,073 places where the DNA was chemically modified differently than in the “no smoking” newborns. About half of these locations could be tied to a specific gene.

London and her colleagues found that this collection of genes related to lung and nervous system development, smoking-related cancers, birth defects such as cleft lip and palate, and more. “Many signals tied into developmental pathways,” says Bonnie Joubert, an epidemiologist at the NIEHS and a co-first author on the paper. In a separate analysis, many of these DNA modifications were still apparent in older children whose mothers had smoked during pregnancy.

Epigenetics, defined as the regulation of gene expression beyond the primary information encoded by DNA, is established science. The extent of its influence may be far greater than geneticists had imagined.

Alan Lenhoff

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New Studies

Mount Sinai researchers assess accuracy of commercially available lab tests. Scientists from the Icahn School of Medicine at Mount Sinai performed an in-depth comparison of basic blood tests run by commercial laboratories to assess comparability of the tests among the different laboratories, finding that testing service and time of collection significantly influenced results. The study highlights the importance of accuracy and variability of test results.

The study, first designed in early 2015 with data collected last July, analyzed results from comparable blood tests on healthy adults conducted at LabCorp, Quest Diagnostics, and Theranos. Researchers collected multiple samples from the same individuals and controlled for factors such as age, sex, and time of blood collection, among many others, but still found that more than half of test results showed significant differences among test providers. Triglyceride levels and red blood cell counts were among the most consistent results, while white and red blood cell counts were among the most variable.

In a total of more than 18,000 data points, the researchers identified characteristic differences in a number of virus proteins. The results suggested that only a few changes in one Ebola virus protein, VP24, may be necessary to turn the Reston virus into a virus that can cause human disease. There may be a risk, therefore, that Reston viruses acquire the few mutations necessary to cause disease in humans and to develop into a novel health threat.

Antibody assays and other tests for diseases like Zika are among the most promising tools in efforts to control outbreaks. But scientists have long noted inconsistencies in test results that can lead to erroneous conclusions from scientific or clinical studies. A research team led by University of Arkansas scientists has developed an alternative therapeutic approach to fighting antibiotic-resistant infections. The novel method uses a targeted, light-activated nanodrug consisting of an antibiotic-loaded nanoconstruct, which are nanoscale cages made of gold and coated with polydopamine. The antibiotic is loaded into the polydopamine coating. The gold nanocages convert laser irradiation to heat, resulting in the photothermal effect and simultaneously releasing the antibiotic from the polydopamine coating. MicronaNo's platform for delivering antibiotics is nanoscale cages that are free-floating rather than contained within a biofilm of—both methicillin-sensitive and methicillin-resistant S. aureus strains. However, the method was subsequently shown to be effective even in the context of an intrinsically resistant biofilm.

Ebola

Research shows potential for emergence of new Ebolavirus. A team from the University of Kent’s (England) School of Biosciences examined the differences between Ebolaviruses that cause severe disease in humans and the Reston virus, which does not.

The Reston virus, which is known to circulate in domestic pigs in Asia and occasionally infect humans, is currently the only member of the Ebolavirus family not to have been reported as causing life-threatening disease, including hemorrhagic fever in humans.

Using computational analysis of the sequences of the genomes of Ebolaviruses and a computational prediction of the effects of sequence variations on virus function, the researchers identified characteristic differences in a number of virus proteins. The results suggested that only a few changes in one Ebola virus protein, VP24, may be necessary to turn the Reston virus into a virus that can cause human disease. There may be a risk, therefore, that Reston viruses acquire the few mutations necessary to cause disease in humans and to develop into a novel health threat.

First commercial serological tests available for ZIKV detection. Euroimmun AG, a manufacturer of test systems and instruments for medical diagnostics with headquarters in Luebeck, Germany, has developed the first system of comprehensive tests available for the serological detection and differentiation of Zika virus infections. The tests were granted the CE mark in February, making them eligible for sale in the European market. They are available in the U.S. under research use only labeling.

The team used as the proof-of-principle pathogen to demonstrate the potency of its nanodrug. The combination of achieving a photothermal effect and controlled release of antibiotics directly at the site of infection was achieved by laser irradiation at levels suitable for rapid screening of large patient volumes and therefore provide efficient and effective monitoring of the virus spread.

Serological analyses may help determine whether long-term consequences, such as microcephaly and Guillain-Barré syndrome, are a result of a previous Zika virus infection, may be useful for screening sample donations at blood centers and blood banks in hospital settings, and may monitor the growing epidemiological reach of the Zika virus.

Infectious Diseases

New potent nanodrug to combat antibiotic-resistant infections. A research team led by University of Arkansas scientists has developed an alternative therapeutic approach to fighting antibiotic-resistant infections. The novel method uses a targeted, light-activated nanodrug consisting of antibiotic-loaded nanoconstructs, which are nanoscale cages made of gold and coated with polydopamine. The antibiotic is loaded into the polydopamine coating. The gold nanocages convert laser irradiation to heat, resulting in the photothermal effect and simultaneously releasing the antibiotic from the polydopamine coating. MicronaNo’s platform for delivering antibiotics is nanoscale cages that are free-floating rather than contained within a biofilm of—both methicillin-sensitive and methicillin-resistant S. aureus strains. However, the method was subsequently shown to be effective even in the context of an intrinsically resistant biofilm.
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Automation advances microbiology to operational excellence

By Nathan A. Ledeboer, PhD

The past few years have seen significant changes in clinical microbiology. On the regulatory front, as more assays receive FDA clearance, labs increasingly have the option to replace laboratory-developed tests (LDTs) with commercially available IVD tests. Respiratory panels are a good example. Second, technological advances continue to reduce turnaround time drastically, and, at the same time, a better understanding of how test results can be used to improve care is raising physician expectations. For example, while a turnaround time of eight to 24 hours for a flu test was previously acceptable, a 20-minute to two-hour time to result is now standard of care. Likewise, while a turnaround time of >24 hours for generating a C. difficile result was previously acceptable, a 1½- to three-hour time to result is becoming the standard of care.

Patient management, the decision to admit, and infection control measures often hinge on test results, with significant health outcome and cost ramifications. Microbiology results, once viewed as confirmatory and often delivered after patient management decisions were made, are now integral to the clinical workflow. Patient-centric care, the mantra of today’s healthcare, translates into patient-centric testing in the microbiology lab, with far-reaching implications for the lab workflow, how the lab is structured, and even how patient specimens are delivered to the lab.

Along with this trend toward patient-centric testing has come a massive shift toward automation, driven by the need to better support clinical decisions with high-quality, timely results efficiently and cost-effectively. This trend is enabled by advances such as molecular diagnostics, digital microbiology, and matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS). These advances open the door to greater standardization of processes and results, automation, and a new level of operational excellence and performance. Efficiency gains in the lab are especially needed, with continuing pressure on reimbursement due to the Protecting Access to Medicare Act of 2014 (PAMA).

Enabling technologies continue to evolve. Clinical microbiology has traditionally been associated with a diversity of patient specimens and transport media, lengthy culture, and visual results requiring human review. These factors, all of which hamper standardization, a prerequisite of automation, have left the microbiology lab in the dark ages. All this is changing with new technological advances that are enabling automation at a time when microbiology must needs it—to meet the multiple challenges of today’s healthcare environment, declining reimbursement, and the shortage of trained personnel.

Molecular diagnostics has truly been a transformational force in microbiology. The sensitivity it offers has allowed us to detect and identify more organisms faster, without having to wait for culture results. Mycoplasma is a case in point. Another example is testing for sexually transmitted infections like Chlamydia trachomatis and Neisseria gonorrhoeae. In many ways, molecular diagnostics has made diagnostics more relevant. Previously, a patient suspected of chlamydia or gonorrhea would be treated empirically. Today, with faster time to result, treatment can begin after the pathogen is properly identified, reducing the unnecessary use of antibiotics. A study comparing clinical and economic outcomes before and after initiation of molecular testing of methicillin-resistant Staphylococcus aureus (MRSA) in positive blood cultures demonstrated a mean reduction of 6.2 days in hospital stays and a $21,387 savings when molecular testing was combined with timely infectious disease consult and appropriate antibiotics use.

Molecular diagnostics offers other advantages—the availability of automated platforms, options in standalone specimen preparation and handling systems, and connectivity to the chemistry lab. All of these can help advance clinical microbiology through automation and better integration with the rest of the healthcare system.

A second transformational technology is MALDI-TOF, first commercially available for clinical microbiology in 2009. MALDI-TOF provides a cost-effective, standardized, and rapid method for identification of clinically significant bacteria, fungi, and mycobacteria. Importantly, MALDI-TOF procedures are relatively simple and do not vary based on organism. The integration of MALDI-TOF into the clinical microbiology workflow has decreased time to organism identification from days to hours. The impact on patient care is significant. One study on adult patients with bacteremia and candidemia demonstrated that the combination of MALDI-TOF diagnostic testing and an antimicrobial stewardship team decreased time to effective and optimal antibiotic therapy, which translated into lower mortality rate, shorter intensive care unit stays, and reduced recurrent bacteremia (Figure 1, pg. 9). For the first time, standardizing the identification process of bacterial isolates is now possible, enabling automation, improving workflow, and increasing efficiency.

The evolution of digital microbiology is changing the way in which culture plates are read, impacting not only turnaround time but also quality of results. Digital microbiology integrates...
automated imaging systems to capture images of culture plates at specified time intervals, robotics to move specimens across the lab, and software to process captured images and determine the presence of positive colonies for review and confirmation. For example, with digital imaging software, preset color thresholds, as defined by hue, saturation, and value, are employed to detect growth in chromogenic agar (Figure 2). In this way, negative plates can be identified for quick screening to confirm negative results, while only positive plates are reviewed one by one. This reduces substantially the number of plates reviewed and ensures better use of laboratorian time when trained personnel are scarce. The ability to rule out negative plates quickly not only saves personnel time but can expedite clinical decisions and reduce unnecessary intervention.

The advent of liquid transport media has been highly influential in improving specimen quality and enabling automation. Elution of specimens from newer flocked-style swabs into liquid phase has been shown to increase the release of viable organisms from the swab, improving sensitivity. And the liquid-based transport enables inoculation of the specimen with automated liquid-based specimen processors, an important step toward greater efficiency and standardization.

**Microbiology automation—indications of success**

While microbiology automation is only at the early stages of implementation—an estimated 10 percent of labs in the U.S. having adopted some automation technology—quantifiable improvements in turnaround time, productivity, and quality have been reported.

In a multi-center study, molecular diagnostics was shown to reduce time to results for MRSA testing from 24 to 48 hours to less than two hours. A study comparing routine microbiology with automated identification and susceptibility testing on patients with positive blood cultures found a mean reduction of 13 hours in turnaround time for identification and 20 hours for susceptibility results. The combination of automation of front-end specimen processing with MALDI-TOF yielded a 30.6-hour result. The preintervention results. The combination of automation of front-end specimen processing with MALDI-TOF yielded a 30.6-hour result.

**Quality improvement** is an important benefit of automation, which allows standardization of techniques and reduction of human errors. A recent study demonstrated that automating specimen processing, specimen incubation, imaging of MRSA growth, and automated analysis reduced the number of false negatives. Compared with manual screening, sensitivity was 100 percent across three sites using three different commercially available culture media, and specificity ranged from 90.7 percent to 92.4 percent. Automated analysis identified all positives identified manually, while 2.9 percent of the discrepant results (identified as positive by automated analysis and negative by manual reading) were found to be positive upon manual re-examination. In another study comparing automated imaging and analysis with manual review of 92 urine specimens, automated analysis identified four additional positive cultures missed by manual reading due to overlooking a pathogen in heavily mixed cultures.

Related to quality improvement are traceability and documentation. By automating the confirmation of multiple patient identifiers at multiple steps from specimen transport vessel to plates, the lab can prevent medical errors due to incorrect patient identification. In combination with inexpensive electronic data storage, digital microbiology facilitates documentation with image archiving for further review, for correlating Gram stain images with cultures, for use in teaching, and to share with inquiring physicians.

Perhaps the most important benefit of automation is its value in optimizing the lab workflow, which in turn positively impacts the clinical workflow. For example, changing from reading plates when personnel can get to them to reading them when they are ready to be read can make all the difference in optimizing turnaround time. In turn, this means availability

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**Figure 2.** Automated detection. Color thresholds are defined by hue (H), saturation (S), and value (V). Plates are marked negative if no pixel contains an HSV score outside the preset threshold.
of results when physicians need them. Knowing that the majority of specimens arrive at the lab between 8 PM and 2 AM, for example, the lab can plan to read plates until 10 PM, transition the staff to processing to get the plates to the incubator earlier, and start reading again at about 2 AM, when the plates are ready to be read by the automated imager. In this way, results from specimens that arrive the night before will be in the physician’s in-box the next morning. Another example is group A strep, with most specimens coming from Outpatient and arriving between 8 PM and 2 AM. With automated molecular diagnostics, results can be waiting for physicians the next morning. With the availability of technologies that offer group A strep results in 20 minutes, physicians have the option to diagnose and begin treatment while the patient is still in the office. These changes have a very positive impact on physician satisfaction ratings.

Implementing microbiology automation

Microbiology automation is not without challenges. Cost is a significant barrier to automation, with the initial investment in capital acquisition, facility modifications, and, importantly, IT and connectivity to integrate the entire process from test requisition and specimen collection to final result. Overcoming the initial resistance of lab personnel is also sometimes a factor.

While many labs have implemented some automation solutions, especially in molecular diagnostics, the majority of labs in the U.S. are still in the planning process or looking to build on what they have started. As with any significant initiative, thorough need assessment, planning, and securing the buy-in of all stakeholders are key. In this context, it is difficult to overemphasize the importance of two areas of focus in the planning stage—workflow and IT.

Automation cannot be done in a vacuum, and it is important to consider the overall workflow of the lab, not just specific processes being automated. Studies have shown that implementing automation without considering the overall workflow makes little impact on quality of care. To understand the overall lab workflow and the clinical workflow and how best to derive the maximum value from automation, labs need to review all facets of current lab operations. These include, for example, the mix of specimen types (i.e., whether processing can be automated), time they arrive at the lab, and expected time to result. A detailed snapshot of current hourly workload and staffing needs will guide how staffing might be redistributed after automation. The goal is to make sure there is clear understanding of how automation will be incorporated and how it will impact the overall workflow and, ultimately, patient care.

A second planning parameter that is sometimes left as an afterthought is IT. In the current imperfect world of connectivity, making sure that computer systems—from automation technology to MALDI-TOF to LIS to HIS—talk to each other is paramount. The need for integrated information flow cannot be overemphasized. Thus, getting the IT team involved from the beginning is a critical success.

Figure 3. Productivity increase. Manual methods were compared against automated specimen processing, plate incubation, and digital imaging at three hospitals in the U.K. Productivity was measured by number of samples processed per FTE per day.9
factor. As higher-quality information is generated in a more timely manner, it is just as important to get it into the physician’s hands without delay. Of course, there are myriad other factors to consider in planning automation—space planning is one example. Mapping out the post-automation workflow to reallocate staff time is another. A clear picture of the expected results and metrics for post-automation assessment will help track progress and guide adjustments once implementation begins.

Looking ahead

Even as labs are implementing the many advances that are reshaping clinical microbiology today, new technologies are on the horizon. One example is the quick identification of multidrug-resistant organisms and antibiotic susceptibility assessment directly from clinical samples, without the need for traditional enrichment, culture, or sample preparation processes. Currently, a new system is being evaluated in multiple sites across the U.S. The system has automation capabilities such as random access, familiar to the chemistry lab.

REFERENCES

TEST QUESTIONS

1. Which quality measure is becoming a standard of care and raising physician expectations for the clinical microbiology lab?
   a. increased employee competency documentation
   b. decreased nosocomial infections
   c. decreased specimen rejection
d. all of the above

2. What trend in healthcare has caused the microbiology lab to make changes with regard to the clinical workflow?
   a. overcoming access barriers
   b. change in Medicare payments
   c. patient-centric care
d. none of the above

3. According to the article, what is/are another trend(s) toward which the clinical microbiology lab is currently facing a massive shift?
   a. automation
   b. increased FTEs for more timely plate reading
   c. both a and b
d. neither a nor b

4. Factors that have hampered standardization in the microbiology lab include a diversity of patient specimens and transport media, lengthy culture time, and human review of visual results.
   a. True
   b. False

5. Examples of the advances in the microbiology lab include:
   a. molecular diagnostics
   b. digital microbiology
   c. MALDI-TOF
   d. all of the above

6. What advantage(s) does the use of molecular diagnostics contribute, with regard to healthcare outcomes?
   a. faster turnaround time
   b. reduces unnecessary use of antibiotics
   c. both a and b
d. neither a nor b

7. According to the MDx study on MRSA referred to in the article, the mean reduction in hospital stay was how many days when molecular testing was used?
   a. 6.2 days
   b. 6.5 days
c. 6.9 days
   d. 7.5 days

8. In what year did MALDI-TOF become commercially available for use in the clinical microbiology lab?
   a. 2015
   b. 2005
c. 2012
d. 2009

9. MALDI-TOF has the capability of identifying all clinically significant organisms, except:
   a. bacteria
   b. parasites
   c. fungi
d. mycobacteria

10. The use of MALDI-TOF has decreased time to organism identification from
    a. months to weeks.
b. days to seconds.
c. hours to minutes.
d. days to hours.

11. According to the MALDI-TOF study, its use made a significant impact on patient care in which way(s)?
    a. lower mortality rate
    b. shorter ICU stays
    c. reduced recurrent bacteremia
d. all of the above

12. Digital microbiology technology captures images of culture plates at specified time intervals and determines the presence of positive colonies for review and confirmation.
    a. True
    b. False

13. Factors which make digital microbiology a useful tool for clinical microbiologists and clinicians include all but:
    a. expedites clinical decisions.
b. saves personnel time.
c. reduces specimen rejection.
d. reduces unnecessary intervention.

14. The use of liquid transport media has been shown to decrease the release of viable organisms from the specimen swamp, improving sensitivity.
    a. True
    b. False

15. What percentage (est.) of microbiology labs in the U.S. have adopted some form of automation technology?
    a. 50%
b. 25%
c. 10%
d. 5%

16. Which factor(s) contribute to quality improvement through the use of automation?
    a. reduction of human errors
    b. standardization of techniques
    c. both a and b
d. neither a nor b

17. What is the most significant barrier to automation in the clinical microbiology lab?
    a. cost
    b. resistance of lab personnel
c. resistance by physicians
d. space

18. What new technology in clinical microbiology is currently on the horizon for implementation?
    a. electrophoresis for identification of mycobacteria
    b. rapid detection of antibiotic-resistant organisms
    c. ELISA testing of direct samples
   d. non of the above
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Transforming the practice of pathology with digital technology

By Robin Weisburger, MS, HTL(ASCP)

Over the past three decades, the practice of pathology has evolved tremendously. In the 80s and 90s, viewing microscopic images was limited to looking through a pair of microscope oculars. Publications and presentations took hours of preparation using 35mm cameras that were adapted to the microscope. The exposed film was sent to a developer, and the resulting slides were submitted for journal publication or projected at a teaching conference on a standard carousel projector.

Some medical centers were fortunate enough to be able to invest in projection microscopes. A luxury for many, these “microscopes on wheels” could be transported from the laboratory to lecture hall to conference room. Images were projected directly from the slides to the screen. There was no video cable or computer, just a microscope, light source, and projection lenses.

Twenty-five years later, digital cameras transmit images from microscopes to remote computers for rapid assessment of frozen sections and fine needle aspiration prep in real time. “Whole slide imagers” are able to produce a high-quality digital image of a microscope slide with-in minutes which can be sent anywhere via the world-wide web for collaborative review. Whether for clinical, research, or educational applications, digital technology has transformed the way pathology is practiced today.

The pros and cons in a nutshell

What is driving the trend toward digital whole slide image technology? The biggest driver is the realization that being able to digitally capture an entire stained slide offers greater flexibility and utilization of microscopic images. Images can be annotated and shared easily among network users. New laboratory workflows reduce the handling of glass slides and improve pathologists’ flexibility and productivity. These new workflows also reduce the risk of loss of important patient material and reduce costs for managing slide archives.

So, why isn’t everyone embracing digital whole slide image technology? Cost is the primary reason. Although they’re trending down, investment costs for an image scanner and storage infrastructure can be formidable. In addition, support for implementation and operation of a digital pathology system requires teamwork across departments to ensure success. Pathologists who are unfamiliar with whole slide imaging technology may be overwhelmed and not want to depart from their familiar processes.

In fact, change is difficult, and it may require an investment of time, money, and trust before rewards are seen. To achieve success in this new practice of pathology, we must help our colleagues and ourselves overcome this resistance to change.

Process: decision-making strategy

In the last five years, whole slide scanners have improved in quality and come down substantially in cost. Larger medical centers find them invaluable in the preparation of material for research and teaching, and for support of many clinical applications such as quality assurance and tumor boards. Some of these centers are ready to take a bold next step by embracing telepathology to support their remote practice partners by collaborating on difficult cases. How will these centers change their current practice paradigm so they can realize the full potential of their digital pathology system?

A change of this magnitude benefits by having a well-defined strategy that considers departmental and organizational goals. Knowing what needs to be achieved, when it needs to be achieved, and by whom it needs to be achieved provides a framework to guide purchasing decisions, timelines, and even staffing decisions.

There is much to be considered when purchasing a whole slide imager. Quality of images, magnification options, throughput, cost, and service are key factors in the decision-making process. Also to be considered is the relative value of each of these factors in case one needs to be compromised for another.

Other costs to be considered include that of an image storage server and of the technical staff to provide support for the service. Each whole slide image can range from 300 megabytes to several gigabytes. Adequate storage and backup of the image repository is critical to the long-term success of a digital pathology service. Staff support from both the laboratory and hospital information services is also required. These partners are vital to ensure the smooth operation of the digital pathology service from image acquisition to workflow management to the archiving of the images and their associated cases.
Implementation

Using a project management approach will assist with defining objectives, timelines, responsibilities, and key players to help ensure a successful process from purchase through implementation. The project will require the collaboration of a multidisciplinary team including organizational leadership, ancillary network experts, pathology staff, and, as needed, members from the vendor team.

The Team Leadership must provide a clear vision of what needs to be accomplished and when. It is their responsibility to articulate the project goals and to provide the resources, support, and commitment needed for success.

All team members must collaborate to consider hardware needs, calculate storage needs, and create a reasonable timeline to complete each phase of the project. It is critical to clarify the parameters of the project to prevent “scope creep.” Too often, implementation of a new work process can be sidetracked if time is spent on details not originally intended to be part of the project’s scope of work. Regular meetings to define tasks, assign responsibility, and report progress are vital to ensure the project stays on track.

Most team members will be juggling multiple priorities. Agendas, meeting notes, and updates to key stakeholders will assist in maintaining accountability for the work being done.

Key factors

Missteps can be avoided by focusing on a few specific considerations. Training, testing, standardization, and support are all key factors to ensure the successful implementation of a strong digital pathology service:

- **Training:** Do not underestimate the importance of proper training and support. Some staff may want to forego formal training, believing they can best learn by doing. Then, if the system does not perform as expected, they may blame product inadequacies instead of lack of user knowledge. Training and written documentation of processes for user reference are critical to success.

- **Validation testing:** Whole slide images must be validated to ensure that their quality is on par with glass slides, and the workflow platform must be validated for performance. Documentation of validation testing must be completed and maintained on file for regulatory inspections.

- **Standardized workflows:** Documentation of the new workflows is critical to ensure that all users and support staff know what steps happen in what sequence. This documentation serves as a roadmap for how the workflows are navigated. At the technical level, work processes for scanning slides, accessioning cases, and triaging the work must be defined, and all staff must follow them. If work is standardized and sound quality control measures are in place, these activities become part of the lab’s daily routine to support their pathologists’ digital service.

- **Pathologist support:** Some pathologists may be reluctant to change to using whole slide images for quality assurance, tumor board activities, case reviews, or other routine work. If a standardized high quality digital service is provided by the laboratory, pathologists will begin to gain confidence in the new workflows. Users who become early adopters can support their colleagues as they come on board with this new way of work.

Pathology workflows

A repository of whole slide images does not constitute a digital pathology service. It is the work that can be accomplished with these images that provides the real value. Most whole slide scanners are packaged with proprietary software that facilitates pathology workflows. Annotation and measurement tools can assist with research, preparation of study sets, and tumor board presentations. Quality assurance activities can be streamlined and documented for regulatory review. Collaborative case reviews between colleagues can be performed in real time whether the pathologist partner is down the hall or across the continent.

Third-party platforms that are scanner agnostic and can integrate with a user’s laboratory information system (LIS) have been proven to expand the utility of an organization’s repository of whole slide images. No longer are laboratories constrained by proprietary software specific to an individual scanner. Instead, pathologists and laboratories can take full advantage of the benefits offered by whole slide digital images regardless of the scanner that created them or the LIS storing the patient’s information.

These powerful new platforms contain the tools that elevate a digital pathology system to a truly comprehensive clinical workflow suite.
Anatomic pathology meets analytics

By Eleanor Herriman, MD, MBA, and Tim Kuruvilla, MBA

What is anatomic pathology’s (AP) role in value-based healthcare? How can AP groups best position themselves for what’s to come? How can pathologists define and ensure better transparency to add to the value and efficiency that AP services deliver? These are questions being asked by many in the AP field, and the answers are not trivial.

We’re all familiar with the challenges we face in our industry: declining reimbursement, policy changes, consolidation, and staff shortages. Let’s look at some of the measures AP labs are taking to navigate the challenges that are inevitably coming their way, including taking a patient-centric approach to quality, driving efficiency, and highlighting AP value.

Patient-centered approach

• Disease-based testing. Pathologists are at the center of the personalized medicine revolution, and realizing the value of this position requires expanding their role by offering intelligent services and analytics that provide rules-based test protocols for specific diseases and tissue, molecular, and other tests.

• Patient-centered reporting. Overwhelmed clinicians sometimes struggle with interpreting asynchronous, complex test results when working up patients with a wide variety of tests. Pathologists can use analytics systems to integrate findings and generate patient-specific summary diagnostic services.

• Minimizing follow-up errors. A frequent cause of diagnostic errors involves failure of clinicians to receive or appropriately act upon AP test results. Pathologists can add value to their services by using analytics systems to identify these potential errors and intervene to mitigate risk.

Driving efficiency

Laboratories have to be as cost-efficient as possible. However, multiple studies have proven that up to two-thirds of workflow process in AP labs is non-value-added. While significant efforts are being made on workflow improvement and cost management initiatives, it is critical to create sustainable performance improvements in the lab. Analytics enable AP labs to drive sustainable efficiency in the following areas:

• People. Pathology lab leaders should staff by analyzing historical trends from which they can more accurately predict their needs by day, hour, or month, rather than anecdotally. They should also ensure that team members know how their performance is measured, and that they have real-time insight into their performance metrics and the tools to be able to impact those metrics.

• Process. Using real-time analytics, lab leaders should empower the lab to identify and respond to errors in a timely manner. They should make sure they have detailed turnaround time information, enabling them to identify points in the process where there may be opportunities without having to seek them out. To manage backlogs and reallocate resources appropriately, real-time workload analyses are critical; they enable labs to react in a timely fashion.

• Tools. Investments in laboratory equipment are made to leverage people and processes. It’s important to ensure that they optimize staff productivity. Ensuring that the use of those tools is synchronized with AP workflow can have tremendous impact on efficiency.

Highlighting value

While AP has already experienced significant declines in reimbursement, the shift to bundled and value-based payments will be an even greater upheaval in the reimbursement model. Every healthcare service line, including AP, will have to articulate the value and impact of its services across the continuum of care. Here are ways in which AP labs can achieve that:

• Quantifying. Lab leaders should quantify the true cost and downstream impact of AP services both in the lab and across the care continuum. They need to know and be able to demonstrate the cost of a missed or inappropriate diagnosis, e.g., inappropriate work-ups and treatments for an inaccurate cancer diagnosis, and to be able to identify the cost of a delay in diagnosis. (In the case of cancer, this might include poor outcomes or malpractice consequences.) They need to measure and monitor performance on these key measures of value.

• Sharing. AP labs should proactively share information with key constituents: health plans, patients, and providers. Full transparency on service levels which trends are occurring within the patient population, and test utilization recommendations develop “stickiness” and trust among clinicians the lab serves. For example, payers developing oncology management and bundling programs are interested in accessing oncology AP results in a timely manner, enabling decision support interventions. Transparency and proactive, information-based communication are no longer luxuries; they are expectations.

• Engagement. Working collaboratively with other areas of the lab will allow a unified, strategic approach to the health system. Laboratory testing is often misunderstood, and it’s critical that AP lab leaders drive awareness of how the laboratory can impact organization-wide goals. It is a good strategy to engage physician peers in discussions about the value of laboratory testing and share responsibility for system-wide outcomes and performance.

The value of analytics

These initiatives are challenging to the AP lab, and many questions remain unanswered. The information required to support these efforts is sometimes difficult to access, analyze, and share with the tools currently available to labs. However, AP labs are increasingly utilizing analytic solutions as organizations realize the importance of their data assets, including investments in electronic medical records. In fact, reports show that investment in healthcare analytics is growing at a 26 percent plus CAGR (compound annual growth rate) over the next few years, and is expected to reach more than $18 billion in 2020. It’s time for AP laboratories to align with organizational strategies and invest in analytics to drive many of these key initiatives in the lab, as well as its impact outside of their walls.
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The laboratory of the future moves outside the walls

By Anthony Kurec, MS, H(ASCP)DLM

The clinical laboratory world has undergone significant changes in technology, personnel training, and regulatory mandates over the past several decades that have had an impact on how patient care is provided. Laboratory testing has been recognized as an integral part in the diagnosis and treatment of diseases. Further, due to changes in payment reimbursements, strategies in managing a clinical laboratory have shifted, making laboratory testing a commodity. Yet, as has been well documented, 70 percent of medical decision-making is based on diagnostic laboratory testing, but testing accounts for only 2.3 percent of total healthcare expenditures.²

In addition, there has been a tremendous shift in how and where patients want to receive their healthcare and related information, thus placing a greater demand on physicians, nurses, and other healthcare practitioners to provide timely and accurate patient-focused services. Point-of-care testing, telehealth services, and direct access testing are three areas that have, in part, contributed to this ever-expanding desire for easy access, thus allowing individuals to have greater input in their healthcare decisions. Studies indicate that better patient care is provided when patients and their healthcare providers have easy access to clinical information.²

Point-of-care testing

Point-of-care testing (POCT), or near-patient testing, was introduced several decades ago and has, over time, been incorporated into the daily procedures found in many emergency departments, physician offices, nursing homes, neighborhood clinics, drugstores, and even in the home. The intent of POCT is to offer a way to facilitate patient treatment by targeting healthcare interventions in a more timely and convenient manner.³

While less than four percent of CLIA-certified laboratories are within hospital settings, they perform the majority of laboratory tests (Figure 1).¹ An estimated 12.8 billion laboratory tests are performed each year in the U.S.,⁴ with approximately one-third of these tests involving POCT.⁵ POCT is largely based on CLIA-waived testing, which has expanded over the past few years, making it a significant testing modality within hospitals and other venues by working in concert with central laboratories (Table 1, pg. 20).²⁴

For example, in a survey of 317 U.S. hospitals, 100 percent of them were using POCT for glucose monitoring, 87 percent for coagulation monitoring, and 77 percent for blood gas/electrolytes monitoring—while 32 percent incorporated POCT for cardiac markers and 20 percent for HbA1c.⁶ In another study, 23 percent of hospitals had used six or more POCT instruments in 2011 compared to only five percent in 2007.⁷

Concerns have arisen regarding the accuracy of POCT results, especially when proper quality assurance protocols are not followed. Table 2, found on page 20, lists some common areas that have been identified as sources for potential error.⁵,⁸,⁹ Yet POCT, when managed correctly, can provide accurate and timely diagnostic information that can improve patient care, decrease costs, and make better use of limited personnel resources.

Because of the relative ease of use and its portability, POCT can be done almost anywhere by anyone. Training is key to the proper use and maintenance of equipment used; so is implementing correct quality control procedures. Any deviation in protocol procedures, especially when multiple users are involved, can result in erroneous results. Also, use of multiple brands of POCT equipment can contribute to variable results; thus the need to standardize to a single model. Other concerns involve environmental factors of excessive heat, cold, or humidity due to improper shipping or storage conditions, causing reagent damage.

Confusion may also occur when comparing POCT results with those obtained from the central laboratory, as differences may occur due to variability in methodology. While there are many factors that lead to inaccurate POCT results, proper training, equipment maintenance, identifying unique patient conditions, and strictly adhering to POCT policies and procedures will minimize potential errors.

Teledmedicine/telepathology

A number of healthcare areas have embraced telemedicine as an option to provide services remotely.

Figure 1. Facility location of the 252,000 CLIA-certified laboratories⁴

continued on page 20
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real time, thus allowing for expert review/interpretation of pathology slides. A fourth type of system is a whole slide imaging (WSI) system, which provides the option of scanning an entire slide, digitizing it, and transmitting a single file electronically via cloud technology.

Telepathology as part of pathology services has made some inroads in the past few years, though it is still not extensively used in the United States. It has been more readily accepted in other countries as a way to obtain second opinions and conduct pathology slide reviews and frozen section evaluations, especially in underserved areas lacking certain types of expertise.

Improved storage capacities and adequate transmission bandwidths are paving the way for the expansion of telepathology in the U.S., yet some concerns remain (Table 4, pg. 22).

The second generation of “Web 2.0” offers even more support for telepathology. Web 2.0 offers a more robust interactive opportunity for pathologists to engage in editing, creating content, and commenting on shared cases. This higher level of mutual participation can offer greater diagnostic, consultative, and educational experiences in a timely and widespread manner. User-generated pathology content can be shared in a virtual community where information can be discussed in conjunction with other tele-diagnostic modalities—including x-rays, CT images, and ultrasound images—to provide overall better patient care.

**Direct access testing**

The gateway to proving direct access testing (DAT) began as early as the 1950s, when over-the-counter (OTC) test kits became available for measuring urine glucose and ketones in an effort to provide direct and timely access to a diabetic patient with potential health concerns. Web-savvy health consumers, who can seek out volumes of medical information and are generally better educated, want access to their own healthcare information in order to track health progress and treatment, and to advocate for themselves with their healthcare provider.

Further, maintaining a healthy lifestyle has been embraced by many and is often supported through employer-sponsored workplace wellness programs, such as smoking cessation, gym memberships, stress-control, weight loss, and nutritional offerings, especially in companies with greater than 200 employees. This has stimulated public demands to know what is in the products we consume, such as saturated fat content, sugar levels, milligrams of sodium, whether products are gluten-free, and whether they

<table>
<thead>
<tr>
<th>Errorneous results</th>
<th>Improper equipment maintenance; dirty optical or sensor area; improperly calibrated; poor operator training</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reagents</td>
<td>May produce erroneous results due to improper storage or are expired</td>
</tr>
<tr>
<td>Nosocomial infections</td>
<td>Improper decontamination of instruments</td>
</tr>
<tr>
<td>Occult blood</td>
<td>Sensitive to light, heat, humidity</td>
</tr>
<tr>
<td>Urine dipssticks</td>
<td>Can degrade due to excessive light, heat, humidity; light source (such as fluorescent light) may affect color discrimination</td>
</tr>
<tr>
<td>Blood gases</td>
<td>May be affected due to changes in altitude</td>
</tr>
<tr>
<td>Pregnancy tests</td>
<td>Antibodies may be denatured due to excessive hot or cold temperatures</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>Abnormally high or low hematocrits can adversely affect glucose levels; small amounts of contaminant (lotion, dust, food particles, etc.) on fingernail; certain medications (acetominophen, L-dopa, aspirin, etc.)</td>
</tr>
</tbody>
</table>
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have been organically raised, or are vitamin-enriched. This “wellness revolution” has had an impact on the delivery of healthcare and laboratory services. The move to electronic health records (EHR) has also increased opportunities to easily share health information through secure web portals. Wireless technology through mobile apps and wearable devices can track and monitor basic health functions, providing additional ways to share health data. Subsequently, access to laboratory testing results has become a driving force behind the desire for the lay public to have greater control over their own healthcare information and not rely solely on their healthcare provider.

As of 2014, the Department of Health and Human Services (HHS) issued its final rule amending CLIA’88 and HIPAA privacy rules to allow patients to obtain their laboratory results directly from any CLIA-certified laboratory. Some states require the healthcare provider to send the results. Laboratories must release this information within 30 days of the patient’s request. The estimated cost for administering this program is $59 million over the first five years, which in part would be compensated for by charging patients nominal and reasonable fees for hard copy/mailing/labor costs. Implementation has been slow, with less than one-third of laboratories sharing direct access to clinical laboratory test results with patients, though that number is expected to grow quickly.

More recently, consumer-directed laboratory test ordering has provided another opportunity for greater control over one’s own healthcare. As of this writing, 37 states and the District of Columbia allow for individuals to order their own laboratory tests without a healthcare provider’s input. This opportunity has not gone unrecognized by retail outlets, such as Walmart, Sam’s Club, Safeway, Costco, Walgreens, Concentra, and Whole Foods, which have paved the way to offering one-stop health-care services including eye clinics, blood pressure testing, flu shots, and glucose and cholesterol POCT. Rite Aid Pharmacy has taken this a step further by introducing telemedicine kiosks in a limited number of stores to address minor health issues. These completely enclosed “health centers” offer basic services by connecting to a healthcare provider telephonically.

### Table 3. Weinstein Telepathology Classification System

<table>
<thead>
<tr>
<th>Medical Device</th>
<th>Reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Television</td>
<td>Recognition by third-party payers for payment of telepathology services.</td>
</tr>
<tr>
<td>Microscopy</td>
<td>The hardware and software used for telepathology are considered medical devices and are subject to FDA pre-market approval.</td>
</tr>
<tr>
<td>Dynamic/robotic</td>
<td>As with all personal health care information, patient confidentiality, informed consent, and diagnostic/consultative reports are to be subject to privacy regulations. This may also include information technology (IT) security concerns and access to patient information.</td>
</tr>
</tbody>
</table>

### Table 4. Current concerns with telepathology implementations

<table>
<thead>
<tr>
<th>Licensure</th>
<th>State regulatory requirements that affect interstate diagnosis vs. interstate consultation and physician licensing.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Credentialing</td>
<td>Establishing privileges to practice medicine within a specified facility.</td>
</tr>
<tr>
<td>Jurisdiction</td>
<td>Legal jurisdiction of any conflicts or medical improprieties.</td>
</tr>
<tr>
<td>Malpractice</td>
<td>Malpractice issues that must meet four requirements: 1) patient-physician relationship; 2) negligence; 3) cause of injury; 4) damage or direct harm to the patient.</td>
</tr>
<tr>
<td>Reimbursement</td>
<td>Recognition by third-party payers for payment of telepathology services.</td>
</tr>
<tr>
<td>Medical Device Regulation</td>
<td>The hardware and software used for telepathology are considered medical devices and are subject to FDA pre-market approval.</td>
</tr>
<tr>
<td>Privacy and Security</td>
<td>As with all personal health care information, patient confidentiality, informed consent, and diagnostic/consultative reports are to be subject to privacy regulations. This may also include information technology (IT) security concerns and access to patient information.</td>
</tr>
</tbody>
</table>

### Conclusions

With all this external technology available, it is not surprising that laboratory testing has extended beyond the traditional laboratory footprint that encompasses large pieces of testing equipment and highly trained personnel. Extra-laboratory testing has become a growing business, with major opportunities for hospital laboratory leaders and other entering health professionals to work together to improve patient access to healthcare.

Continuing advances in testing technology, miniaturization of equipment, improved connectivity, and overall easier access to healthcare services and information are on the rise. New concepts include “lab-in-a-briefcase,” where diagnostic testing using a microfluidic ELISA platform can be performed and transported easily to any location in the world. Another evolving technology is “lab-on-a-chip” (LoC), which promises a wide range of laboratory analytics using a combination of nanotechnology, biotechnology, and microelectronics. A single drop of blood can be placed on a chip that may be used in the analysis of genetic material and specific analytes, offering more complex testing than what POCT currently provides.

Smarthones already provide some basic health-monitoring functions. Using LoC technology in combination with smartphones is on the horizon. The synergy between these two technologies will use the advanced properties of communication, social networking, computation, and imaging in ways that will potentially provide quick and simple diagnostic information.

Laboratory services are now being offered beyond the traditional laboratory walls, using non-traditional methodologies in non-traditional locations. Continuing improvements in technology will create an even greater demand for extra-laboratory testing options, empowering individuals by enabling them to play a more active role in managing their healthcare.

### REFERENCES


Orchard Trellis: EHR Connectivity Software for POC Analyzers

With ACOs, PCMHs, and increased focus on patient-centered care, point-of-care testing (POCT) will increase as a way to effectively monitor patient health. But how will POC results get into the EHR? Because of low-volume, remote locations, and limited connectivity capabilities inherent to many POC devices, most POC test results are not being captured in the EHR, or are being entered manually—a time-consuming process subject to clerical errors. Orchard “Trellis” is a cost-effective orders and results management software program that serves as a simple “review, click, and go” bridge for electronics passing orders and results between remote, low-volume POC analyzers and your EHR.

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18. AACC Report: Direct-to-consumer test results should be more patient-friendly. Lab Medica International 2015;2011:

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Anthony Kurec, MS, H(ASCP)DLM, is Clinical Associate Professor, Emeritus, at SUNY Upstate Medical University in Syracuse, NY. Anthony is also a member of the MLO Editorial Advisory Board.

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Looming regulations and FDA oversight mean an uncertain reimbursement climate in 2016

By Rina Wolf

Laboratories continue to face numerous and unrelenting challenges driven by government and regulatory forces that leave many wondering how or if to move forward. Here are some of the major issues currently impacting the future of lab reimbursement.

Medicare reimbursement revision

On September 25, 2015, The Centers for Medicare & Medicaid Services (CMS) published a proposed rule to the Protecting Access to Medicare Act of 2014 (PAMA) that will substantially revise the Medicare reimbursement methodology for clinical diagnostic laboratory tests based on private sector payment rates to be phased in over a six-year period commencing in 2017.

Under these reforms, applicable clinical laboratories are to begin reporting private payer reimbursement rates along with associated test volumes for each test on the clinical laboratory fee schedule (CLFS) that the laboratory performs. The current definition of an applicable lab required to report includes independent and physician office labs that receive more than $50,000 per year in Medicare revenues. However, the current proposal would eliminate most hospital laboratories, which most agree would unfavorably skew the final rates and be less reflective of the true market.

New rates for the CLFS would be determined using a weighted median from this private payer data. CMS proposes to apply different reporting and payment requirements for advanced diagnostic laboratory tests (ADLTs). The maximum reduction allowed to current payment rates for years 2017 through 2019 is 10 percent of the previous year’s rate, and 15 percent of the previous year’s rate for years 2020 through 2022, to achieve parity with private payor rates.

Under PAMA, applicable laboratories may be subject to civil monetary penalties of up to $10,000 per day for each failure to report or reporting error by Current Procedural Terminology (CPT) code.

Under the proposed rule, applicable laboratories were required to collect private payer data from July 1, 2015, to December 31, 2015, and to report the information to CMS by March 31, 2016, with new rates going into effect on January 1, 2017, and continuing through 2022. However, following the commentary period that ended in November 2015, as of this writing CMS has yet to publish a final rule or announce an official delay on PAMA, leaving the industry with no confirmation on who is required to report, what they are required to report, and how to do it.

The FDA’s evolving role in LDTs

Laboratory-developed tests (LDTs), many of which are genetic and genomic-based, are essential to the continued development of personalized medicine and patient-centered care. As practitioners have increasingly adopted the use of diagnostic tests to guide patient treatment decisions, concerns about the management and safety of LDTs have emerged.

The Food and Drug Administration (FDA) has proposed enforcing what it believes is its right to regulate these tests. It plans to introduce new regulatory requirements to include registration, adverse event reporting, and 510K/premarket review over the course of the next decade under a risk-based framework consistent with the FDA’s approach for medical devices. The FDA has historically exercised “enforcement discretion” over LDTs, and oversight has been through CMS under the Clinical Laboratory Improvement Amendments (CLIA).

The FDA issued a draft guidance last year and has announced its intention to issue a finalized guidance sometime in 2016. The Association of Molecular Pathology and others have challenged the FDA regarding examples it provided in a recent report outlining evidence supporting FDA oversight of LDTs. The American Medical Association, the American Clinical Laboratory Association, and numerous industry professionals and organizations support modernizing the oversight framework for LDTs and services through reform of the CLIA versus involvement from the FDA.

Many believe that any increased oversight must be done through rule making, rather than guidance, and Congress has conducted hearings on this issue. The FDA estimates that half of the LDTs on the market would be classified as low-risk under the agency’s proposed framework. The FDA’s initial focus will be on reviewing LDTs with the same intended use as an FDA-approved or cleared companion diagnostic or Class III medical device, and certain LDTs for determining the safety or efficacy of blood or blood products.

Commercial payor challenges

On the commercial payor side, documentation is becoming more and more critical, and front-end requests for additional information to process claims are increasing. Back-end medical necessity audits are also increasing, with recoupment requests based on medical necessity being seen as much as 12 to 18 months after payments are remitted.

Five of the most common commercial payor claim issues include:

1. Services billed with no medical necessity documentation to support the claim;
2. Documentation for a service by a health professional deemed insufficient;
3. Services provided to a patient deemed experimental or investigational;
4. Claims for services coded incorrectly and/or claims that include NOC (Not Otherwise Classified) codes; and
5. Patient shares of cost not handled in a compliant manner.

While much progress has been made in molecular diagnostics and genetic testing, lack of consistent payor policy and adequate reimbursement is impeding availability of these innovative tests. Payors are increasingly reimbursing only for tests that they believe can clearly demonstrate “clinical utility” and improved outcomes.

While there are still considerable upfront investments in studies to demonstrate the clinical value of genetic tests, the continually raising bar is occurring during a time of decreasing reimbursement and pricing turmoil in the laboratory industry. This is creating an environment of unrest and uncertainty just as precision medicine initiatives are gaining national attention.

As addressed in the Personalized Medicine Coalition’s report, “The Future of Coverage and Payment for Personalized Medicine Diagnostics” (http://www.personalizedmedicinecoalition.org/Userfiles/PCCorporatefiles/pmc_the_future_coverage_payment_personalized_medicine_diagnostics.pdf), it is crucial that payor reimbursement be adequate enough to allow innovators and investors to recover the cost of development, and continue to develop a pipeline of innovative tests requiring substantial risk-based clinical research.

Importance of financial management systems

These new regulations, and particularly PAMA, will impose a significant burden on clinical laboratories, requiring an investment in
resources to track, collect, and report private payor payment rates and implement the necessary financial management and compliance systems. Labs should take advantage of every opportunity to ensure that they will be able to aggregate and report their data now, while the final rules are pending.

It will be imperative to capture the necessary reporting information either through a billing system that properly accounts for allowable costs on paid claims, or directly from the electronic remittance advice. Lab leaders should review 2015 data to ensure accuracy of payments prior to reporting. To comply with deadlines, systems must routinely capture and retain historical payment detail and flag payments inconsistent with contract provisions. Data points will need to be refined when final instructions are released.

At a minimum, systems must be able to capture: 1) date of service; 2) date paid; 3) payor type; 4) number of tests for each procedure code; 5) amount allowed and paid by insurer plus patient share of cost; 6) contractual rates, including volume and other discounts; and 7) aggregate data in timely buckets (e.g., 7/1/15–12/31/15).

To support the increased specificity and comprehensiveness of the ICD-10 code set, it will be critical for providers to capture detailed documentation in patient charts in order to avoid potential claims denials and the risk of fines from audits going forward.

Laboratories should continue to monitor updates and guidance from CMS on reporting details while preparing for data gathering and implementation, and watch for final rules from the FDA this year.

**Bundled payments**

Medicare continues to press forward with alternative reimbursement models such as accountable care and bundled payments, with plans to move 30 percent of non-managed care spending into contracts by the end of 2016, and 50 percent by 2018. It was recently announced that the 30 percent target benchmark has already been reached for 2016. CMS also recently introduced its Oncology Care Model, which incentivizes cancer providers to reduce hospital and pharmacy costs.

Some healthcare institutions are beginning to develop their own bundled programs with payors, which requires a very detailed understanding of the cost drivers for particular diagnoses and episodes of care. While there is much discussion about the rising costs of pharmaceuticals and drug waste, estimated to be as much as 50 percent, little voice is being given thus far to the role that lab diagnostics can play in alleviating this waste.

As providers continue to move toward alternative payment models with the dual goal of reducing costs and improving patient outcomes through patient-centered and personalized, genetically-guided care, lab diagnostics will become increasingly critical to these initiatives as a means to manage downstream costs and ensure the best possible treatment and patient-specific outcomes.

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PAMA and bundled payments force labs to feel a reimbursement shift

By Kim Futrell, MT(ASCP)

Laboratories are beginning to feel the effects of healthcare’s shift from fee-for-service (FFS) to value-based reimbursement systems. New payment models are focused on patient outcomes and eliminating the misaligned FFS incentives that can lead to overutilization. Healthcare’s new mission is to simultaneously reduce costs and improve care. Labs are a part of this goal.

Labs are a crucial part of diagnostics in the overall healthcare picture. Traditionally, labs have been revenue centers, but in the new healthcare model, lab testing will be considered an expense that is part of the cost of delivering care. We are beginning to see this unfold in new reimbursement models, such as bundled payments. Another looming element of this transition is the H.R. 4302—Protecting Access to Medicare Act of 2014 (PAMA), which labs have been awaiting with trepidation because it signals the beginning of big changes in reimbursement.

Even before PAMA, in 2014 the Centers for Medicare & Medicaid Services (CMS) began bundling payments for hospital outpatient visits. These bundled payments include lab testing, with the exception of molecular pathology tests. Tests are reimbursed according to the Hospital Outpatient Prospective Payment System (OPPS), and are billed by the hospital rather than the lab. Of course, when testing takes place outside of the bundled cases, reimbursements still depend on the Clinical Laboratory Fee Schedule (CLFS). This puts the onus on hospitals to develop budgets within this complex framework.

CMS has also implemented the Bundled Payments for Care Improvement (BPCI) initiative, which bundles payments across a continuum of care. The idea is to incentivize better care coordination. The BPCI initiative was developed by the CMS Medicaid Innovation, which was put in place by the Affordable Care Act to begin to pilot some of the value-based payment models. As of January of this year, the BPCI initiative has 1,574 participants.

On the heels of these bundled payment initiatives rests PAMA. Many labs took a proactive stance by voicing their opinions to the CMS regarding the impact of PAMA and the concept of a market-based approach to fee setting are good concepts, it is widely agreed upon by the laboratory industry that the lack of a final ruling will likely delay the January 2017 start date to 2018.

The biggest controversy, which led to 1,300 comments, developed after the law was refined and only certain applicable labs were designated as being required to submit their payer rates. Only independent labs and physician office labs (POLs) that receive more than $50,000 per year from Medicare were required to report payer reimbursements, while hospital labs and smaller labs (< $50,000 from Medicare) were considered exempt. Most hospital labs fell under the exemption as well because the law states that 50 percent of the entity’s total Medicare revenue must come from the Physician Fee Schedule (FFS) or the CLFS. This means that most large hospitals, about 50 percent of independent labs, and 90 percent of POLs were exempt. In the original wording, about half of the data used to create the new fee schedule would come from the largest five laboratories (mainly LabCorp and Quest), who typically have largely discounted pricing.

While we do not know for certain, industry experts report that CMS is likely to respond to the outpouring of comments and make changes to the definition of an applicable lab to include hospital laboratories in the calculations so that the new payment rates will more accurately reflect the market. While price transparency and the concept of a market-based approach to fee setting are good concepts, it is widely agreed upon by the laboratory industry that the methodology the CMS originally planned to use to set future CLFS pricing was severely flawed.

PAMA and the future

Many labs are already feeling the transition in healthcare from FFS payments to value-based payments and are transitioning from profit centers to cost centers. The $2.5 billion cuts in lab reimbursement spell a significant change in lab payments. Not only will many labs have to adjust to reporting volumes and reimbursements; they’ll also need to prepare for the long-term reimbursement changes as they see less revenue for the same volume of tests. While we do not know exactly what the future holds, it is time for lab leaders to think differently, plan ahead, and make sure they understand PAMA’s full financial impact on their laboratory.

In order to face legislative changes like PAMA, laboratory leaders must refocus their efforts and find additional ways to demonstrate their value. The laboratory is central in supporting disease management and treatment, so it certainly will not go away. Rather, a shift in testing volumes, menus, and locations, and an expansion of the laboratory’s role are predicted for the future. While the lab is not the problem in rising healthcare costs, it can be a huge part of the solution.
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Cost-effectiveness considerations with molecular diagnostics in oncology

By John Brunstein, PhD

I t is an unfortunate reality that costs and expected benefits of any medical process, including diagnostics, need to be considered in determining the appropriateness of performing the process. The need for this consideration is equally relevant regardless of whether it is done in the context of a user-pay system (where the patient or patient needs to make a value judgement) or a centralized payer system, where difficult decisions must be made by administrators to attain maximal benefit for all covered people with a finite pool of funds to work from. Either case demands responsible, informed decision-making based on the best available data for the associated costs and benefits.

Frequently, reports of a novel MDx method will provide detailed information on the analytical performance of the test (sensitivity, specificity), turnaround times, throughput, and other “hard” metrics of performance. Costs, however, are often dealt with more vaguely; or, where firm per-test cost values are provided, close review suggests the reported costs may only be relevant in the narrow situation as applied at a specific site, with questionable generalizability. Detailed, in depth analysis not just of the direct costs of a test method but also of its indirect costs (or cost savings) in terms of such factors as reduced length of hospital stay, reduced risk of nosocomial infections, and the like are rare.

This common weakness is not a reflection on study authors, who are aware of and generally at least allude to these issues; rather, it reflects the complexities involved in addressing MDx cost-effectiveness in a truly rigorous and defensible fashion. In this month’s Primer, we’ll briefly consider what some of these complexities are and how they can possibly be addressed; then we’ll consider, for the narrower subset of oncology-related MDx, a representative handful of publications that have attempted to shed light on this issue. Understanding their assumptions—implicit and explicit—can help in determining goodness of fit of their conclusions to other situations.

Factors to consider

With that context in mind, let’s consider some of the inherent complexities in assigning costs and values to an MDx test in an oncology setting.

1. What is the probability of the test returning an “informative” result? Consider, for example, an oncogene panel, of the sort discussed in last month’s Primer installment. (Brunstein J. Oncogene panels: a window into the individuality of cancers. MLO 2015;48(4):18-20.) If a patient sample is tested by MDx panel and the results don’t add any actionable information (i.e., information that dictates a change in treatment strategy) over what was indicated by classical identification and classification means, then it could be argued that the test cost is wasted. If zero is the value assigned to this type of result, then a first step in assigning net value to the test is to know what fraction of samples will yield actionable information from the test. For example, if 20 percent of cases yield actionable results, then 80 percent do not and the immediate “value” of the test is only one-fifth of its possible maximum. Knowing this fraction with any certainty requires significant sample population sizes, but the knowledge can probably be gleaned from pooled multisite data if uniform population inclusion criteria are applied.

2. The term “informative” itself, as used in Point 1, is debatable and may not be applied equally in all settings. It may well be argued that even a non-actionable test result has value, in assuring the clinician that alternative treatment strategies are not warranted. If this line of reasoning is taken, then some partial value of a non-informative test result, as compared to an informative test result, must be applied.

3. Individual cancers may change molecular characteristics over the course of disease progression, particularly if approaches such as chemotherapies apply selective pressures to the cancer cells. Detecting this change may be useful in modifying therapy, but the concept of detecting change implies one or more prior “baseline” measurements for comparison. If this sort of time course progression data is desirable, then, similarly to Point 2, all measurements, regardless of “actionability” of result, have some intrinsic value.

4. Localized costs of assay performance can be highly variable. Particularly if a test is not a complete “sample to answer” system and relies on discrete steps or devices for nucleic acid preparation, molecular manipulation such as qPCR, and detection/analysis of results, then there exists a possibility that the laboratory may already have or more of the required devices being used for other test functions. This, of course, amortizes the infrastructure cost over several test streams, making it cheaper per test. (This would also impact throughput considerations, our next point.)

5. Test throughput and scale can dramatically alter the per-test performance cost. Higher throughputs (utilizing instrumentation near capacity) and batching of specimens to optimize use of laboratorian time both can act to significantly reduce direct per-test cost. Reference 1 is a specific study of this, and suggests in the study setting (Brazil) that a 30 percent utilization rate for various MDx tests resulted in cost-per-test increased of between 169 percent and 412 percent over at-capacity costs, depending on test methodology.

Insights from studies

Now that we can appreciate what some of the challenges are in assigning both cost and value to a given MDx test, and in taking cost/value data from one location to another, let’s consider a few representative published studies from the oncology field.

Our first example relates to thyroid cancers. Najafzadeh and coauthors2 examined adding MDx to fine needle aspiration biopsies (FNAB). The authors suggest that FNAB with classical methods alone may yield indeterminate results in up to 25 percent of cases, and propose a model assuming 95 percent sensitivity and specificity for the MDx test. Results of this model suggested the addition of MDx methods gained 0.046 quality adjusted life years (QALY), with a per-patient cost savings of $1,087 (assuming the MDx test cost nothing to perform). While this might at first glance seem an odd way to present their findings, it’s actually perhaps the clearest way to allow another
site to apply the results to their situation by directly inserting local cost-of-test estimates. The authors conclude that if the test costs are less than $1,087, then there is both a net cost savings and a gain in QALY. (Recall that one QALY equals one year at “perfect” health; a year at less than perfect health, then, equates to something under one QALY, by whatever fractional decrease is associated with disease states.)

The authors provide highly detailed descriptions of their model assumptions as well as clear graphic representations of the impact of different levels of MDx sensitivity and specificity. Sensitivity more than specificity is shown to impact the sensitivity and specificity. Sensitivity more than specificity is shown to impact the value outcomes.

Our second example is by Hagen and coauthors3 and focuses on MDx in the context of HNPPC (hereditary non-polyposis colorectal cancer). This is an interesting analysis of four different testing models with and without MDx components. While the body text is in German, the English language abstract indicates cost per patient life-year gained, with an optimal tiered methodology (application of MDx only in suggestive family history contexts) showing roughly 3x better cost-effectiveness of the least effective approach of blind population MDx screening. While these are the rank order results one would expect a priori, the magnitude of the value is instructive. As the authors point out, however, decreases in assay cost will start to make blind screening more attractive. This highlights the importance of considering publication year of such studies, as the intervening eight years have made MDx methods significantly cheaper, with corresponding impacts on study conclusions.

Our third example, a study by Djalalov and coworkers4 in the context of NSCLC (non-small cell lung cancer), highlights additional complexities in making cost-benefit analyses for MDx when it is applied as a companion diagnostic. In this study, subsequent to a number of defined assumptions, the authors report that MDx (specifically, EML4-ALK fusion testing by FISH) did improve patient outcomes by an average of 0.011 QALY, with a relatively minimal cost differential of an additional $2,725 per patient—of which only a very modest $60 is directly attributable to the MDx assay component. The overall interpretation of cost-benefit in this situation, however, changes dramatically when the cost of the companion drug (crizotinib) is included. The authors’ final conclusion, in fact, is that testing in this case is “not likely to be considered cost-effective,” but, also tellingly, “the model was not sensitive to the costs of molecular testing.” The generalizable message from this example is that where companion diagnostic MDx is considered, these assays are by nature tightly coupled to the cost of the specific associated drug.

In conclusion, if your facility is considering introduction of an MDx method in an oncology setting, and wants to address cost-effectiveness issues in determining whether this is a good use of resources, the preceding provides some ideas on how to most logically go about doing so. While identification of relevant publications is a critical first step, assessing what assumptions to adjust in applying the conclusions to another location is far from trivial but not impossible. As more sites add MDx protocols to their oncology diagnostics workflows, we should appreciate those that publish or otherwise share their cost/benefit results; doing so is of great help to other sites in tackling the challenges of good economic stewardship.

As a final note, readers interested in a more in-depth discussion of how to formalize assessment of clinical utility for MDx assays may be interested in the final reference provided,5 which deals specifically with this issue.

REFERENCES
Government addresses opioid addiction crisis

By MLO staff

It has been bubbling beneath the surface of widespread public awareness for years—though it certainly was well known to laboratorians and other professionals involved in the healthcare delivery system all along—but this past winter it emerged as a major national news story. It was widely discussed by presidential candidates in both parties, particularly when they were campaigning in the New Hampshire primaries, and it made headlines nationwide. “It,” of course, is the crisis in opioid addiction that plagues not only hard-hit New England but all regions of the United States.

March was something of a watershed month for the issue. Legislation designed to reduce opioid overdose was introduced in the U.S. Senate. Two federal agencies—the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA)—issued new directives on the crisis. And, in a major speech, President Obama drew attention to the crisis and suggested new approaches.

On March 11, Senator Ed Markey (D-MA) introduced S. 707: Opioid Overdose Reduction Act of 2015. Its full title is “A bill to provide certain protections from civil liability with respect to the emergency administration of opioid overdose drugs.” According to the nonpartisan Congressional Research Service, “this bill exempts individuals from liability for harm caused by the emergency administration of an opioid overdose drug under certain circumstances.” The bill has five cosponsors: Sens. Kelly Ayotte (R-NH), Timothy Kaine (D-VA), Patrick Toomey (R-PA), Elizabeth Warren (D-MA), and Richard Blumenthal (D-CT). It was assigned to the Senate Judiciary Committee, which will consider it before possibly sending it on to the Senate as a whole.

CDC guideline

On March 15, the CDC released the “CDC Guideline for Prescribing Opioids for Chronic Pain, United States, 2016.” The document was designed to help primary care providers ensure the safest and most effective treatment for their patients. The guideline provides recommendations on the use of opioids in treating chronic pain (that is, pain lasting longer than three months or past the time of normal tissue healing).

Among the 12 recommendations in the guideline, the CDC highlights three key principles to improving patient care:

- Non-opioid therapy is preferred for chronic pain outside of active cancer, palliative, and end-of-life care.
- When opioids are used, the lowest possible effective dosage should be prescribed to reduce risks of opioid use disorder and overdose.
- Providers should always exercise caution when prescribing opioids and monitor all patients closely.

“Doctors want to help patients in pain and are worried about opioid misuse and addiction,” said Debra Houry, MD, MPH, director of CDC’s National Center for Injury Prevention and Control. “This guideline will help equip them with the knowledge and guidance needed to talk with their patients about how to manage pain in the safest, most effective manner.”

FDA warnings

On March 22, the FDA announced enhanced warnings for immediate-release (IR) opioid pain medications and that it is requiring class-wide safety labeling changes for IR opioid pain medications. Among the changes are a new boxed warning about the serious risks of misuse, abuse, addiction, overdose, and death.

The FDA is also requiring several additional safety labeling changes across all prescription opioid products to include additional information on the risk of these medications. This is part of the agency’s overall effort to help inform prescribers about the importance of balancing the serious risks of opioids with their role in managing pain.

As part of the boxed warning on IR opioid analgesics, the FDA now requires a precaution that chronic maternal use of opioids during pregnancy can result in neonatal opioid withdrawal syndrome (NOWS), which may be life-threatening if not recognized and treated using protocols developed by neonatology experts. NOWS may occur in a newborn exposed to opioid drugs for a prolonged period while in utero.

Presidential initiatives

On March 29, at the National Rx Drug Abuse & Heroin Summit in Atlanta, Georgia, President Obama announced that the Department of Health and Human Services (HHS) is issuing a proposed rule to increase the current patient limit for qualified physicians who prescribe buprenorphine to treat opioid use disorders from 100 to 200 patients, with the goal of expanding access to this evidence-based treatment while preventing diversion. HHS is also finalizing a rule to strengthen access to mental health and substance use services for people enrolled in Medicaid and Children’s Health Insurance Program (CHIP) plans by requiring that these benefits be offered at parity, meaning that they be comparable to medical and surgical benefits.

In addition, the Substance Abuse and Mental Health Services Administration (SAMHSA) is releasing a new $11 million funding opportunity to states to purchase and distribute the opioid overdose reversal drug naloxone and train first responders and others on its use, along with other overdose prevention strategies. Also, SAMHSA is releasing a new $11 million funding opportunity for up to 11 states to expand their medication-assisted treatment services, and distributing 10,000 pocket guides for clinicians that include a checklist for prescribing medication for opioid use disorder treatment.

The opioid addiction crisis has Washington’s attention. Will the momentum to combat the crisis continue to build?
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Increasing lab excellence with three principles of peak performance

By Jeff Osborne

Health systems are undergoing a major transformation. They are being evaluated and inspected to ensure they’re running at peak performance. Weak links are being identified, and in today’s competitive healthcare industry weak links in a growing value-based healthcare environment are considered unacceptable. These transformative times make speed more important than ever for clinical labs—some of which run well below capacity and efficiency—to maximize performance and increase their value.

Typically the lab represents at most five percent of a health system’s costs, but it is undeniably a critical link in the delivery of patient care, with 80 percent or more of each patient’s medical record flowing through the lab. A lab that’s running at peak performance—improving the continuum of patient care while showing increased efficiency—can offer a health system a much-needed competitive edge as care delivery options continue to expand in most communities.

To improve health system service and quality through lab operations, health systems must retain, optimize, and evolve their labs. This means keeping the lab in-house, rather than divesting—and investing—in processes and technologies that drive higher quality, better service, and demonstrable value. Broadly, this can be achieved by employing three principles of lab excellence: operate with speed, operate with accuracy, and operate with efficiency.

Sounds like a no-brainer, right? The trick is finding a balance among these practices. They must all work together in harmony, and none can be compromised, or the overall results will suffer greatly. As more than 3.5 billion tests are annually processed through health system-based clinical labs, not finding that balance is at the core when labs run into problems, and, via a domino effect, threatens the health system’s capacity and efficiency.

**Speed**

Data-driven operational intelligence and insights help speed real-time decision making in the clinical lab and foster best practices at their point of need. For example, visibility and transparency into the processing of a specimen from collection to result is critical. Ensuring everything from accurate specimen labeling, to reliable logistics, to an optimized process in the lab ultimately enables turnaround time. From the clinician’s perspective, this is what enables him or her to deliver a patient’s diagnosis and begin care faster.

In many cases, in-house testing services enable speed to decision, through support of broad test menus which reduce send-outs. When tests are sent to external labs, additional points of failure outside the control of the health system are introduced, which can result in delays in getting results to doctors.

**Accuracy**

Of course, accuracy is crucial to patient care, and inaccurate lab results are likely to be detrimental to a patient and have major cost and efficiency implications for a health system. An error in a test order entry can immediately render everything subsequent in the testing process—specimen collection, processing, resulting, and reporting—meaningless if not corrected. Each of these stages depends on the accuracy of the preceding one. A lab’s accuracy is the foundation on which speed and efficiency can be improved, not the other way around.

The right tests must be performed and run quickly, and the lab must have strategies in place for test menu optimization and utilization, as they are key drivers of lab efficiency. Continual monitoring of lab tests and test orders is vital to achieve measurable improvements in efficiency. All areas of the lab, from the bench to supplies and test menu, must be examined carefully to uncover inefficiencies.

Efficiency

A comprehensive approach to people, process, and technology in the lab that optimizes and modernizes operations helps to achieve measurable improvements in efficiency. All areas of the lab, from the bench to supplies and test menu, must be examined carefully to uncover inefficiencies.

For example, lab test menus continue to evolve and expand as testing technologies advance, challenging health systems to respond and adapt accordingly. A lab must have strategies in place for test menu optimization and utilization, as they are key drivers of lab efficiency. Continual monitoring of lab tests and test orders is vital to achieve measurable improvements in efficiency. All areas of the lab, from the bench to supplies and test menu, must be examined carefully to uncover inefficiencies.

Efficiency must work in tandem with speed and accuracy. The right tests must be performed and run quickly, and the lab must provide accurate results.

**Conclusion**

So, how can we tell we’re improving on all fronts—speed, accuracy, and efficiency? Incorporating performance standards and benchmarks that gauge lab quality and service is an important starting point for measuring a lab’s effectiveness beyond the dollars. Then, understanding the cost stack will provide the greatest insight into opportunities and focus.

The lab is a critical hub of the patient care continuum, yet it is an aspect of the healthcare system that is often overlooked. By leveraging the best approaches to performance management, the lab can save health systems a significant amount of money while accelerating lab performance to the highest standards of operational excellence. This is the best way to ensure the unity of speed, accuracy, and efficiency—strengthening a key link in the chain of care that saves a health system money, while providing an immense benefit to communities it serves.

Jeff Osborne serves as Chief Executive Officer of Accumen, a San Diego-based healthcare transformation company.
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What’s the buzz in antibiotic stewardship?

One aspect of initiatives to aid antibiotic stewardship is to increase the development and use of rapid molecular diagnostic tests for identifying infections and also characterizing the presence of any resistant bacteria. Within the area of sexually transmitted infections (STIs), Mycoplasma genitalium (MG) can serve to illustrate the problems and promise of molecular diagnostic technology with regard to antibiotic resistance and stewardship.

MG is an STI that can cause symptoms including urethritis, cervicitis, and pelvic inflammatory disease. It has been largely underreported due to the difficulty of isolating and cultivating the organism, as it can take months to do so. This means that molecular testing (qPCR, TMA) is the only practical method of reliably identifying MG.

Identification of the bacterium alone is no longer sufficient to guide effective treatment due to increasing macrolide resistance. However, recent advances in multiplexed molecular techniques are improving the sensitivity and selectivity of qPCR enough that detection of the organism can be performed at the same time as detection of resistant mutations. There is now a multiplexed qPCR test for MG that can target the five mutations involved in azithromycin resistance in the 23S rRNA gene. Patients with detectable mutations at A2058 or A2059, who may fail azithromycin treatment, can be directed faster to a second-line treatment. Timely detection of antibiotic resistance will enable the development of better algorithms for the treatment of MG infection and promote responsible stewardship of antibiotics.

—Elisa Mokany, PhD
Vice President, Research and Development
SpeeDx Pty Ltd.
Provider of the M. genitalium ResistancePlus Kit

Antibiotic stewardship is one of the most critical components of reducing the incidence of superbugs across the entire healthcare continuum of care. Given the significant mortality and morbidity associated with antibiotic resistance, serious changes are necessary—most significantly, collaboration and communication across the entire clinical care team. The United States Centers for Disease Control and Prevention (CDC) has released new core elements of an antibiotic stewardship program that guide healthcare professionals and facilities in the proper steps to reduce resistance and improve antibiotic prescribing practices. Many antibiotics are also prescribed in outpatient settings, such as urgent/primary care, ambulatory surgery centers, and dental practices. The diversity of prescribers and healthcare settings requires collaboration across disciplines to include physicians, nurse practitioners, physician assistants, pharmacists, patients, and infectious disease professionals. Antibiotics are one of the most precious resources that we have in our medical arsenals and, as such, they must be treated with the utmost respect and diligence when prescribing.

Vice President of Clinical Affairs
PDI, Inc.
Provider of Prevantics, a line of vascular infection prevention solutions

Antibiotics continue to be powerful weapons to fight infections, but inappropriate use makes the treatment of microbial infections increasingly challenging. Successful antibiotic stewardship can help mitigate the development of antimicrobial resistance and lead to better outcomes. Our organization supports The Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance, which was signed by 85 companies at the World Economic Forum in January 2016. It represents a commitment to invest in a range of innovative antibiotics, vaccines, alternative technologies, and diagnostics for resistant infections.

We believe it will require a nationally coordinated effort among healthcare providers and partners to develop an effective antibiotic stewardship program. The lab will play a critical role, being uniquely positioned to provide data critical to bring key groups together, including patients, providers, policy makers, regulators, payers, and manufacturers.

Where do manufacturers fit into this effort? One area is the development of state-of-the-art testing with high medical value. Some examples include procalcitonin, molecular markers of resistance, and rapid real-time polymerase chain reaction (PCR) testing at the point of care that de users highly accurate results for flu, strep, respiratory syncytial virus (RSV), and more while the patient is still in the office. Providing greater certainty about whether antibiotics are needed and, if they are, ensuring the right antibiotic is delivered will lead to more appropriate antibiotic use and potentially slow the development of antimicrobial resistance.

—Alan Wright, MD, MPH
Chief Medical Officer
Roche Diagnostics
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Using laboratory analytics to manage quality assurance and reduce errors in the laboratory

By Thomas Joseph, MBA, MT(ASCP), Tim Bickley, MBA, MT(ASCP), CPHIMS, and Kristina Ziagura, BA (Hons)

Many laboratories today are still measuring their data manually, a time-consuming process easily subject to human error. Laboratory managers often struggle to obtain timely metrics, as laboratory information systems provide only limited management reports, and often the metrics received are a month old and thus of limited value in improving quality and reducing errors. As a result, laboratories are increasingly turning to laboratory analytics/business intelligence as a solution to these challenges for their data mining needs. A lab analytics system, however, processes a wealth of laboratory data in seconds, not only ensuring that laboratory management has more time to focus on other tasks, but also providing the means for managers and supervisors to monitor and maintain higher standards of quality. Laboratory analytics are proving to be a beneficial tool in ensuring that large amounts of data can be analyzed and presented in meaningful insights and analytics are proving to be a beneficial tool in ensuring that large amounts of data can be analyzed and presented in meaningful insights. With an effective laboratory analytics system in place, managers can easily view all specimens for hemolysis and QNS rates and take necessary corrective action. The laboratory business intelligence/analytics system provides insight into where a hemolyzed specimen came from, what clinic, which ward, and even the nurse or phlebotomist who drew the specimen. By performing hemolysis and QNS audits to identify patient locations and collection staff members with the highest number and proportion of occurrences, laboratory management can take action to identify which staff members require retraining to improve quality. While it may not be possible to retrain everyone for all quality problems, it is possible to identify where most QA issues originate, providing management with the insight to focus retraining for the greatest effect. Defective test results can pose significant financial implications to the health system when lab tests are misinterpreted and misused. An analytics system can generate a comparison of test results that allows lab management to see definitive analytic results to quickly answer questions about instrument performance over time. With data available daily, management can ensure that a performance problem never goes undetected and that quality managers and lab directors are kept aware of the source of laboratory problems.

Inappropriate test utilization

The consequences of unnecessary testing for patient care can include latent anemia, time spent on insignificant abnormal results, incorrect diagnoses, and longer length of stay. Various strategies can be employed to reduce overutilization of testing, including requisition redesign, hard and soft stops in the computerized physician order entry (CPOE), test formularies, education, and audits. No one strategy is sufficient, however, and an auditing capability plays a critical role. With the data from a real-time analytics system, laboratory managers will know the most important areas of unnecessary testing so rules can be developed for the EMR, providing soft stop guidance to physicians. A real-time analytics system also identifies common categories of unnecessary testing. These common categories range from screening/reflexing/normalcy, such as ordering an FT4 when the TSH is normal, to redundant testing such as CKMB ordered in the ER, together, to excessive frequency of repeat testing (e.g., HbA1c should not be ordered more than once every 21 days). From this, laboratory management can identify benchmarks based on tests per inpatient admission, length of stay, and length of stay vs. tests per admission. Using this data and benchmarks, laboratories can develop strategies, and measures can be taken to limit obsolete tests, limit esoteric tests, and minimize bundles of tests.

Shifts and trends in analyzer results

A laboratory analytics system can assist in reducing lab errors by providing a means to monitor Quality Control (QC) and assist in identifying shifts and trends in analyzer results. For example, analysis using either CVR (Coefficient of Variation Ratio) and SDI (Standard Deviation Index) or a standard analytical null hypothesis theory provides two different approaches to quickly determine if any instruments are reporting differently than others. An analytics system’s QC system also supports laboratories implementing the CMS/CLIA prescribed Individualized Quality Control Plan (IQCP) based on CLSI EP23 guidelines. Best practices are identified using sigma ratings of instruments for each analyte to determine the appropriate number and frequency of QC samples to run. With real-time assessment of instrument performance, laboratories can know immediately if an instrument problem occurs and if their instruments are not reporting in line with other analyzers. Access to this type of analytics ensures that QC practices are properly implemented so laboratories can avoid repeat testing, unnecessary follow-up testing, and misdiagnoses.

Conclusion

With data readily available, laboratory management can view all of their test results and not only identify errors but also retrace their root cause, delivering actionable information to monitor and improve QA processes. Subsequently, this improves the quality of laboratory measurements and enables management to verify that all processes are operating to set standards of performance. Daily management with a laboratory analytics system and an engaged leadership team are essential components in monitoring quality assurance and reducing lab errors. When laboratory data is managed daily, dramatic improvements can be made and errors can be eliminated, resulting in improved specimen quality, utilization, instrument/analyte performance, and patient safety.

Thomas Joseph, MBA, MT(ASCP), serves as President and CEO of Visiun, Inc., provider of the Performance Insight lab analytics system. Tim Bickley, MBA, MT(ASCP), CPHIMS, serves as Director of Sales for Visiun, Inc., and Kristina Ziagura, BA (Hons), serves as Marketing Manager for Visiun, Inc.
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Assayed quality control material

AUDIT MicroControls Linearity LQ Special Diabetes is intended to simulate human patient serum samples for the purpose of determining linearity, calibration verification, and verification of reportable range. It is a ready-to-use liquid product, consisting of five levels that demonstrate a linear relationship to each other when assayed for C-peptide, fructosamine, and insulin. This product has an open vial stability of 7 days when stored at 2-8°C. It also provides Auditor QC, a free on-line, real time data reduction program that offers Levey-Jennings charts and peer group analysis for daily quality control product users, as well as linearity graphs and peer group analysis. Report results are given immediately in an "Inspector friendly format" and stored on the Auditor QC website for future reference. AUDIT MicroControls, www.rsleads.com/605ml-152

Hemoglobin A1c testing system

Bio-Rad’s D-100 Hemoglobin A1c testing system is a combination of high-performance liquid chromatography (HPLC) technology and innovative solutions to maximize workflow efficiency for laboratories that demand an accurate HbA1c result rapidly and effortlessly. The D-100 is fully automated and designed to meet the needs of medium- and high-volume clinical laboratories, for greater throughput, high quality results, and simplified workflow for A1c testing. The system delivers rapid results without sacrificing the ability to detect hemoglobin variants, which can interfere with interpretation of test results. BioRad, www.rsleads.com/605ml-153

Automated hemoglobin A1c analyzer

EKF Diagnostics’ Quo-Test analyzer has been designed for easy and reliable HbA1c measurement for the monitoring and management of diabetes in point-of-care settings such as diabetes clinics and doctors’ offices. The Quo-Test HbA1c is a fully automated hemoglobin A1c analyzer that uses patented boronate fluorescence quenching technology to measure glycated hemoglobin from a 4 μl sample taken from a finger prick or venous whole blood. Sample results are available within four minutes and are reported in IFCC and DCCT standard units. Quo-Test is unaffected by most hemoglobin variants. EKF Diagnostics, www.rsleads.com/605ml-154

Rare blood control for glucose meters

Eurotrol’s CueSeeGlucose is a real blood control for validating precision and accuracy of glucose meters. Its real blood matrix makes it highly commutable and compatible with all glucose devices with minimal matrix effects. Low imprecision makes it comparable to human blood. The ACU-Drop II packaging form is a dual-chambered device keeping the fractions separated, preventing reactions between components of the desired matrix. Push a button to combine fractions, mix, and the sample is ready to use from the built-in dropper bottle or by attaching a syringe. Use for QC, calibration verification, proficiency testing, competency assessment, method validations, and lot comparisons. Eurotrol, www.rsleads.com/605ml-155

Zinc autoantibody ELISA assay kit

The KRONUS Zinc Transporter 8 Autoantibody [ZnT8Ab] ELISA Assay Kit is for the semi-quantitative determination of autoantibodies to zinc transporter 8 (ZnT8) in human serum, and may be useful as an aid in the diagnosis of type 1 diabetes mellitus (autoimmune mediated diabetes). Autoantibodies to ZnT8 (ZnT8Ab) have been detected in approximately 60 percent to 80 percent of patients at T1D onset and are more prevalent in children than in adults. Autoantibodies to ZnT8 have been found in T1D patients previously classified as autoantibody-negative, and when ZnT8Ab measurement is combined with the measurement of GADAb, IA-2Ab and IAA, the rate of detection of autoimmunity at diagnosis may increase. KRONUS, www.rsleads.com/605ml-156

continued on page 42
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...what, exactly, are you measuring?

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Automated adiponectin assay

Body Mass Index (BMI) has been used to measure health for years; however, debates surrounding its accuracy highlight that muscle, age, gender, or fitness are not accounted for. Patients with a “healthy” BMI could still be at risk of developing heart diseases, cancers, and type 2 diabetes mellitus (T2DM).

Research suggests that abdominal visceral fat (AVF) has a stronger link to these chronic diseases, perhaps even predicting T2DM. The analyte adiponectin is inversely correlated with AVF, and allows a more accurate measurement of risk. The Randox automated adiponectin assay can be used on most biochemistry analyzers. Randox, www.rsleads.com/605ml-157

HbA1c control

Streck’s A1c-Cellular is an HbA1c control with intact red blood cells. It tests the entire HbA1c procedure, including the lysing of the red blood cells—a step omitted with other controls. This important step ensures the instrument, reagents, and technologist’s process are accurate. A1c-Cellular is ready-to-use; it reduces prep time with no reconstitution and no thawing required. It is appropriate for immunoassay and ionic exchange HPLC methodologies and assayed for popular chemistry instruments. It is available in plastic cap-pierceable vials which allow for autosampling by an analyzer. A1c-Cellular has 180-day closed-vial stability and 30-day open-vial stability. Streck, www.rsleads.com/605ml-159

HPLC analyzer

The Tosoh G8 (Tosoh Automated Glycohemoglobin Analyzer HLC-723G8) is an FDA-cleared HPLC analyzer to aid in diagnosis of diabetes and identify patients who may be at risk for developing diabetes. HPLC methodology allows for the visual identification of hemoglobinopathies that can interfere with the HbA1c result. NGSP-Certified, the Tosoh G8 has demonstrated high pass rates and CVs of less than two percent in proficiency tests. Tosoh, www.rsleads.com/605ml-159
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Multiplex testing for infectious disease enables prompt diagnosis and therapy

How would you characterize Luminex Corporation’s primary areas of expertise? Luminex Corporation develops, manufactures, and markets proprietary biological testing technologies, with applications throughout the life sciences industry. Our mission is to empower companies and laboratories to deliver reliable, timely, and actionable answers, and help providers identify and treat diseases effectively, thereby advancing healthcare.

What are the major categories of solutions that Luminex provides for its customers? As a pioneer in multiplexing, our xMAP Technology has been used by customers since 1999 across a wide range of applications and markets. In fact, xMAP technology-based systems are already in use by leading research laboratories as well as major pharmaceutical, diagnostic, and biotechnology companies. We continue to provide solutions for both clinical diagnostics and research markets with application areas such as infectious diseases, genetics, genomics, and proteomics research.

The company is well-known for its infectious disease multiplex panels, including the recently FDA-cleared NxTAG Respiratory Pathogen Panel. How can this product enhance the offerings of clinical labs? Many commonly encountered respiratory pathogens are difficult to diagnose based on symptoms alone, as they have similar clinical presentation. This presents a problem since clinicians need to be able to accurately identify an illness in a patient in order to effectively define treatment and control the spread of infection.

The NxTAG Respiratory Pathogen Panel enables laboratories to easily and simultaneously detect 20 respiratory pathogens in a single closed tube system, including the atypical bacteria Chlamyphila pneumoniae and Mycoplasma pneumoniae. The panel requires only minutes of hands-on time with no upstream reagent preparation, and has a simplified workflow that allows extracted samples to be added directly to pre-plate, lyophilized reagents. The closed tube format easily scales to accommodate changes in throughput needed to respond to seasonal changes in demand, especially during flu season.

With advantages such as rapid time to results and target masking for panel customization, the NxTAG Respiratory Pathogen Panel offers clear benefits.

ARIES System and ARIES HSV 1&2 Assay were also approved by the FDA last year. What are their key features? There has never been more pressure on clinical laboratories to increase efficiency while improving the overall quality of patient care through the delivery of accurate and timely data. The ARIES platform was designed to streamline workflow and raise the performance bar for all laboratory professionals, no matter how big or small the setting.

The ARIES System is a sample-to-answer molecular diagnostic system designed to increase laboratory efficiency, ensure results accuracy, and fit seamlessly into today’s lean laboratory environment. In order to minimize errors, it uses internal barcode scanning and other advanced features. Two independent modules each support from one to six cassettes, allowing for both STAT and batch testing. Both IVD and MultiCode Analyte Specific Reagents can be run simultaneously with a common Universal Assay Protocol.

Luminex supplies molecular reagents for a number of assays. How do you serve the clinical lab through that segment of your business? Luminex distributes reagents and instruments to exclusive partners spanning a wide range of industries and specialties, including clinical diagnostics. These partners add value to our technology, create powerful, customizable kits, and deliver service and support. They also offer the industry, market, and application expertise necessary to respond to customer needs quickly and effectively.

What are your chief functions as leader of a rapidly expanding biotechnology company? What impact have you had on Luminex since you became president and CEO in October 2014? How has it impacted you? I believe the main priorities of a CEO differ depending on the company’s stage of development. I joined Luminex at a time when its general business model had been established, had more than $200 million in revenue, and was profitable—yet the company’s dominance in multiplex testing technology had waned over the last few years. Therefore, my main focus has been getting Luminex back to that leadership role; making smart resource allocation decisions that prioritize projects to get us back in the role of “industry innovator” and that enable us to regain leadership in the markets we address.

Now in my third position as President and CEO of a publicly traded company, I have learned over the years that my job is like being a conductor of an orchestra. A good conductor will set the tempo, unify performers, and ultimately shape the sound of the ensemble. He or she will know how to get the best out of each instrument, and ensure that each one is synchronized with the rest of the orchestra. Take the violin, for example; it’s my role to ensure that the strength of the violin is harmonized with the rest of the ensemble. Conductors and leaders inspire the highest possible performance from the groups that they lead. I strive to continue to bring out the best in my team to ensure the best results for our customers, employees, and investors.
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