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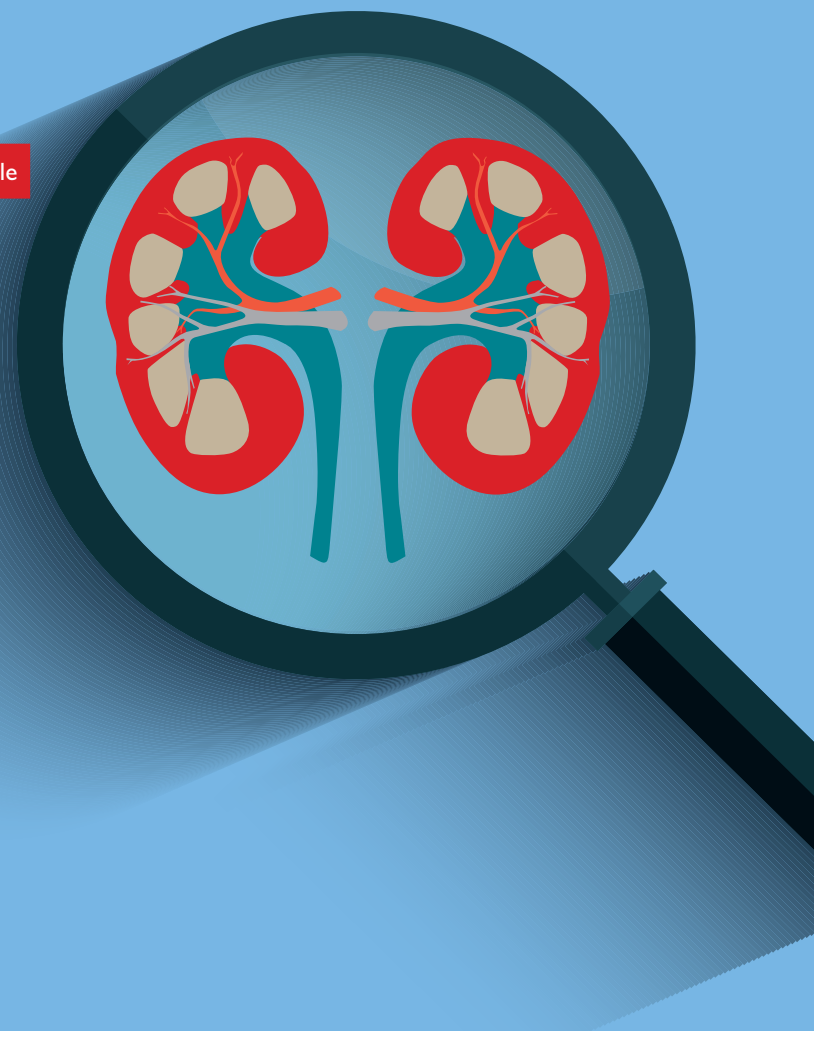

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The LEAN lab: automation, workflow, and efficiency

COVER STORY 8

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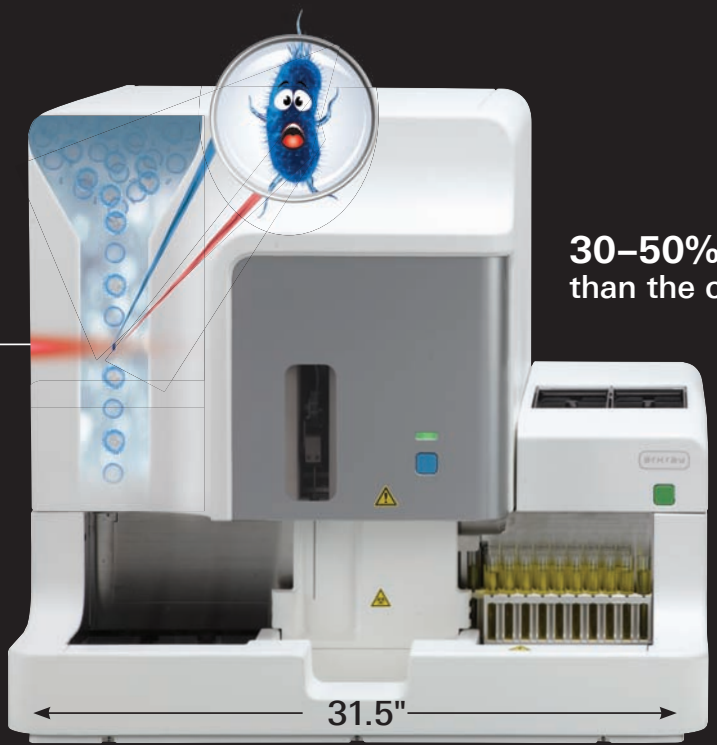

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Easing blood donor guidelines for gay men

I'm going to let other people write most of my column this month—but I have some pretty good proxies: the U.S. Food and Drug Administration, the Red Cross, AABB.

From an FDA statement by Commissioner Margaret Hamburg:

"Over the past several years, in collaboration with other government agencies, the FDA has carefully examined and considered the available scientific evidence relevant to its blood donor deferral policy for men who have sex with men, including the results of several recently completed scientific studies and recent epidemiologic data. Following this review, and taking into account the recommendations of advisory committees to the U.S. Department of Health and Human Services (HHS) and the FDA, the agency will take the necessary steps to recommend a change to the blood donor deferral period for men who have sex with men from indefinite deferral to one year since the last sexual contact.

"This recommended change is consistent with the recommendation of an independent expert advisory panel, the HHS Advisory Committee on Blood and Tissue Safety and Availability, and will better align the deferral period with that of other men and women at increased risk for HIV infection. Additionally, in collaboration with the NIH's National Heart Lung and Blood Institute (NHLBI), the FDA has already taken steps to implement a national blood surveillance system that will help the agency monitor the effect of a policy change and further help to ensure the continued safety of the blood supply.

"The FDA intends to issue a draft guidance recommending this proposed change in policy in 2015, which will also include an opportunity for public comment. We encourage all stakeholders to take this opportunity to provide any information the agency should consider, and look forward to receiving and reviewing these comments."

From a response issued by the American Red Cross, America's Blood Center, and the AABB:

"AABB, America's Blood Centers and the American Red Cross believe all potential blood donors should be treated with fairness, equality and respect, and that accurate donor histories and scientifically supported donor deferral criteria are critical to the continued safety of blood transfusion.

The FDA's decision to take steps to recommend a change in the blood donation deferral for men who have had sex with men (MSM) from a lifetime deferral to a one-year deferral is consistent with the position of our organizations that the current lifetime deferral is unwarranted.

It is important to note that this process is just beginning and that the lifetime blood donation deferral for MSM is currently still in place. Blood centers comply with all FDA blood donation eligibility criteria. The process to change this will take time. We will review the draft guidance that is scheduled to issue in 2015, and will implement the guidance as soon as possible after it is finalized.

The top priority of AABB, America's Blood Centers and the American Red Cross is the safety of the ultimate recipients of blood and our volunteer blood donors. Our organizations strongly support the use of rational, scientifically-based deferral periods that are applied fairly and consistently…."

To my knowledge, no reputable organization in the blood industry has voiced opposition to the FDA proposal. With our current ability to screen blood for pathogens, even the one-year restriction may be overcautious.

Having said that, let me play the devil's advocate for a just moment: might it be a good idea to "make assurance double sure," in Macbeth's phrase, and be very conservative about this? AIDS was never really a "gay disease," even at the beginning, and it certainly isn't now, but, statistically, there will probably be a higher proportion of HIV-positivity among "MSM" than in the overall population.

The issue is arguable, and it will be argued, but I side with the FDA and the allied organizations: Public health policy should be based on science, not prejudice or vague feelings of unease, and it should reflect "fairness, equality and respect."

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Infectious Disease

■ **CDC urges aggressive perscribing of antivirals to combat flu.** In a telebriefing with reporters held on January 9, Centers for Disease Control and Prevention (CDC) head Thomas Frieden, MD, MPH, confirmed what many Americans have observed—that a harsh flu season is underway in the United States. He called 2014-2015 "a bad year for flu, especially for older people and people with underlying health conditions." According to government statistics, 26 children had died of flu as of early last month, and hospitalizations among patients over 65 had increased significantly. One reason, Frieden indicated, is that the predominant strain this year is the unusually virulent H3N2. Moreover, approximately two-thirds of the observed H3N2 strains were not included in this year's flu shot.

Dr. Frieden used the forum to urge physicians to prescribe antiviral medications such as Roche's Tamiflu even before cases are confirmed by laboratory analysis as part of efforts to control the disease. "In the context of an H3N2 predominant season, with a less effective vaccine, treatment with anti-flu drugs is even more important than usual," he said. There has been considerable debate about the value of the antivirals; the Cochrane Collaboration, an international group formed to review clinical trials, has strongly questioned the efficacy of Tamiflu. One recent Cochrane news release asserts that "there is no good evidence to support claims that it reduces admissions to hospital or complications of influenza." According to Frieden, however, CDC scientists are satisfied that there is "compelling evidence" that, particularly when used within the first 48 hours of infection, antivirals help to reduce the severity and duration of the flu.

Molecular Diagnostics

■ **AMP releases a white paper describing "A Molecular Diagnostic Perfect Storm."** The Association for Molecular Pathology (AMP), a nonprofit organization serving molecular testing professionals, announced the release of a white paper addressing the consequences of regulatory and reimbursement forces directed against molecular diagnostic testing that the organization says threaten patient care.

"The breakthroughs made possible by mapping the human genome—a multi-billion dollar project that took more than a decade to complete—are being threatened by government regulations, which in turn are threatening patient access to truly revolutionary treatments," says Victoria M. Pratt, PhD, Indiana University School of Medicine, lead author of the paper. "We hope that this manuscript further enlightens regulatory and reimbursement stakeholders about the storm brewing in Washington that could dismantle the development and coverage of important molecular diagnostic tests."

Medical professionals in universities, cancer centers, clinical laboratories, and pharmaceutical/manufacturing companies across the country have honored the public trust in the Human Genome Project by developing hundreds of innovative diagnostic tests and therapies that are advancing modern medicine in ways that would have been impossible without this breakthrough. By eliminating the barriers outlined in "The Perfect Storm" paper, genome-based research will continue to play a critical role in the development of more powerful tools to treat complex diseases such as cancer, diabetes, and cardiovascular disease.

The white paper identifies threats stemming from efforts by the U.S. Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS), the two federal agencies that oversee molecular diagnostic testing, as the cause of this "Perfect Storm."

It argues that the FDA's new policies will effectively reformulate existing medical device regulations and consider medical professionals as manufacturers, and that this will impose substantially new and duplicative requirements on clinical laboratories and hospitals.

Meanwhile, CMS, whose actions are frequently mimicked in the private sector, has taken what AMP representatives are calling a heavy-handed approach in denying coverage or reducing payment for several medically necessary molecular pathology tests. Healthcare providers—those developing and delivering innovative diagnostic tests—along with patients, who are the ultimate intended beneficiaries, are caught in the middle.

"AMP is addressing the consequences of this gathering perfect storm of regulatory and reimbursement challenges directed against molecular diagnostic testing with recommendations designed to preserve patient access to these essential medical services," says AMP President Janina Longtine, MD. "We are greatly concerned that these forces are coalescing to bring about consolidation of laboratory testing, to the detriment of local testing. This would have far-reaching negative effects on the healthcare system. As such, AMP is committed to working with the regulatory and reimbursement bodies to find a resolution that optimizes patient safety and offers access to important medical tests."

"A Molecular Diagnostic Perfect Storm: The Convergence of Regulatory & Reimbursement Forces that Threaten Patient Access to Innovations in Genomic Medicine" is available at *http://www.amp.org/publications_resources/position_statements_letters/PerfectStorm.cfm*

Genetics/Genomics

■ **Biogen Idec and Columbia University Medical Center will conduct Collaborative Genetics Research.** Biogen Idec and Columbia University Medical Center have formed a $30 million strategic alliance to conduct genetics discovery research on the underlying causes of disease and to identify new treatment approaches. As part of this agreement, a sequencing-and-analysis facility will be established at Columbia to support collaborative genetics studies. The agreement will integrate genomics research conducted at Columbia with Biogen Idec's understanding of disease mechanisms and pathways and expertise in discovering new medicines.

"Our understanding of human genetics is rapidly expanding, and there is growing recognition that the elucidation of the genetic causes of disease will have a transformative effect on both patient care and drug development in many different diseases," says David Goldstein, PhD,

founding director of Columbia University's Institute for Genomic Medicine. "This collaboration marries the drug development expertise of Biogen with the genomics expertise at Columbia. It will not only focus on target identification and validation at the early stages of drug development, but also facilitate genetically informed evaluation of treatments."

The new facility will have broad genetic research capabilities and the capacity to launch and complete whole-genome sequencing projects rapidly. It will allow for rapid population-scale DNA sequencing across a broad range of disease areas, focusing on diseases with significant unmet clinical need such as amyotrophic lateral sclerosis (ALS) and idiopathic pulmonary fibrosis.

Cancer

■ **Researchers identify novel breast cancer gene.** A new multicenter study has identified a gene that is especially active in aggressive subtypes of breast cancer. The study suggests that an overactive BCL11A gene drives triple-negative breast cancer development and progression. The research, which was done in human cells and in mice, provides new routes to explore targeted treatments for this aggressive tumor type.

There are many types of breast cancers that respond differently to treatments and have different prognoses. Approximately one in five patients is affected by triple-negative breast cancer; these cancers lack three receptor proteins that respond to hormone therapies used for other subtypes of breast cancer. In recent years it has become apparent that the majority of triple-negative tumors are of the basal-like subtype.

Although new treatments are being explored, the prognosis for triple-negative cancer is poorer than for other types. To date, only a handful of genomic aberrations in genes have been associated with the development of triple-negative breast cancer.

The team looked at breast cancers from almost 3,000 patients. Their search had a particular focus: they examined changes to genes that affect the behavior of stem cells and developing tissues, because other work they have done suggests that such genes, when mutated, can often drive cancer development. Among these was BCL11A.

Higher activity of the BCL11A gene was found in approximately eight out of ten patients with basal-like breast cancer and was associated with a more advanced grade of tumor. In cases where additional copies of the BCL11A gene were created in the cancer, the prospects for survival of the patient were diminished. When BCL11A was inactivated in an experimental system in mice, no mice developed tumors in the mammary gland, whereas all untreated animals developed tumors.

Researchers propose that BCL11A is a strong candidate for development of a possible targeted treatment.

Prenatal Testing

■ **New molecular diagnostic methods could reduce risk of miscarriage in prenatal testing for genetic diseases.** Early diagnosis and treatment are crucial to improving patient prognosis for 22q11 deletion syndrome and Wilson disease, two potentially life-threatening genetic conditions. Breaking research in the "Molecular Diagnostics" issue of *Clinical Chemistry*, the journal of AACC, shows for the first time that a more precise technology for quantifying DNA could enable all newborns to be tested for 22q11 deletion syndrome; and that a new method known as cSMART can diagnose a fetus with Wilson disease without the risk of miscarriage that comes with traditional prenatal tests.

22q11 deletion syndrome is considered one of the most common chromosomal deletions associated with birth defects and leads to a wide range of health problems, from heart defects to behavioral disorders. Proposals have been made to include 22q11 deletion syndrome in newborn screening panels so that infants can be diagnosed and treated immediately after birth. The current gold standard method for diagnosing this disorder, however, is too expensive and labor-intensive for screening all newborns.

A team of researchers led by Flora Tassone, PhD, has shown for the first time that a method for quantifying DNA known as droplet digital polymerase chain reaction (ddPCR) can reliably and cost-effectively diagnose 22q11 deletion syndrome. To determine this, the researchers blindly intermixed blood spot cards (the sample form used in newborn screening) from 26 22q11 deletion syndrome patients with 1,096 cards from the general population. Using ddPCR to analyze each sample, they were able to correctly identify the 26 cases of 22q11 deletion syndrome with 100% accuracy and at a cost of only $5 to $6 for reagents per reaction.

Wilson disease results from a mutated version of the gene ATP7B that, when inherited from both parents, causes liver and neurological damage and eventually death. If it is detected and treated early enough, patients with Wilson disease can lead normal lives. Currently, prenatal diagnosis of Wilson disease is performed by analyzing fetal cells collected by either chorionic villus sampling or amniocentesis. Both of these invasive methods come with the risk of complications such as miscarriage, but Wilson and other single-gene disorders like it are difficult to diagnose using safer non-invasive methods—which analyze fetal DNA in the mother's blood—because the fetal gene of interest is present in the mother's blood at such low levels.

A research team led by Lingqian Wu, PhD, has developed a new non-invasive prenatal testing method named circulating single-molecule amplification and resequencing technology (cSMART). In a study of four pregnancies where both parents were Wilson disease carriers, the team demonstrated that cSMART can diagnose Wilson disease if the sequences of the parents' mutant *ATP7B* variants are known. The researchers used DNA sequencing to determine each couple's *ATP7B* variants, then used both standard invasive prenatal testing and cSMART to test for these respective variants in each couple's fetus. Among the four pregnancies, invasive prenatal testing detected two carrier fetuses who had inherited mutant paternal ATP7B, one unaffected fetus, and one fetus with Wilson disease. cSMART successfully made the same diagnoses.

The LEAN lab: automation, workflow, and efficiency

By Linda Covill, MS, BS, MT(ASCP)

Rethinking workflow and processes can have an impact on the ability of any clinical laboratory to do more with less—and to do it well, providing greater value for the healthcare dollars spent. By looking at a clinical lab the way a workflow consultant would, a lab manager can evaluate the products, tasks, ergonomics, repetition, safety, and best practices that can make a lab more productive and increase efficiency and quality.

Automation as a way of improving processes

For clinical laboratories, efficiency equates to reducing the number of process steps. Automation tailored to the needs of a lab can expedite workflow and optimize the use of personnel and equipment, improve safety by reducing contact with potential biohazards, and allow staff to spend more time on abnormal or critical results.

In addition to improving operating efficiency by decreasing the number of labor-intensive hands-on steps and the potential for error, automation can improve metrics and the level of service they represent, including turnaround time (TAT) and TAT consistency. A lab with persistent downtime, extensive reruns due to questionable results, or a cumbersome manual storage system can see dramatic changes by automating its processes. In turn, these improvements can build confidence in the lab's ability to deliver consistently accurate results in a timely manner.

Four issues tend to affect most labs' ability to deliver timely, predictable results: TAT, management of STAT samples, transportation of samples, and post-analytic storage.

Four issues tend to affect most labs' ability to deliver timely, predictable results: TAT, management of STAT samples, transportation of samples, and post-analytic storage. Automation can improve performance in all four.

TAT

Healthcare institutions and their physicians depend on fast, predictable turnaround time to optimize patient care and control costs. When TAT is not dependable—when it fluctuates or is delayed—timely diagnosis and therapeutic intervention become more difficult to achieve, potentially calling into question a laboratory's capabilities and institutional standing. When appropriately configured, a total lab automation system demonstrates its measurable ability to streamline and shorten TAT and TAT variability, even during peak workflows.

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LEARNING OBJECTIVES

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

1. Identify ways in which automation can improve lab operations.
2. Identify how to implement the LEAN system.
3. Identify the purpose and process of performing "health checks."

STATs

Effective management of STAT samples depends on the efficiency of the workflow. Given the critical nature of the time-sensitive information needed, improving the handling of STAT samples in order to expedite delivery of results has the potential to have a positive impact on patient care. One way to increase efficiency is to use automation that ensures true STAT prioritization throughout the entire process. This maintains one process for all samples, whether routine or STAT, but allows STATS to bypass all other samples that are not urgent.

Transportation of samples

Automated handling of samples offers the benefit of time savings with little or no need for human intervention. Staff touch a specimen tube once, and the system handles it the rest of the way.

Installing a transportation system between pre-analytics and analytics and between analytics and storage can markedly improve efficiency and reduce manual steps by as much as 80%, but that is not the only thing that can be done. To increase efficiency further, it's important to know how traffic is routed on the transport lines. Ideally, the transport system should be bi-directional and, when it becomes available, multi-level. This separates full samples from empty ones in dedicated lanes and gives labs fast, predictable TAT, even during peak workflows.

Storage

Manual processes often result in delays in locating archived specimens for add-on or reflex testing. One way to reduce or eliminate potential workflow disruptions is to automate storage and retrieval.

Manual archiving processes can require logging each specimen's rack location in an Excel spreadsheet or placing samples into a plastic rack based on accession numbers. In either case, the specimen racks are manually transported to a refrigerator. When a sample is required, a laboratorian can go to the refrigerator to find it for an add-on test. If the sample is not there, he or she returns to the bench and computer terminal to search for another sample. It can require 10 minutes or more to retrieve a single specimen.

There are different levels of automation that can minimize or eliminate these manual steps and provide quick access to the sample and immediate transport to the analytics for testing. Semi-automated systems archive samples in trays that are manually transported to the refrigerator. Fully automated systems take this a step further, with automated delivery to the storage unit and automated retrieval once a subsequent test is ordered.

Improving processes using LEAN principles

LEAN is a customer-centric methodology used to continuously improve any process through the elimination of waste. It is a pathway to better quality and lower costs.

LEAN management, as a concept, goes back to the efficiencies that Henry Ford brought to the manufacture of automobiles a century ago. It is famously associated with theories put into practice by the Toyota Corporation, particularly under the visionary Taiichi Ohno (1912-1990) in the decades after World War II. In 1990, the very influential book *The Machine That Changed the World: The Story of Lean Production—Toyota's Secret Weapon in the Global*

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Car Wars That Is Now Revolutionizing World Industry, by James P. Womack, Daniel T. Jones, and Daniel Roos, gave the concept more widespread currency. LEAN practices have been incorporated into a very large number of industries during the last few decades, including the clinical laboratory.

Adaptability as an attitude is essential to LEAN practices, starting with the ability to study a process and see it with fresh eyes. The following are the steps a lab manager can take to streamline lab processes, taking advantage of LEAN principles and a strategic approach to workflow assessment.

Eyes wide open: take a walk

In LEAN practice, the first step in improving the efficiency, quality, and productivity of a lab is to take a fresh look at every process. By taking a walk through the laboratory and observing carefully, following a process from start to finish, a lab manager is able to see what works and what doesn't; for instance, workload requirements and challenges regarding TAT, bottlenecks, nonstandard practices, problems that laboratorians are consistently facing. If the way a process is currently being handled is causing frustration—that presents an opportunity for improvement.

In Lean practice, improvement is never finished; the process is continual. As a lab manager and staff work on assessments and improvements, rethinking workflow and processes, they will continue to raise the bar on what can be accomplished.

Selecting a team and a process

The next step is to bring together a team to focus on one process or part of a process. The team, selected from staff members who do the specific work under consideration, should ideally also include a vendor. LEAN-certified vendor-consultants can provide a valuable viewpoint in two ways: they can provide simulation studies on their equipment, and they can look at the rest of the process objectively.

Here are guidelines for working with the team:

- Clearly define the scope of the task at hand.
- Choose one process and begin there.
- Include how success will be measured.

Here are examples of a goal whose success can be unambiguously measured:

- Reduce overall turnaround time from 90 to 60 minutes.
- Send results for all emergency department samples within 45 minutes.
- Reduce non-value-added steps in the processing area by 50%.

Observing the process: establishing baseline metrics

The team measures and collects data on the process under study, using the information first as a baseline before implementing changes, and then as a way to see the improvement after implementing changes. Metrics can also reveal where further improvement is needed.

Some critical-to-quality metrics, depending on a lab's goals:

- Reduction in TAT
- Improved consistency of TAT
- Improvements in reliability/reproducibility of results
- Greater patient and operator safety
- Reduction in overtime
- Increase in results/paid hour
- Reduction in non-value-added steps
- Increase in autoverification
- Overall medical value as defined by the people your lab serves.

The standard work document

Perhaps the team's most challenging task is to create a standard work document for the process being studied. This is a detailed, step-by-step process that all staff will follow in order to reap the benefits of working LEAN. In the laboratory, the desired outcomes typically include improving consistency, reproducibility, quality, efficiency, and patient and employee safety, and the potential to reduce costs and increase return on investment (ROI). To do this, the team observes and maps the process, beginning to end, breaking it down to its basic components, noting the order of the steps, what resources are used, who or what performs the task, and the outcomes.

As the team studies the process and its steps on the way to creating a standard work document, opportunities for improvement will become apparent.

What are value-added steps?

In LEAN terms, value is seen as the steps that are absolutely necessary in order to complete an analysis. For a clinical chemistry lab, for example, value-added steps might include drawing the sample (or receiving the sample), centrifuging, analysis, and release of results. To streamline a lab's processes and improve efficiency and productivity, the goal is to eliminate as many of the remaining non-value-added steps as possible.

Training and implementation

After standardizing a process, it is necessary to train everyone, including supervisors, to that standard. Consistency in the way a process is performed helps to increase efficiency and eliminate variability. Implementation follows, using the standard work document developed by the team.

Monitoring the process

As the team members implement the new version of the process, they monitor the process against the standard work document. Whenever possible, every shift needs to perform the work the same way, according to the standard the team has established. The team then observes the process again and gathers data to evaluate the progress and potentially uncover further opportunities for improvement.

Analysis and adjustment

Analysis of the data the team collects shows progress compared to the starting point. The outliers, data that stand out by being out of line with the rest of the observed performance, suggest opportunities for further improvement.

Repeating the process

Looking at processes one at a time, a lab manager and staff can analyze and improve each of the processes that matter most to the goals of the lab. These typically are related to cost, quality, service, and productivity. For example, a team can look at reruns, rework, and the reasons for them. By identifying the problem, the team can concentrate on solving it.

Tip: go after "low-hanging fruit" first

What qualifies as low-hanging varies from lab to lab. A process or part of a process that can be implemented quickly or simply to

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make a notable difference is a good first choice. Another option is to choose the one change that would have a major impact on efficiency.

Some possibilities:

- **Sample movement** in the processing area. From time received to analytics, what is the process, and how can the process be improved?
- **Visual cues.** Can the staff tell—without asking—what's happening to a sample? Where are the opportunities for visual or audio control?
- **TAT and STAT samples.** Is standard TAT being met and monitored? Are STAT samples easily identifiable throughout a process?

- ✓ Take a walk and observe.
- ✓ Select a team that includes the people doing the work.
- ✓ Define the project scope: Identify the process to be evaluated.
- ✓ Observe the current process. Establish a baseline of metrics.
- ✓ Create a standard work document. List desired steps and workflow.
- ✓ Implement changes, including training supervisors and employees to the standard.
- ✓ Monitor the process against the standard work document.
- ✓ Analyze the data and adjust the process accordingly.
- ✓ Repeat with another process or target for improvement.

Checklist for improving workflow and efficiency

Tip: use auto-verification

For improving processes, auto-verification is an area where efficiency and improvement can be impressive. Improving the current auto-verification percentage (to as high as 95%) can help to eliminate waste that comes from having to verify too many samples manually, improve TAT and management of STATs, and improve the efficiency and productivity of the lab by automating repeats and reruns.

Improvement, continued

In LEAN practice, improvement is never finished; the process is continual. As a lab manager and staff work on assessments and improvements, rethinking workflow and processes, it's likely that they will continue to raise the bar on what can be accomplished. Seeing improvement as an ongoing goal rather than a one-time task can encourage a lab to become increasingly innovative about eliminating waste, improving productivity, increasing quality, and providing value for healthcare dollars spent. That focus can lead the lab toward solutions that can contribute to the overarching goals of the institution, including better outcomes for patients. ☐

Linda Covill, MS, BS, MT (ASCP) is a laboratory process consultant and a Certified Lean Six Sigma Black Belt. She is part of the Roche Diagnostics Laboratory Consulting Team.

Automation and optimization: the importance of the health check

By Alistair Gammie, PhD

Automation is one of the biggest investments a laboratory can make. The goals of automation are to make workflow more efficient, improve the turnaround time and predictability of test results, and reduce errors. Many factors must be considered when exploring automation solutions. One important requirement is the need to choose an automation partner that has the expertise and capability to help manage the changing needs of the lab over the course of the automation contract.

The implementation of laboratory automation begins well before any contract is signed, with selection and institution of the project-management methodology that will be used throughout the project. As the engagement proceeds, it is important to manage the installation and implementation process according to the project plan as well as to establish the key performance indicators that will demonstrate that the process has been successful.

Health checks: what and why?

The period following the implementation go-live date is the beginning of a new phase in project management—the health check or optimization phase. There are three main reasons why health checks are necessary: internal forces, external forces—and peace of mind.

Internal forces include change-management issues that prevent necessary process changes, even though the implementation of the automation system proceeds as originally planned. Also, changes to service-level agreements often challenge the planned-for test volume and utilization.

External forces include changes to regulations such as ISO 15189 and to working terms and conditions, both of which can refocus staff activity. Healthcare as a whole is going through a period of consolidation, and workloads may change dramatically due to mergers and acquisitions.

Even without disruptive forces such as these, it is still essential to ensure that this expensive acquisition is delivering the appropriate level of production and return on investment.

Initial health check

It is critical to perform an initial health check on an automation installation within three months of go-live; the initial timing depends on the complexity of the installation. The goal of this first health check is to take the pulse of the system and understand how it is performing as a whole.

During implementation, the focus is on ensuring that the track, individual modules and analyzers, and requested IT workflow are in place and functioning correctly. In contrast, the health check assesses how the entire production system is working, from the time the sample enters the laboratory until the result is generated and the tube is disposed. The health check examines the human-machine interaction and takes a snapshot of the laboratory's current performance characteristics.

Making adjustments: action plan

The results of the initial health check help to set the performance benchmark for the laboratory moving forward. If performance is below target, an action plan is devised.

The action plan may include a rapid improvement event which may involve dissecting and rebuilding the current process, removing non-value-added steps. The new process is then implemented, measured, and refined as necessary, following the Plan-Do-Check-Act steps of traditional continuous improvement.

The action plan may also include specific training events, technical refinement of the system, or a combination.

If an action plan is required, the health check is repeated within a month of its completion to ensure that the improvements have been realized.

Health check

After the initial health check and any required improvements, health check events should be performed annually, although they may need to be conducted more frequently.

In an optimization, it's recommend that two to three days' worth of log and middleware files be collected and then analyzed in four distinct categories: production, utilization, turnaround time (TAT) analysis, and errors.

In the production analysis, each module and analyzer should be assessed to see how many tubes and tests are being processed per hour. Analysis criteria may include the distribution of processing within module and analyzer groups, the load balance, and how samples are being processed (e.g., batch size, front loading, etc.).

Utilization looks at the theoretical and effective capacity of each module and analyzer (depends on tube and test density) in order to monitor the effect of annual growth rates, identify capacity for service improvements, and make decisions to increase capacity by adding individual modules. The utilization analysis can identify specific pressure points and help the laboratory make informed decisions for service improvement.

TAT analysis looks at routine and STAT samples, measuring standard deviation, mean, and 95th percentiles, and considers other statistical parameters if necessary. The TAT analysis is conducted holistically but can be driven down to analyzer, analyzer group, and test level. It can also be stratified by time segment. For example, TAT analysis could assess test order time to time the tube is first seen on the track, which allows an understanding of pre-analytical TAT. It could also look at time on track to time out of centrifuge to determine whether the centrifuge operating characteristics are set correctly to manage the workload.

Error analysis assesses the number and type of errors and information messages recognized and recorded by the automation system and attached modules; many of these messages are unimportant when seen in isolation, but very high numbers or patterns seen across days can highlight sample-handling issues that reflect on the human-machine interface. This is particularly helpful when looking across operation of all three shifts.

After data collection and analysis, a one-day, on-site observational analysis allows integration of the collected data with what is actually happening in the laboratory. A review of the analysis and observations may result in a clean bill of health, or a few recommendations, or a full action plan.

This brings us back to peace of mind. A deep understanding of laboratory performance provided by health checks can help the laboratory director to achieve that often-elusive goal. □

Alistair Gammie, PhD, serves as Senior Director HCS, for Siemens plc, Healthcare, Diagnostics Division. He is involved with the Laboratory Consulting Services, looking at workflow, simulation, modelling, Lean Six Sigma projects, laboratory design, automation and re-organization. Dr. Gammie has studied workflow in laboratories throughout Europe, the Middle East, Africa, Asia, the United States, and South America and has looked at working practices in most disciplines of Pathology.

THE LEAN LAB: AUTOMATION, WORKFLOW, AND EFFICIENCY and AUTOMATION AND OPTIMIZATION: THE IMPORTANCE OF THE HEALTH CHECK

MLO and Northern Illinois University (NIU), DeKalb, IL, are co-sponsors in offering continuing education units (CEUs) for this issue's article on **THE LEAN LAB: AUTOMATION, WORKFLOW, AND EFFICIENCY and AUTOMATION AND OPTIMIZATION: THE IMPORTANCE OF THE HEALTH CHECK**. CEUs or contact hours are granted by the College of Health and Human Sciences at Northern Illinois University, which has been approved as a provider of continuing education programs in the clinical laboratory sciences by the ASCLS P.A.C.E® program. Approval as a provider of continuing education programs has been granted by the state of Florida (Provider No. JP0000496). Continuing education credits awarded for successful completion of this test are acceptable for the ASCP Board of Certification (BOC) Credential Maintenance Program (CMP). Readers who pass the test successfully (scoring 70% or higher) will receive a certificate for 1 contact hour of P.A.C.E.® credit. Participants should allow three to five weeks for receipt of certificate. The fee for this continuing education test is $20. **This test was prepared by Jeanne M. Isabel, MSEd, MLS, SH^{CM}, MLS Program Director and Associate Professor, School of Allied Health and Communicative Disorders, Northern Illinois University, DeKalb, IL.**

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February 2015

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CE QUESTIONS

1. **Automation tailored to the needs of a laboratory can improve efficiency by**
   a. expediting workflow.
   b. optimizing personnel and use of equipment.
   c. improving safety.
   d. all of the above

2. **According to the article, which of the following does *not* affect most labs' ability to deliver timely results?**
   a. management of STAT samples
   b. transportation of samples
   c. collection of patient samples
   d. post-analytic storage

3. **Turnaround time for patient results must be dependable for optimal diagnosis and therapeutic intervention.**
   a. True
   b. False

4. **Patient care is dependent on effective management of STAT samples and can be achieved by using automation that**
   a. allows STAT samples to bypass non-urgent samples.
   b. maintains a steady workflow without prioritization.
   c. runs STAT samples along with all other patient samples.
   d. none of the above

5. **A transportation system can be installed to connect the process of**
   a. pre-analysis and analysis.
   b. analysis and storage.
   c. storage and reporting.
   d. both a and b.

6. **Storage of patient samples is necessary for**
   a. add-on testing.
   b. reflex testing.
   c. mistaken orders.
   d. both a and b.

7. **LEAN management as a process is associated with practices put into place by which corporation?**
   a. Chrysler
   b. Honda
   c. Toyota
   d. Chevrolet

8. **A manager interested in adapting LEAN principles should take all of the steps below except:**
   a. Take a fresh look.
   b. Obtain an outside consultant team.
   c. Measure and collect data.
   d. Create a work document.

9. **Through observation, a lab manager should be able to identify bottlenecks in workflow and non-standard practice.**
   a. True
   b. False

10. **When selecting a team to identify LEAN practices, guidelines for their work should include**
    a. taking a broad look at the task at hand.
    b. focusing on multiple processes together.
    c. determining how success will be measured.
    d. incorporating several hospital administrators.

11. **A LEAN team should collect data on a process before implementing changes and again after changes have been put in place.**
    a. True
    b. False

12. **All of the following are examples of metrics that may be goals for a LEAN program except:**
    a. Reduce turnaround time.
    b. Increase overtime.
    c. Increase results per paid hour.
    d. Increase autoverification.

13. **A standard work document prepared for a LEAN process would include**
    a. process mapping from start to finish.
    b. ordering of steps.
    c. listing resources used.
    d. all of the above.

14. **In LEAN terms, improvement of efficiency comes from eliminating value-added steps.**
    a. True
    b. False

15. **In monitoring the new process, it is not necessary for every shift to perform the work the same way.**
    a. True
    b. False

16. **A good first choice for making a change in a process is one that**
    a. can make a notable difference.
    b. is easy to implement.
    c. causes employee stress.
    d. costs a lot.

17. **Improving autoverification to as much as 95% can eliminate waste from manual verification.**
    a. True
    b. False

18. **The period after implementation of an automated processing system in a lab is defined as**
    a. autoverification.
    b. health check.
    c. external forces.
    d. archiving.

19. **The recommended timing for checking the implementation of an automated system after going "live" is**
    a. one month.
    b. three months.
    c. six months.
    d. one year.

20. **Adjustments to performance can be made by implementing an action plan that may include specific training events.**
    a. True
    b. False

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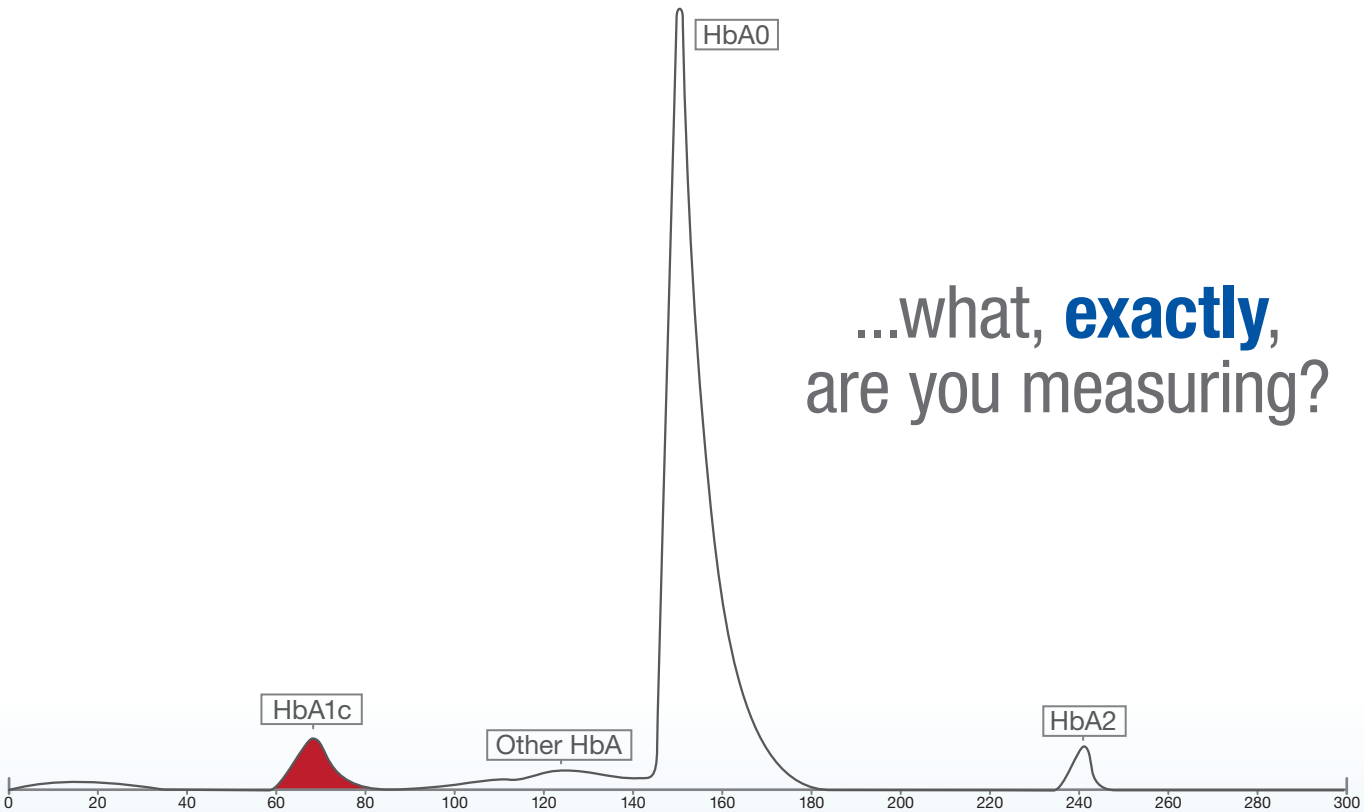

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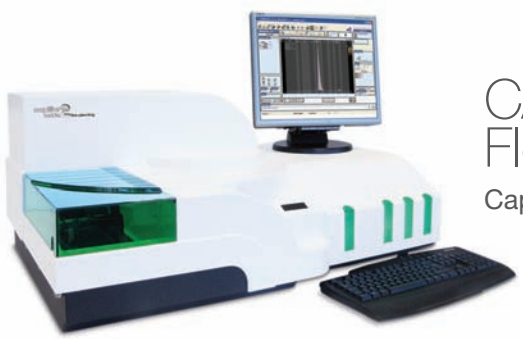

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Liquid biopsy: the time is right

By Lyle Arnold, PhD, and Raaj Trivedi

Cancer is the second-leading cause of death in the United States, after heart disease. Major advances have been made in diagnosis using solid tumor biopsies that have fundamentally changed how we target and treat various types of cancer. The completion of mapping the human genome and subsequent technological advances in genomic medicine have led to the development of solid tumor diagnostics that use individualized tumor information to personalize treatments which can ultimately prolong life and sometimes even cure patients with cancer. Molecular testing of tumors using high-throughput genomic technologies, such as next generation sequencing (NGS), has further expanded our knowledge of oncogenic pathways. Access to NGS enables the genomic profiling of tumors and facilitates individualized approaches to cancer treatment by sub-classifying cancer types based on genomics. Physicians can use an in-depth understanding of cancer at a molecular level to optimize therapy by selecting the most appropriate drugs based on known targets.

Numerous genomic alterations have been transformed into diagnostic markers for treatment with targeted therapeutics, and several anti-cancer drug labels require that pharmacogenomic information is obtained. Examples of oncology diagnostic tests that comprise the new standard of care include ER and HER2 in breast cancer, bcr-abl in chronic myeloid leukemia, c-Kit in gastrointestinal stromal tumors, BRAF in melanoma, and EGFR and ALK in lung cancers. With increasing development of targeted biological therapeutic agents in oncology comes a corresponding need for personalized treatment strategies. These strategies will facilitate the selection of patients who are most likely to benefit from a particular therapy, while simultaneously avoiding the cost and morbidity of futile interventions.

Despite the availability of these new technologies, a key limitation found in solid tumor oncology is the lack of tissue biopsy material necessary to run the battery of tests needed at the time of initial diagnosis as well as throughout the course of disease treatment. As an alternative, in many cases, medical professionals are opting for a non-invasive diagnostic method known as a liquid biopsy. Rather than staging and monitoring cancer using tumor tissue, the liquid biopsy enables a serum testing to identify specific biomarkers that can help direct the course of treatment.

A major advantage of a liquid biopsy over solid tumor testing is that physicians can monitor changes in tumor genetics over time to modify treatment accordingly, to achieve better patient outcomes. Until recently, the availability, robustness, and validation of methods for analyzing key biomarkers for solid tumors using patient blood have been limited, but the sensitivity of blood-based diagnostics is improving.

A liquid biopsy provides an alternative sample type when solid tumor sampling is unavailable or difficult to obtain. In some cases a patient may have had a biopsy, but it has been exhausted, not allowing further diagnostic tests to be performed. In other instances, it may be quite difficult to obtain a biopsy from a patient due to tumor location. For example, tumors in bone, brain, lung, pancreas, or other organs may be hard to access, or could put the patient at risk due to the invasive nature of the procedure. Ultra-sensitive methods to capture circulating tumor cells (CTCs) or methods that permit the sensitive analysis of cell-free circulating tumor DNA (ctDNA) provide physicians with the resources to test for important biomarkers that inform therapeutic decisions.

New clinical offerings from a number of cancer diagnostic companies are beginning to demonstrate that the technology and timing of blood-based biomarker testing for solid tumor indications have reached a key inflection point that may have poised the technology for mass adoption. Well-validated studies continue to demonstrate that blood-based biomarker testing using CTCs and ctDNA are able to identify predictive biomarkers with high correlation to those same markers found in the tumors.

Technical advances that have been achieved in recent years have significant implications for clinicians and medical laboratories. Medical professionals now have the ability to interrogate a hard-to-access tumor using a liquid biopsy. Previously this was only possible using invasive procedures that posed significant adverse risks to patients. Innovations in liquid biopsy have also made it possible to profile tumor cells on a continual or on-demand basis—at the time of initial diagnosis and repeatedly thereafter. This monitoring capability enables clinicians and doctors to track ongoing changes in a patient's disease state through a repeatable, non-invasive procedure and modify a patient's treatment plan as needed.

In order to achieve these potential treatment monitoring benefits without solid tumor tissue, highly sensitive analysis from blood-based CTCs or ctDNA is crucial. Although relatively abundant in late-stage diseases, the amount of tumor burden found in the blood is not close to the number of cells obtainable via tissue biopsy. Most key predictive biomarker tests would need sensitivities at the single-cell level in order to successfully be detected in blood. In a best-case scenario, detection of expression, amplification, and mutation changes requires sensitivities of one tumor cell in 100,000 nucleated blood cells. However, tumor cells are more likely to occur at only 1:1,000,000, or even down to 1:100,000,000 in the total nucleated cell population.

Today, for a tissue biopsy, sensitivity rates reach approximately 1:20–1:1,000 at best. Therefore, the shift in sensitivity from tissue biopsy to a liquid biopsy requires significant advances in lab-based technological platforms. This reality does not address the various informatics hurdles that come from managing the wealth of data that is produced from a single biopsy sample. Cutting-edge platforms to extrapolate tumor information from blood-based samples must also be implemented in a manner that proves to be scalable, cost-effective, and reproducible.

Liquid biopsy, combined with personalized therapies, has the potential to transform cancer from a deadly disease to a chronic but manageable one. As newer and more effective therapies reach the market, the need to monitor patients' cancer-associated molecular profiles on a regular basis is essential. A liquid biopsy enables physicians to appropriately monitor and modify the course of treatment for patients based on their response to therapy. Physicians have the ability to save and extend lives without solid tumor tissue now that diagnostics assessing genetic biomarkers have advanced to a point where meaningful information can be gleaned from a blood-based sample. As the future of cancer treatment becomes increasingly personalized, clinicians will need to carefully consider how liquid biopsies fit into their diagnostic and treatment decisions. □

Lyle Arnold serves as Senior Vice President and Chief Scientific Officer for Biocept, Inc. Raaj Trivedi serves as Vice President, Commercial Operations for Biocept.

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Combined primary immune deficiency: diagnosis by clinical flow cytometry

By Trivikram Dasu, PhD

A mutation/defect affecting any of the processes that aid in the natural ability of the human body to protect itself from infection and disease may compromise the immune system of an individual. Susceptibility to acute or chronic disorders may be biologically explained due to failure or dysfunction of several factors, both internal and external; thus the scientific community constantly engages in advancing technologies and methodologies to delineate the pathophysiological processes involved in causing the damage.

Some of these disorders are inherited congenitally, leading to the growing list of primary immune deficiency diseases (PIDDs), a set of diseases distinguished from acquired syndromes or those occurring secondary to known sequelae. The International Union of Immunological Societies (IUIS) Expert Committee on Primary Immunodeficiency revises the classification of these challenging disorders and compiles an update on a biennial basis. Based on typical immunologic manifestations supported by clinical presentation and genetic abnormalities, all reported and known PIDDs are grouped into eight major categories. For purposes of this article, not all 150+ disorders will be listed, and the reader is referred to the current published report.[1] (Please visit *mlo-online.com* to read references for this article.) An illustration of flow cytometry application by immune-phenotyping patient's blood supplemented by functional testing in the first category of combined immunodeficiencies (CID) will be described here.

Severe combined immunodeficiency (SCID), as well as deficiencies in DNA ligase IV, ZAP-70, Ca2+ channel, MHC I & II, STAT5b and DOCK8, are among the 22 different classes of CIDs described so far. SCID is characterized by profound impairment of both cell- and antibody-mediated immunity due to marked reduction in T cells. A decrease in B cells or natural killer (NK) cells may also present in some forms of SCID due to specific genetic defect. Infants typically present with recurrent bacterial and viral infections, failure to thrive, and reactions to live viral vaccines. Therefore, if undetected, SCID leads to life-threatening complications requiring treatment with hematopoietic stem cell transplantation (HSCT).

Wisconsin was the first state in the United States to initiate a statewide newborn screening program in 2008 for identifying babies born with SCID or other T cell lymphopenias. Several states followed suit, including California, Colorado, Connecticut, Delaware, Florida, Massachusetts, etc. The initial screening consists of quantitating the number of T-cell excision circles (TRECs) using real-time quantitative polymerase chain reaction on DNA extracted from dried blood spots on newborn screen (Guthrie) cards.[2-4] All full-term and pre-term infants who have reached 37 weeks of gestation that do not meet the criteria of passing the NBS-SCID screen for TREC (specified by each state's public health laboratory) are followed up by flow cytometry confirmation and consult by a clinical immunologist.

Fluorochrome conjugated antibodies are used to enumerate the percent and absolute cell counts of T helper cells (CD3+ CD4+), T cytotoxic cells (CD3+ CD8+), B cells (CD19+), and NK cells (CD56+) in the peripheral blood of a patient. This limited panel would suffice to classify the SCID into T-, B+, NK+/-, or T- B- NK+/- types. γ chain deficiency is the only T- B+ NK- SCID type [**Figure 1**] that is inherited in an X-linked manner, while others such as JAK3, IL7Rα, CD45, and Coronin-1A follow the autosomal recessive trait. Several cytokines including IL-2, IL-4, IL-7, IL-9, IL-15, IL-21, etc., produced by a variety of immune and non-immune cells (fibroblasts, stromal cells, epithelial cells) signal through the JAK (Janus associated kinase) - STAT (signal transducer and transcription) pathway. The cytokine receptors are composed of heterotrimeric chains one of which is shared amongst these family members—the common γ chain as the signaling component. Cases have been reported of γc receptor signaling deficiencies with subtle manipulations of the *in vitro* systems to determine the specific cytokine receptor defect.[5]

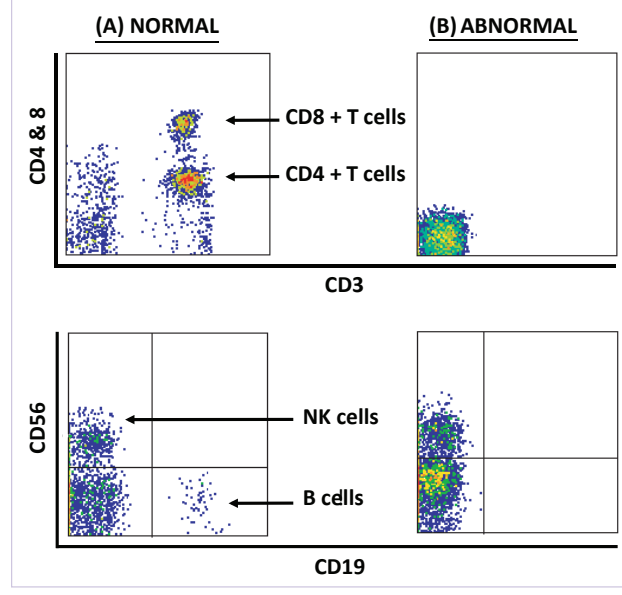

Figure 1. 4-color flow cytometry plots of whole blood of a normal individual (A) and a representative plot of T-/B-/NK- SCID patient (B). Normal peripheral blood contains populations of CD3+ CD4+ helper T cells, CD3+ CD8+ cytotoxic T cells, CD56+ NK cells, and CD19+ B cells.

Peripheral blood mononuclear cells (PBMCs) obtained from patients with CIDs usually do not respond to T cell mitogens, such as lectin from *Phaseolus vulgaris*, phytohemagglutinin (PHA), and Concanavalin A from *Canvalia ensiformis* (Con A). Flow cytometry provides the advantage to determine T cell proliferation to these stimulants without resorting to the traditional [^{3}H]-thymidine incorporation studies, thus avoiding radiation. Briefly, 5(6)-carbosyfluorescein diacetate N-succinimidyl ester (CFSE) labeled PBMCs are incubated with stimulants for four to five days at 37oC/5% CO2 and determine the number of fluorescent peaks corresponding to cell divisions of the parent cell population (**Figure 2**).

PIDDs can also present clinically with aberrations of defense, homeostasis, or impaired surveillance—the three basic functions

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of the immune system. In addition to PIDDs, which have been observed mainly in children, there exist a more frequently encountered group of secondary immune deficiencies that occur both in children and adults. These are the consequences of another disorder or underlying condition (autoimmune disease, sickle cell disease); infectious process (HIV, bacterial infections); genetic disorder or chromosome abnormality (cystic fibrosis, Down syndrome); age (premature birth, elderly population); surgery or trauma (splenectomy, burns): lymphoproliferative malignancies (multiple myeloma, lymphomas) or treatment with immunosuppressive agents (corticosteroids, anti-thymocyte globulin) that result in increased susceptibility to infections.

Dr. Ogden Bruton's observation of agammaglobulinemia in a male child suffering from recurrent otitis media, lacking tonsillar tissue, led to the ground-breaking diagnosis of XLA in 1952.[6] Immunoglobulin replacement is the treatment of choice with intravenous infusion or sub-cutaneous administration of highly purified and concentrated IgG antibodies from pooled healthy donors.[7-8]

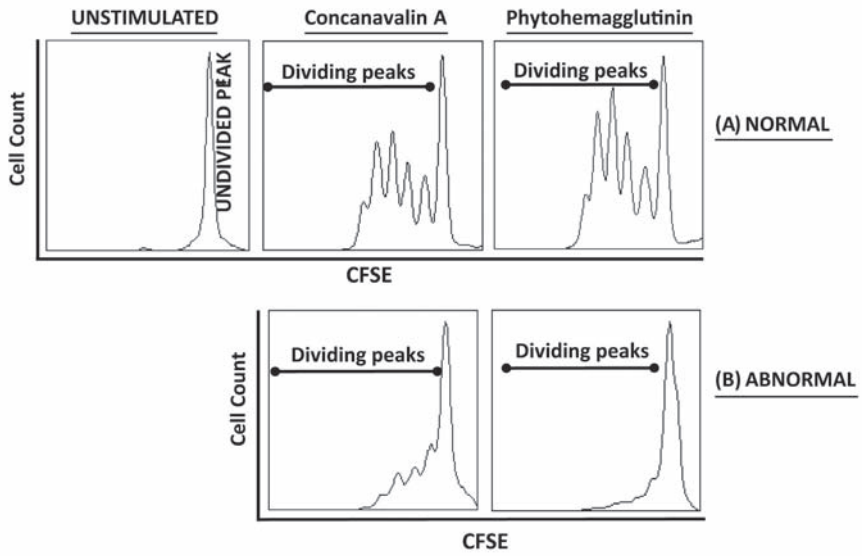

Figure 2. Flow-cytometry based semi-quantitative *in vitro* T cell proliferation. PBMCs labeled with CFSE are incubated with mitogens – ConA and PHA in presence of IL-2 for 4 days. (A) The fluorescent dye CFSE is diluted in half as lymphocytes divide which is seen as histogram peaks of progressive reduction in fluorescence. (B) Reduced/abnormal and asynchronous proliferation to the common T cell mitogens.

Flow cytometry applications are not limited to the two examples described here. Detection of intracellular cytokines, phosphorylated proteins, and apoptotic events is also possible with the newer instruments with lasers capable of multi-color analyses. □

Trivikram Dasu, PhD, serves as the Admin/Tech Director of the Clinical Immunodiagnostic & Research Lab at the Medical College of Wisconsin, Milwaukee, performing testing for primary immunodeficiency disorders. He is an active member of the Association of Medical Immunologists (AMLI), Clinical Immunology Society (CIS), International Clinical Cytometry Society (ICCS), and Clinical Laboratory Standards Institute (CLSI).

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Personalized medicine, pharmacogenomics, and companion diagnostics

Current and future applications of molecular diagnostics will influence these emerging fields.

By John Brunstein, PhD

One particularly powerful outcome of the Human Genome Project has been the appreciation of how much small-scale genetic diversity, in the form of single nucleotide polymorphisms (SNPs), exists across the apparently normal general population. Large and still growing databases of these variations are behind the topic of this month's examination of the growing fields of personalized medicine and companion diagnostics (CDx).

Genetics and pharmacogenomics

Note the use of the word "apparently" in the paragraph above. Let's consider a simple example in the form of an SNP known as rs671. Residing on Chromosome 12 at chromosomal nucleotide position 111803962, this occurs within the gene for aldehyde dehydrogenase 2 (ALDH2). The base at this locus commonly exists as either an adenine (A) or guanine (G), with fairly strong correlation to ethnic background: people of central European descent are essentially 100% certain to have the homozygous G:G genotype, while people of Asian heritage are roughly 40% likely to be A:G heterozygotes and 10% likely to be A:A homozygotes.

(Two quick reminders in case anyone is puzzled: while DNA is double-stranded, we generally only refer to the sequence of one strand in any given sequence location, as the other strand is defined through Watson-Crick base pairing; thus the locus is really either a G:C or A:T base pair, not just a lone floating G or A. Second, since Chromosome 12 is an autosome, everyone has two copies and thus we need to describe both individual loci; thus the "G:G" or similar shorthand notation.)

In most situations, whether a person is of the G:G, G:A, or A:A genotype has little known significance. However, this single apparently innocuous nucleotide change has a very obvious and immediate physical manifestation (phenotype) when people carrying the differing genotypes are exposed to alcohol. ALDH2 is the second enzyme on the breakdown pathway for ethanol where ethanal (the aldehyde coming from ethanol in the first step of the path) is converted to ethanoic acid, and there's a difference in the kinetics, or functional speed, of the enzyme as coded for by the different genotypes. The G form ALDH2 is a fast enzyme, catalyzing the rapid breakdown of ethanal before it can build up, whereas the A form ALDH2* is slower, and as a result, ethanal levels build up. The result is a rapid—and often very highly visible—flushing of the face, known sometimes as "Asian Flush" because of its most common appearance in people of Asian heritage. As one might guess, the phenotype is most apparent in people with the A:A genotype (all slow enzyme) and less so in G:A heterozygotes, where about half the available enzyme is the fast isoform. In addition to the flushing, people with the A:G or A:A genotype also tend to suffer from very severe hangovers from even moderate alcohol consumption; not surprisingly, many of these people learn to avoid alcohol altogether.

While this particular example is not of much medical significance, it serves to demonstrate how a single seemingly innocuous change in the genome can have a dramatic impact on how a specific substance such as a drug may be metabolized differently in different people. It's this link between genotype and drug metabolism—pharmacogenomics—which is leading the drive into applications of personalized medicine and companion diagnostics.

A single seemingly innocuous change in the genome can have a dramatic impact on how a specific substance such as a drug may be metabolized differently in different people.

A familiar example: warfarin

A clinically relevant example comes from warfarin (Coumadin) dosing. In use since the 1950s as a clotting inhibitor through indirect action on vitamin K processing, warfarin is prescribed for many people at risk of thrombotic episodes such as strokes or deep venous thrombosis, or recurrent myocardial infarction. While use of warfarin is generally thought to be highly beneficial in these cases, it's critical to adjust the dosing level such that while unwanted clotting doesn't occur, neither is the patient put at unacceptable risk for uncontrolled bleeding. It's been known for a long time that different people seemed to have very different sensitivities to this drug, requiring careful trial and error testing of patients to establish a therapeutic dose level.

The reason for this diversity of response lies primarily in polymorphisms in two genes: VKORC1 (vitamin K epoxide reductase 1; also on the vitamin K processing pathway) and CYP2C9 (cytochrome P, which acts to clear a wide range of circulating drugs including warfarin). Just as in our ALDH2 example, SNPs in these two genes (rs9923231 for VKORC1, and most commonly rs1799853 and rs1057910 in CYP2C9) impact drug kinetics and cause large variations in what constitutes a therapeutic dose for warfarin. The molecular ability to genotype relevant patients for these critical alleles prior to introduction of warfarin therapy was hailed as a large help in estimating appropriate initial dose ranges and avoiding relatively common adverse reactions from over- or under-

dosing prior to establishing individual patient response data. In fact, genotyping for warfarin sensitivity was indicated as early as 2007 by the U.S. Food and Drug Administration (FDA), making this one of the first widely applied and best known pharmacogenomic tests. At present, the jury is still out on the true utility in this specific example; while numerous case studies have indicated availability of genotypic data has helped prevent adverse reactions to warfarin dosing, it's also been reported that in this particular case, physicians have such a long familiarity with having to control dosing through trial and error that little true benefit is added by addition of genetic data. (Readers interested in one example of a recent review of these conflicting conclusions may see reference 1.)

Regardless of whether the warfarin example will stand the test of time with regard to true utility, other applications of pharmacogenomics are clearly apparent. In particular, companies active in drug discovery and development are increasingly interested in knowing genotypic profiles of subjects enrolled in clinical trials. It is not hard to imagine scenarios where in aggregate across an entire test population, a drug in testing may not show statistical efficacy; however, analysis of responding versus non-responding patient populations might demonstrate a genetic basis for identification of particular genetic backgrounds where efficacy is observed. Similarly, adverse drug reactions may be identified as being associated with a particular genotype. This increased granularity, as it were, of the patient populations promises to both more frequently identify useful drugs (in appropriate patient genotypes) and also identify genetic-based contraindications.

Companion diagnostics

This concept of personalized medicine, treatment tailored to the genotype of the patient, is taken a step further in oncology. Here, rather than focusing on the genotype of the patient, it is the genotype of the cancerous cells which is of interest. In particular types of cancers, there are frequent commonalities with respect to particular cell growth signalling pathways being deregulated. Mutation of a gene along such a pathway can lead to a form of signalling molecule in an "always on" form, constantly signalling for growth when it should not be. Elucidation of some of these common oncogenic pathways has allowed for the development of examples of highly effective and specific drugs which can block their respective target pathways. A key concept, however, is that these drugs are only effective at blocking growth signals which are in effect "upstream" of the drug in the signal path; if an ectopic signal is being created "downstream" of the drug action point, the drug has no effect.

In a personalized approach to oncology, rather than focusing on the genotype of the patient, it is the genotype of the cancerous cells which is of interest.

Perhaps the best-known example of this relates to the epidermal growth factor receptor (EGFR) pathway and the KRAS and BRAF genes. Oncogenic mutations upstream of the receptor can be effectively blocked or inhibited by drugs like Erbitux (cetuximab) or Vectabix (panitumumab), but mutations in KRAS or BRAF—effectively downstream of the receptor—are not responsive to these drugs. Knowledge of this allows for significant cost savings to the medical system through avoidance of non-productive use of these costly medicines, and also saves time by allowing immediate progression to alternate second-line therapies more likely to be effective.

Examples of this type of personalized medicine, wherein a specific genetic test is tied to the expected efficacy of a drug, are referred to as companion diagnostics (CDx), in the sense that they are a "companion" to a particular drug; the test is employed in assessing the likely utility of the drug treatment. A review of the FDA website "List of Cleared or Approved Companion Diagnostic Devices (*In Vitro* and Imaging Tools)" has a total of 19 entries (at this time of writing), with five being PCR-based, and seven being based on *in-situ* hybridization molecular methods. (Other methods in this list include immunohistochemistry methods and one magnetic resonance imaging [MRI]-based method). Of the 19, a total of 10 drugs are covered, out of which 18 are related to cancer. Of these 18, a full 10 CDx tests relate to use of just one drug (Herceptin).

These small and focused numbers, compared to the total number of drugs on the market, should give the reader reason consider just how much room for growth there is in the CDx field. The significance of this has not been lost on drug development (or molecular diagnostics) companies, which are actively expanding in this direction. One recent report predicted a growth rate in excess of 18% for this field between 2013 and 2019.[2] As this growth proceeds, clinicians will increasingly have access to highly specific molecular-based tools not just to diagnose the patient, but to select the most effective drug treatments, to guide therapeutic dose selections, and to avoid adverse drug reactions. □

John Brunstein, PhD, a member of the *MLO* Editorial Advisory Board, is President and CSO of British Columbia-based PathoID, Inc.

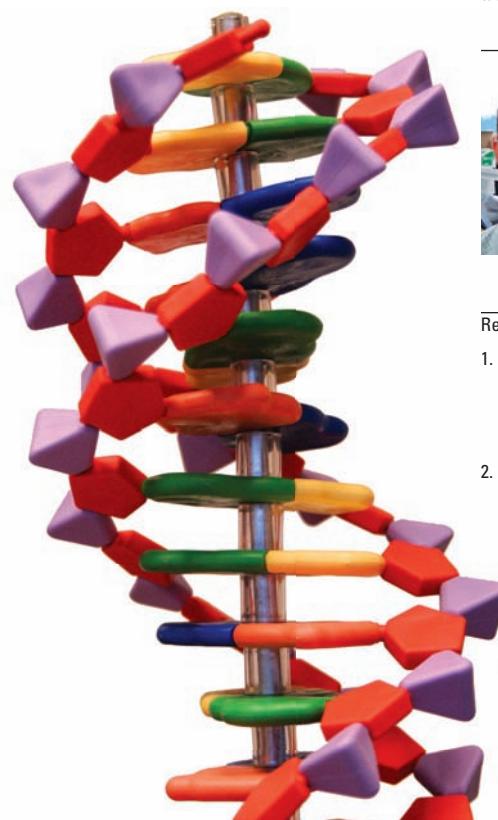

Photo by Maggie Bartlett, NHGRI

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Paving the way for prediabetes diagnostics: biomarkers that reflect insulin resistance

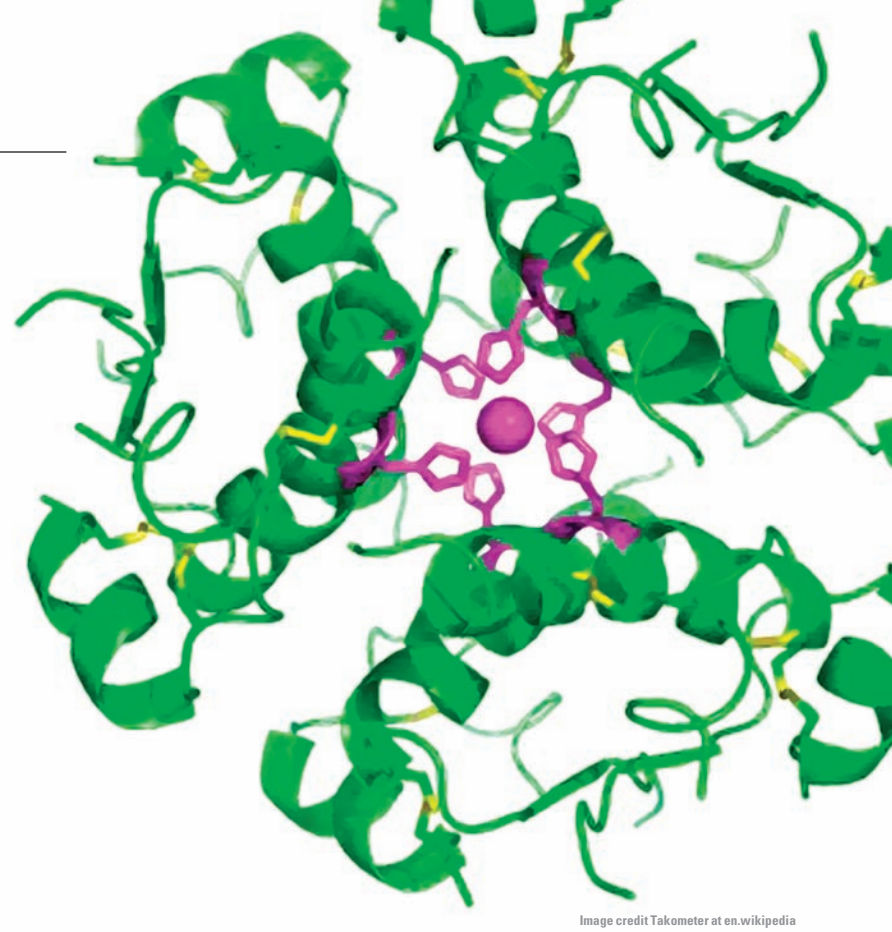

Image credit Takometer at en.wikipedia

By Doug Toal, PhD

Type 2 diabetes is a chronic disease characterized by reduced sensitivity to insulin in muscle, liver, and adipose tissue, a condition referred to as "insulin resistance." Insulin resistance develops before the onset of diabetes and is a predictor of the disease. In fact, insulin resistance can be present more than 10 years prior to diabetes and can be seen prior to any changes in glycemic measures.[1] Most people with insulin resistance are able to maintain normal glycemic levels by increasing β-cell secretion to compensate for diminished insulin activity. Over time, though, the β-cells of the pancreas may not produce sufficient insulin to compensate for the increased resistance, and this leads to progressive glucose intolerance (prediabetes) and diabetes.

The current gold-standard test for insulin resistance is the hyperinsulinemic euglycemic clamp. This test is impractical for a clinical setting because it is arduous for the patient, time-consuming (takes several hours to complete), and costly. The patient is continually infused with insulin to maintain hyperinsulinemia while also receiving variable levels of glucose. Blood glucose levels are checked frequently, and the glucose infusion rate is adjusted until a steady state is achieved and glucose uptake by all tissues of the body can be calculated. Given these limitations, the hyperinsulinemic euglycemic clamp is reserved for the research setting.

A simple blood test that can detect insulin resistance prior to the onset of hyperglycemia is needed for clinical practice. Such a test would have an immediate impact on clinical practice by allowing the identification of at-risk patients earlier on the disease continuum. Researchers have turned to the study of metabolomics to address this need.

Metabolomics is the global interrogation of the biochemical components (i.e., small molecular weight biochemicals or metabolites < 1,500 Da) in a biological sample, and the metabolome is a measure of the output of biochemical pathways. The identification of metabolic biomarkers has traditionally relied upon the analysis of individual biochemical levels and, as such, provided only a partial view of the metabolic fingerprint. The promise of metabolomics (and, incidentally, its major challenge) has been to develop a technology that can extract, identify, and quantitate the entire spectrum of small molecules in a biological sample. By interrogating the entire biochemical spectrum of a clinical sample, it is possible to identify meaningful patterns in multi-analyte levels spanning diverse and interrelated metabolic pathways. The ability to interrogate a clinical sample in an "unbiased" manner to gain a complete picture of metabolism sets the stage for biomarker discovery.

While diabetes is defined by dysfunctional carbohydrate metabolism, the disease evolves in a progressive process that also includes changes in lipid and protein metabolism. By applying metabolomics to the discovery of insulin resistance biomarkers, it is possible to extend beyond the boundaries of glycolysis to identify metabolic changes in various pathways such as amino acid and lipid metabolism.

Using a metabolomic approach to screen a large, well-characterized cohort of non-diabetic subjects with a wide spectrum of insulin sensitivity, researchers identified α-hydroxybutyrate (α-HB) as an important biomarker for insulin resistance.[2] α-HB is elevated during insulin resistance and is produced by amino acid metabolism (threonine and methionine) and glutathione anabolism (cystathionine pathway). The biomarker may become elevated by at least two mechanisms: a) elevation of oxidative stress leading to an increased demand for glutathione production, and b) elevation of the NADH/NAD+ ratio due to increased lipid oxidation. Both mechanisms are consistent with the metabolic disturbances that are known to exist leading to diabetes.

Linoleoyl-glycerophosphocholine (L-GPC) has also been identified as a biomarker for insulin resistance.[3] Unlike α-HB, which is elevated during insulin resistance, L-GPC levels decline. L-GPC is a lysophosphocholine formed by the action of

phospholipase A2 in the liver and by lecithin-cholesterolacyl-transferase in the circulation. Therefore, adipose tissue insulin resistance leads to elevated free fatty acid (FFA) concentrations. Raised circulating FFA reconstitutes phospholipids from circulating lipids, resulting in a decline of L-GPC.

Recently, Cobb et al., used fasting blood levels of α-HB, L-GPC, oleate, and insulin to develop a multiple linear regression algorithm that reflects insulin resistance.[4] By combining oleate levels, a fatty acid that is elevated during insulin resistance, and insulin levels with α-HB and L-GPC levels into a single algorithm, the investigators were able to show correlation with insulin resistance. Specifically, the clinical test demonstrated an AUC of 0.79 and outperformed other simple measures of insulin resistance such as fasting insulin, fasting glucose, homeostatic model assessment of insulin resistance (HOMA-IR), and body mass index, which are commonly used in place of the gold-standard clamp.

The above examples demonstrate the advantage of global technologies such as metabolomics in the discovery of biomarkers. This is particularly true in the case of diabetes, which is a complex metabolic disease involving multiple pathways.

The American Diabetes Association estimates that more than 29 million Americans have diabetes and that the cost of this disease has risen from $174 billion in 2007 to $245 billion in 2012. Research aimed at better understanding the metabolic disturbances underlying diabetes is paving the way for advanced diagnostics. New biomarkers will identify individuals at risk for disease earlier than current glycolysis-based tests and provide a more comprehensive picture that may allow personalized approaches to therapy.

As clinical laboratories look to advancements in next-generation DNA sequencing and proteomics to expand test menus, we should not lose sight of the unique and critical role that biochemical analysis of metabolism plays in the assessment of health and disease. Advanced technologies in nuclear magnetic resonance spectroscopy and mass spectrometry have created renewed interest in metabolism and the unique metabolic fingerprints of diabetes and other metabolic diseases. Metabolomics is creating opportunities for clinical laboratories to consider the potential of "next-generation" metabolic assays that address unmet needs in innovative and meaningful ways. □

Doug Toal, PhD, serves as Vice President of CLIA Laboratory Operations for North Carolina-based Metabolon, Inc., where he leads the development of metabolomics-based assays for use in the clinical laboratory. Metabolon has launched Quantose IR and Quantose IGT as LDTs for prediabetes and diabetes testing.

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Diabetes: new guidelines for Asian Americans

The American Diabetes Association (ADA) is lowering the Body Mass Index (BMI) cut point at which it recommends screening Asian Americans for type 2 diabetes, aligning its guidelines with evidence that many Asian Americans develop the disease at lower BMI levels than the population at large. The new recommendation appears in a position statement recently published in *Diabetes Care*.

"The position statement highlights, for the first time, the physiologic differences seen between Asian Americans and other populations affected by diabetes," says Jane Chiang, the Association's Senior Vice President for Medical Affairs and Community Information. "Asian Americans are a heterogeneous group and have historically been underrepresented in studies, so it is important to keep in mind that this is just the beginning. Clearly, we need more research to better understand why these distinctions exist."

For members of the general population, the Association recommends testing for diabetes when BMI reaches 25 kg/m2 or higher. Based upon an exhaustive review of the literature, it is now recommending that for Asian Americans screening be done at 23 kg/m2 or higher. It is believed that Asian Americans develop diabetes at lower BMI levels because of differences in their body composition: weight gain tends to accumulate around the waist in Asian Americans, rather than in other parts of the body. The waist is the area in which adiposity is considered most harmful from a disease standpoint.

"Clinicians have known this intuitively for quite some time," says William C. Hsu, MD, Vice President, International Programs, Joslin Diabetes Center, and Assistant Professor, Harvard Medical School, who was lead author of the position paper. "They can see that Asian Americans are being diagnosed with diabetes when they do not appear to be overweight or obese according to general standards. But if you use the previous Association standard for diabetes screening of being age 45 or older with a BMI of 25 kg/m2 or above, you will miss many Asian Americans who are at risk

"Given that established BMI cut points indicating elevated diabetes risk are inappropriate for Asian Americans, establishing a specific BMI cut point to identify Asian Americans with or at risk for future diabetes would be beneficial to the potential health of millions of Asian American individuals," the position statement concludes.

The Asian Americans Native Hawaiian and Pacific Islander (AANHPI) Diabetes Coalition began drawing attention to the need for changes in clinical management guidelines for Asian Americans, who experience twice the prevalence of type 2 diabetes than Caucasian Americans despite having lower rates of obesity under current federal BMI standards, following a 2011 State of the Science Scientific Symposium on Diabetes in Hawaii.

"A thin Asian person may be at risk for developing diabetes. Research has shown that BMI may not be the best marker in this population. This paper is a significant step in the right direction of widely recognizing the diabetes disparity that exists in our populations and communities," says Ho Luong Tran, MD, President of the National Council of Asian Pacific Islander Physicians. "The next steps are to increase the amount of clinical research and data on this diverse population, while simultaneously pushing for policy change that will positively impact health outcomes."

Answering your questions

Editor's Note: We thank a reader for asking this interesting four-part question. Expert Anthony Kurec, MS, H(ASCP)DLM, provides an answer for each segment of the question. Anthony is Clinical Associate Professor, Emeritus, at SUNY Upstate Medical University in Syracuse, NY.

Q Our laboratory has an extensive competency program focused on meaningful tasks that satisfy the "intent of the law." Management has decided to refocus on the competency program, and one area that seems to be problematic is the definition of a test system.

Using chemistry as an example: is each kit test (mono, preg, TCA, HP) a test system? Or, are manual tests such as pregnancy or mono grouped together as a manual test system? The implication of the former is a survey for mono, maintenance for mono, a problem for mono, etc., leading to extra work in a time of diminishing FTEs and budget cuts. And the question would be "what is the value of this?" if one were making something up to have a maintenance/function test to check off.

A CLIA's definition is: "A test system means the instructions and all of the instrumentation, equipment, reagent, and supplies needed to perform **an assay or examination** and generate test results."[1]

College of American Pathologists defines a test system as: "The process that includes pre-analytic, analytic, and post-analytic steps used to produce a **test result or set of results**. A test system may be manual, automated, multi-channel or single-use and can include reagents components, equipment or instruments required to produce results. A test system may encompass multiple identical analyzers or devices. Different test systems may be used for the same analyte."[2]

According to CMS (CFR 493.1252), each test system must meet the manufacturer's instructions and the laboratories "stated performance specifications," as addressed in CFR 493.1253.[3,4] The laboratory is responsible for defining criteria that address how reagents and specimens are stored, ensuring proper test systems' functionality, and the reporting of accurate test results.

The article cited[5] addresses these issues as related to blood bank and transfusion medicine, yet is applicable to other laboratory sections. The author states that "each method used defines a test 'system' and constitutes the need for a competency assessment activity. When tests are done on an automated instrument and all of the testing has the same problems and there are no unique aspects, the competency assessments can be combined."

A test system would include any procedural function that may be used to aid in generating a test result. With the example of the chemistry instrument, one instrument performs a number of different tests using different reagents and could be considered a test system. It would be the lab's responsibility to ensure that the instrument functions correctly (i.e., temperatures, clean probes, tubing, electrical fluctuations, water purity, etc.) in order to ensure correct measurement of each analyte.

Manual tests generally use reagents from a manufacturer's validated kit, regents that are not to be mixed with other kits ["(e) Components of reagent kits of different lot numbers must not be interchanged unless otherwise specified by the manufacturer."[2]] Thus to assume all manual tests fall under a single test system ("manual test system"?) would not necessarily fit these established criteria. If a single kit produces multiple laboratory test values, then that could be considered a test system.

Furthermore, each test kit would require validation. CFR 493.1253 states a laboratory "that introduces an unmodified, FDA-cleared or approved test system must do the following before reporting patient test results: (i) Demonstrate that it can obtain performance specifications comparable to those established by the manufacturer for the following performance characteristic…"[3] These characteristics include establishing accuracy and precision and developing

normal, age-based reference intervals. In addition, calibration and control protocols must be established, validated, and documented accordingly.

Q This brings me to another question. Does a kit test actually have a maintenance/function test that is appropriate? Droppers are included in most kits, and we do not routinely test timers. There is no instrument involved.

A Maintenance and function checks must be completed for each test system as defined in section 493.1254: "The laboratory must perform and document the following: (a) (2) Function checks as defined by the manufacturer and with at least the frequency specified by the manufacturer. Function checks must be within the manufacturer's established limits before patient testing is conducted."[6] Thus, function checks would be done only if the manufacturer's guidelines indicate that it must be so and provides a timetable of how often it must be done.

Q The third question is similar to the chicken vs. the egg. Should the technical consultant check everyone, or should he or she be checked as well, since he or she works on the bench part of the time? Or, should the checkers be only management or general supervisors as designated by CLIA?

A "Clinical consultants, **technical consultants**, technical supervisors, and general supervisors who are performing testing on patient specimens are also **required to have a competency assessment** including the six procedures."[7,8] The six procedures include the following:[8]

1. Directly observing performance of routine patient testing
2. Monitor[ing] how test results are recorded and reported
3. Review of intermediate test results/worksheets, quality control results, proficiency testing, and preventive maintenance records of equipment
4. Directly observing the performance of instrument maintenance and function checks
5. Appraising test performances by retesting of previously analyzed specimens, testing blind test samples, or proficiency testing samples
6. Evaluating problem-solving skills.

Q The last question concerns the review of intermediate test results. Recording a normal test released that was a manual entry with no intermediate clipboard to verify against seems not to be the intent. By definition, intermediate indicates that a result is transferred from one source to another.

A CLIA regulations state:
"The laboratory must have an adequate manual or electronic system(s) in place to ensure test results and other patient-specific data are accurately and reliably sent from the point of data entry (whether interfaced or entered manually) to final report destination, in a timely manner. This includes the following: (1) Results reported from calculated data. (2) Results and patient-specific data electronically reported to network or interfaced systems. (3) Manually transcribed or electronically transmitted results and patient specific information reported directly or upon receipt from outside referral laboratories, satellite or point-of-care testing locations."[9]

And as noted in section 493.1413 standard, a technical consultant is responsible for the: "(iii) Review of intermediate test results or worksheets, quality control records, proficiency testing results, and preventive maintenance records."[8] A system needs to be in place to ensure test results, whether intermediate or otherwise, are reliable before they are released.

The medical director of the clinical laboratory is ultimately responsible for interpreting and implementing CLIA and/or other agency guidelines. The intent of these guidelines is to ensure quality laboratory services are provided to patients, and to protect them and staff from untoward outcomes.

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Digital cell image analyzers in the hematology laboratory

By Carl Trippiedi

Digital cell image analyzers, which automate the WBC differential process, are becoming standard equipment in busy laboratories. Cell image analyzers are allowing automation to enter into the realm of hematology smear review, which has traditionally been a very manual and labor intensive task within the laboratory. These analyzers locate cells on the glass slide, and use digital image technology to present the operator with a pre-classified listing of white blood cells which can increase the speed and accuracy of WBC differentials. This technology is assisting hematology laboratories to better meet the demands for increased testing volume with shorter turnaround times.

In addition to the WBC differential, cell image analyzers also assist with red cell morphology assessments and platelet estimates through automation. Staff shortages and the lack of experienced hematologists are two reasons that laboratories of mid- and large-size hospitals are deploying these analyzers to provide 24/7 expertise for the important differential portion of the CBC. Although digital cell image technology has been available for several years, the refinement of the technology and the ability to integrate cell image analysis into hematology automation lines has stimulated laboratory interest.

Automated CBC analyzers

Ten years ago automated CBC analyzers would flag qualitatively abnormal samples for microscopic review by a laboratorian. Typically these were samples with immature or abnormal white cells and could make up 25% to 30% of a daily workflow. In 2005, studies were undertaken at Massachusetts General Hospital to report on the accuracy of white cell classification by an automated analyzer versus a microscopic differential review by a laboratorian.

The study[1] reported that new cell recognition software had a sensitivity of 95% and a specificity of 88% for immature myeloid cells. It was also highly specific and sensitive for blasts: 100% and 94% respectively. For unusual WBCs and nucleated RBCs, sensitivity and specificity were 100% and 97% respectively.

Today, these analyzers are being integrated onto fully automated hematology lines to report results that can be used as a part of an auto-verification system for reporting CBC and differential results with minimal review time when combined with the use of laboratory defined, rules-based middleware.

The benefits of standardization

Cell image analyzers promote a more standardized differential result throughout a single laboratory or an entire integrated healthcare network. Automation helps to remove the inherent subjectivity demonstrated with manual microscopic analyses.

Using a digital cell image analyzer, a laboratorian can view cells that have been pre-classified by the software to improve the accuracy of cell identification and proper reporting of the differential.

The automated analyzers will provide a standardized teaching platform when also used for staff training. Additionally, they can assist to improve the morphology skills of a laboratory's entire staff, which may be rotating through the hematology department on varied schedules.

Workflow improvements

Using a digital cell image analyzer, a laboratorian can view cells that have been pre-classified by the software to improve the accuracy of cell identification and proper reporting of the differential. An on-board library of reference cells will assist less experienced morphologists to identify cell types more efficiently.

Through the use of optional remote review software, multiple differential stations can be established throughout the laboratory by using existing network PC workstations. This will also contribute to a decrease in turnaround time even during peak volume hours.

Differential workflow has traditionally been a challenge especially when dealing with leukopenic samples. Automated cell image analyzers typically have the ability to merge multiple slides made from low white count samples into a single case, eliminating the need for a buffy coat preparation prior to a manual differential.

Finally, the ability to automate body fluid differentials can also become a reality with optional add-on software, streamlining lab workflow to an even greater extent.

Connectivity adds value

What makes cell image analyzers even more valuable today is their ability to support clinicians with real time differential expert consultation. This is easily accessible through the analyzer's ability to share the cell images over the hospital network. Similar image sharing has been shown to be of high value in the field of radiology. The use of digitally captured images allows computed/digital radiography to be practiced in virtually any setting. Digital cell image analyzers translate the same flexibility for "electronic-consulting" capabilities now for digital hematology.

New levels of connectivity between clinical laboratories and clinicians mean that digital cell images of interest can be shared both for the purposes of consultation and education regardless of location. Hematology laboratories can now connect with one another and with off-site expert support from pathologists and/or morphology experts. This is particularly important in hospitals that may not always have pathologists on site.

The power of integration

It is indeed a brave new world: Today's laboratorian can place a primary tube in a sample rack, then place it on an analyzer, and then walk away to perform other critical testing within the lab. He or she can then return to find that the sample has a complete CBC result. If that result is outside of normal parameters, as defined by onboard rules, one or multiple peripheral blood smears have been automatically prepared, robotically fed into a cell image analyzer, yielding pre-classified and sorted cell images ready to be displayed on a high-resolution monitor.

Through a routine review process, the complete hematology profile for this sample can be released rapidly into an LIS or hematology middleware solution. The technical refinements to digital cell image analysis allow the differential to be as accurate and reproducible as other parameters within the CBC. Easily stored images can be made available for supervisory or hematopathologist review and help standardize teaching within and across health network sites. They also offer bi-directional communication with the LIS to support automated reporting to the patient's chart. □

Carl Trippiedi serves as Senior Product Manager for Sysmex America, Inc.

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How has the analyzer evolved to meet the needs of the modern molecular diagnostic laboratory?

By Rajasri Chandra, MS, MBA, and Min Ding, MS

A clinical laboratory functions to assist the management of patients by providing information to aid in the diagnosis, treatment, and prevention of disease, all based on the analysis of patient samples. The aim of the lab, therefore, is to generate this information and communicate it to the physician as accurately and as quickly as possible. The laboratory analyzer, with its specialized hardware and software, processes the patient samples, analyzes the results, and provides the data for further interpretation by the physician and communication to the patient. The analyzer is the key to the functioning of a successful clinical laboratory.

A history lesson

That was not, however, always the case. In the early twentieth century, clinical diagnoses depended almost solely on a physician's ability to identify disease based on the patient's history and physical examination. The physician diagnosed and treated patients via his observations and incisive questioning. Physicians prided themselves on their intuitive skills in making a diagnosis by the use of their senses alone; to a significant degree, diagnosis was more of an art than a science. At that time, due to the limitations in available methodologies, the diagnostic and therapeutic value of laboratory testing was not appreciated, and many physicians viewed clinical laboratories simply as an expensive luxury that consumed valuable space and time.[1]

By the end of the 20th century, however, clinical diagnostics had undergone a significant change. Due to an ever-increasing appreciation of the complexity of disease and a need for more "transferrable" medical knowledge, practitioners looked for more objective methods to assess the health of a patient so that they could more consistently and reliably manage different patients with apparently similar symptoms.

In the early decades of modern clinical laboratory result-based diagnostics, laboratory tests revolved around the areas of Clinical Chemistry, Immunology, Hematology/Cytology, and Microbiology. All used "simple" laboratory analyzers that relied on technologists to process each sample, and the instrumentation was just analytical machines that gave an accurate result with "reasonable" throughput. For many years, this was acceptable laboratory procedure, as the clinical tests required just one analyte, with just one reaction. Further developments served to increase the throughput of the systems via enhancements that led to reduction of operator intervention.

A paradigm shift

With the entry of molecular diagnostics into the clinical laboratory, beginning in the 1990s, however, additional requirements became evident. Due to the innate complexity of molecular medicine, it was apparent that relying on a laboratorian to do the processing and hardware to do the analytics was not going to be sufficient. The use of heavily multiplexed panels that could provide a clinically actionable result required the simultaneous analysis of multiple analytes, each requiring multiple reactions. It quickly became apparent that the biggest issue that needed to be addressed in every molecular diagnostic laboratory was how to automate or simplify the DNA testing process (**Figure 1**).

This need led to the first true evolution of the molecular diagnostic analyzer. Previously, laboratory technicians relied on a combination of manual preparation steps with a thermal cycler and crude data capture systems to generate a usable result. The changing need led to the emergence of two kinds of instrumentation.

- **Automated liquid handlers**, platforms which can be integrated onto a singular automated platform that can automate most of

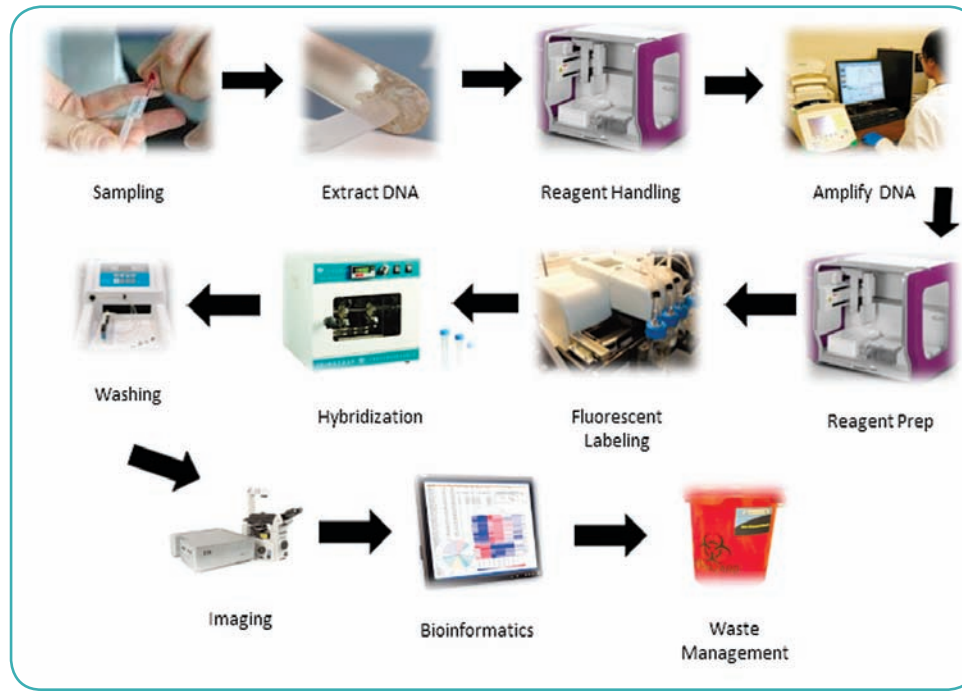

Figure 1. Molecular testing workflow (courtesy AutoGenomics)

the manual preparation steps and thermal cycling. By adding a data analysis platform to the back end, the system is able to achieve a high degree of semi-automation for a completely manual lab testing process. The automated liquid handlers, with their open architecture, help to automate the entire test process, no matter what the test process is, as long as it can be split into logical steps.

- **Commercial analyzers**, which use manufacturer specific reagents, mostly on a closed mechanical analytics system. These resemble the analyzers for other areas of the clinical lab but with a key, distinct feature. Rather than improving upon speed or throughput, the core enhancement made was with regard to ease of use: how much the system can automate in order to minimize user intervention. For the molecular diagnostics laboratorian, running a singular sample for a panel of 20 mutations manually in the "old way" is a monumental task; each mutation can require as many as 10 pipetting steps, which means nearly 200 manual processes for just one sample. But with the new automated analyzers, running a test becomes as simple as adding the sample and loading the analyzer with consumables, and clicking the start button.

With the entry of molecular diagnostics into the clinical laboratory, it became apparent that relying on a laboratorian to do the processing and hardware to do the analytics was not going to be sufficient.

With the arrival of the automated molecular diagnostic analyzers, the molecular laboratory underwent rapid growth and expansion. Automated analyzers provided a number of benefits: the ability to process a large number of samples simultaneously; the elimination of human error to increase accuracy and reliability of results; the reduction in labor costs to enable the performance of "complex" genetic testing.

The expansion of MDx

This growth eventually led to the development and adoption of molecular diagnostics in many new fields, each with varying requirements on laboratory capabilities:

Microbiology, to detect infections (qualitatively and quantitatively) caused by viruses, bacteria, fungi, protozoa, etc., in symptomatic or asymptomatic patients, and monitor the effects of therapy. Because these tests deal with infectious agents, an analyzer is required that eliminates the need for the operator to handle these agents. A secondary requirement is sufficient throughput to enable population screening for these agents.

Oncology, to determine predisposition to a particular cancer by detecting mutations, to detect and determine the extent of disease progression, and to guide appropriate treatment based on individual genetic make-up. Due to the complexity of oncology marker testing, these platforms need to be able to be highly multiplexed.

Genetic disorder testing, to identify the presence of any genetic disorders in fetuses, children, or adults by detecting mutations or copy number variations. As with oncology, because each disease state can have a large number of variants that cause or impart risk, the ideal platform needs to be highly multiplexed.

Pharmacogenomics testing, to enable accurate and targeted treatment selection tailored to individual genetic make-up by detecting mutations and copy number variations. While the number of markers needed for this is not as large in as oncology or other disease state identification assays, due to the large potential volume of testing, a high throughput system would be required.

Sample-to-result and high-throughput

Responding to the new requirements linked to the types of testing outlined above, the evolution of the molecular analyzer has continued, and two additional types of analyzers emerged. The first is the **sample-to-result analyzer**, which can take any test from primary sample tube to result without the need for any operator manipulation of the sample. Essentially, this directly evolved from the previous iteration of automated analyzers by adding on a primary sample handling system. While it may seem like a relatively simple matter to improve, the benefit of this is nonetheless extremely significant since it removes a key complication in infectious agent testing.

The second new development is the emergence of the **high-throughput systems**. These new workhorses can provide an output of several thousand (or more) sample results in the same amount of time. In most cases these benchtop "factories" are not as automated as any of their ancestors, but their ability to run at rapid speeds compensates for their higher manual requirement.

Looking ahead

So, we now have four distinct types of analyzers that can populate a modern molecular diagnostic clinical laboratory to meet the needs of multiple forms of testing: automated liquid handlers, ease-of-use commercial analyzers, sample-to-result analyzers; and high-throughput systems. What's next? Currently, laboratories are observing two new trends:

1. **Consolidation of testing.** As many smaller labs are joining forces, and large labs are looking to absorb smaller regional players, there is a need for analyzers to not only be high-throughput but to have sufficient automation to handle the more complex panels and the ability to perform different kinds of tests in the same system.
2. **Rapid point-of-care testing.** Many physician-offices and small clinics are gearing up to provide rapid genetic testing to their patients. They require analyzers that are fast, easy to use, and have small footprints.

However these new trends develop, they reflect the increased rate of adoption of molecular medicine in the clinical lab. Molecular diagnostics is transforming healthcare, and analyzers with novel technologies may soon emerge to push the molecular diagnostics laboratory into yet another stage of evolution. □

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Managing change in the laboratory

By Jeff Fill, MBA, MT(ASCP) and Stacey Rickman

During the implementation of new equipment in a clinical laboratory the following scenario can unfold: Laboratory staff are unsure of its capabilities and struggle with the validation process. Elements such as reagent availability, instrument training, installation, and operation qualification are not fully understood, and no clear validation criteria is in place to ensure all applicable policies and procedures are followed.

What happened that enabled this situation to develop? Usually, the lab director did not fully recognize the process of change that would be associated with putting the new instrument into clinical use. An opportunity was missed for successful validation of the instrument, and that had a negative impact on productivity and morale. The knowledge, skills, and abilities required to lead laboratory employees through change require more than just technical ability on the leader's part to be successful. Lab leaders, as well versed as they are in the technology, in instrumentation, processes and systems, regulatory compliance, and patient engagement, sometimes fail to manage the emotional component of change. The emotional component requires an understanding of how change affects human behavior.

Humans very often resist change because it goes against our natural desire to achieve some form of equilibrium. Equilibrium in the laboratory equates to the mastery of knowledge and skills required for employees to be successful. As employees are learning new skills and gaining knowledge of a changed process or instrument, they are seeking to return to equilibrium.

Familiarity, predictability, and change

Change destabilizes equilibrium, and employees need to become familiar with and have the ability to predict the outcomes of their tasks. Leaders can enable or hinder employees' abilities to re-establish familiarity and predictability based on how they manage change. Frustrations can arise when employees are faced with a level of unfamiliarity and a lack of direction for their workday. Familiarity and predictability allow for the mastery of knowledge and skills which are precursors for innovation. This is why it is important to engage those affected in the process of change as soon as possible.

Developing a vision and strategy and communicating the change vision speaks to the importance of re-establishing familiarity and allowing for predictability. Leaders cannot simply focus on their laboratory or department's outcomes. They must consider how their employees' outputs align and support other interconnected laboratories and departments as well. So where does a leader begin?

New technology might cause some staff to be energized and excited; others might be anxious about their ability to learn, for instance, new software and instrumentation. Some might feel grief over the loss of the comfortable knowledge—or fear that their skills are being replaced by the new instrument. They may wonder if their skills will still be valued. In addition, other support personnel (quality, IT, maintenance) who do not understand the new technology may be challenged to develop a new support model—and they may react in different ways to the challenge. It is the lab director's responsibility to help these groups embrace change.

Navigate the emotional response to change

Managing the emotional reactions of staff requires establishing an action plan that aligns with and supports the R&D organizational objectives as well as acknowledges and responds to emotions. Here are some tips for lab leaders on managing the emotional component of change—the emotional stages that many employees will go through.

Fear and anger

- Develop a communication strategy and plan that aims to keep employees current throughout the life cycle of the change.
- Trust employees with information. This helps to mitigate fear and anger and reduces anxieties.
- Educate employees on the different stages associated with the change model and help employees recognize where they are in the process. Give them the tools needed to be successful:
  - Clear objectives, direction, and goals
  - Information, resources, and training
  - Assignments that align with their knowledge and skills
  - Timely feedback and positive reinforcement

Jockeying

- Clearly define how you will monitor and measure success, both in terms of deliverables and timelines. This will help mitigate jockeying for what employees' perceive to be in their best interests.
- Share the value you place on teamwork and reward accordingly. Enable the successful transition from "I" to "We."
- Hold individuals and teams accountable for deliverables. Also, seek feedback to learn what you need to do to support the initiative and their success.

Denial and passivity

- As author Stephen Covey once, wrote, "Seek first to understand." If employees are in denial and/or are exhibiting passive-aggressive behaviors, first ask yourself—and employees—what is needed from you.
- Don't just talk about the urgency and importance of the change; let your actions speak about that. Actively show support, demonstrate interest and concern, and gain trust.
- Recognize your own struggles in managing these emotions and the change. Establish ways to manage your emotional health and stability.

Commitment

- Identify lessons learned and take steps to prevent recurrence of negative behaviors. Engage employees in identifying and developing action plans required for continuous improvement.
- Seek feedback on what you could have done better as a leader to support employees. Seize the opportunity to learn and grow.
- And as one colleague once shared, "Treasure what you measure and measure what you treasure." The success of the change is defined by its desired benefits. How will you know?

Change *is* the one constant

As lab leaders seek to effectively manage employees through changing technologies and regulatory requirements, it is important for them to fully grasp how change affects human behavior and engagement. Remember that change is rarely stress-free, so the importance of doing whatever can be done to maintain the emotional health of employees cannot be overstated. Invite employees to discuss what they need in order to be successful with the change initiative. As you begin to listen and learn from employees, the trust you grow will be your most powerful ally during any change initiative. □

Stacey Rickman is a Career Coach and a Learning and Development Associate Consultant supporting manufacturing in a Fortune 500 Pharmaceutical company. Jeff Fill, MBA, MT(ASCP), is a leader and certified Lean Six Sigma Black Belt with 20 years of experience in life sciences. His current role is Director of a Clinical Laboratory in the Pharmaceutical industry.

Ensuring better patient outcomes through quality waived testing

Waived tests have traditionally been considered to have little or no potential to cause patient harm. But research shows that when workers fail to adhere to such basic instructions as following the directions in manufacturers' inserts, testing errors can occur.

Waived testing—simple tests performed at the point of care that are "waived" from most federal and state oversight under the Clinical Laboratory Improvement Amendments of 1988 (CLIA 88)—is on the rise, and with it, the potential for quality problems.

Since 1993, the number of CLIA-waived tests has increased from just nine test analytes and 203 waived testing systems to 120 waived analytes and more than 4,000 waived testing systems. Waived tests are now used to detect everything from HIV, drug abuse, glucose levels, pregnancy, and Lyme disease, to infectious diseases such as influenza A and B and many others.

Waived tests have traditionally been considered to have little or no potential to cause patient harm. They are not complicated to perform, and they can be administered by individuals with little or no laboratory background or specialized training. These traditional expectations of waived tests, combined with their growing prevalence, pose a risk that testing sites may become complacent about following quality guidelines for waived tests.

But research shows that when workers fail to adhere to such basic instructions as following the directions in manufacturers' inserts that accompany waived tests, testing errors can and do occur—and patient care may be impacted.

In a white paper entitled "Federal Government Questions Quality in Waived Testing," COLA documented some of the errors detected at waived testing sites in the United States. According to the research, a persistent percentage of Certificate of Waiver sites do not meet minimal requirements to ensure quality testing. For example, more than 30 percent of the sites studied do not routinely follow manufacturers' product inserts; perform Quality Control testing as specified by manufacturers' instructions; or perform confirmatory testing, as required by the manufacturer and approved by the U.S. Food and Drug Administration (FDA). Moreover, the research showed that most waived laboratory directors and testing personnel did not have formal laboratory training or testing experience, and that there is a high level of turnover of waived testing personnel.

You may be asking "Are stringent quality measures really necessary when it comes to performing such simple tests?" Think of it this way: more than 70 percent of the nearly 235,000 laboratory testing sites in the United States have a Certificate of Waiver. That means that more than 165,000 labs have little to no federal regulatory oversight in the performance of their work, which ultimately impacts millions of patients across the United States.

The reality is that regardless of the complexity of the test being performed and the level of training possessed by the person doing the testing, maintaining and following the highest quality standards should always be a top priority.

There also is mounting evidence that counters the popular notion that errors in waived testing can cause no harm. For example, last May, one major global diagnostic device and services provider which focuses on rapid point-of-care diagnostics initiated a product recall for a waived testing product used to measure blood clotting time in patients on warfarin, following alleged errors that resulted in nine adverse patient outcomes, including three deaths.

Additionally, the FDA reported 100 deaths associated with potential glucose meter inaccuracies between 1992 and 2009 and 12,672 serious injuries from 2004 to 2008.

COLA believes that more education is needed for Certificate of Waiver site directors and testing personnel, stressing the importance of following manufacturers' instructions, adhering to expiration dates, performing Quality Control testing, and proper documentation and recordkeeping. Studies show that increased educational outreach—combined with CMS's random surveillance of Certificate of Waiver sites—has an impact on the performance of waived sites.

There are a wide variety of educational resources available for waived labs from CMS and other resources. COLA offers a comprehensive Waived Testing Manual, online courses, and other waived testing materials.

COLA also has begun documenting examples of adverse patient outcomes resulting from waived testing errors. We encourage our allied health partners and other stakeholders in government and industry to also be vigilant about such errors. The more data we can track, the easier it will be to advocate for the importance of education.

By encouraging the widespread use of educational tools by waived labs everywhere, laboratory and medical industry leaders, manufacturers, states, the Centers for Disease Control and Prevention (CDC), Centers for Medicare and Medicaid Services (CMS), and other stakeholders will be able to proactively manage this important healthcare issue. ☐

Douglas Beigel is CEO of COLA, Inc., a major private accreditor of clinical laboratories. Mr. Beigel is a longtime advocate for quality in laboratory medicine.

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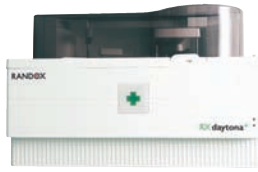

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By Alan Lenhoff, editor

Sigma-Aldrich offers products and services to manufacturers of diagnostics for the clinical lab

How would you characterize Sigma-Aldrich's primary areas of expertise? Sigma-Aldrich is a leading life science and high technology company focused on enhancing human health and safety. Our products, kits, and services are used in scientific research, biotechnology, pharmaceutical development, the diagnosis of disease, and as key components in pharmaceutical, diagnostics, and high-technology manufacturing. We provide scientific solutions to more than 1.4 million customers globally in research and applied labs, as well as in industrial and commercial markets.

How have your company's solutions evolved in recent years to address changing customer needs? As part of our diagnostics business, Sigma-Aldrich previously sold finished *in vitro* diagnostics (IVD) kits. We subsequently divested our IVD business in favor of continuing to supply our customers with raw materials for IVD kit manufacturing. Our new Applied Business Unit focuses on understanding and mapping customer workflows and building our offer to augment those workflows based on customer needs.

Sigma-Aldrich has entered into an agreement under which Merck KGaA will acquire Sigma-Aldrich. This is exciting news, and the combined company will be positioned to deliver significant customer benefits, including a broader range of products and capabilities, greater investment in breakthrough innovations, enhanced customer service, and a leading e-commerce and distribution platform in the industry. Sigma-Aldrich has invested heavily in understanding the complex needs of our current and potential customers. Our teams in strategic marketing, executive management, supply chain, and quality control work collaboratively with customers to stay ahead of changes in the marketplace and the regulatory landscape. By providing a single, global point of contact for customer's unique clinical diagnostic needs, we can create tailored, complete solutions that keep our customers moving forward into the future.

How has the company's launch of its Applied Business Unit a couple of years ago benefited customers? The Applied Business Unit was created primarily to cater to the unique needs of the diagnostics, testing, and industrial markets, where our customers' challenges and opportunities differ significantly from those in the traditional research and commercial markets. The highly regulated nature of the Applied market creates even more demand for a dedicated business unit and sales force to serve customers with enhanced quality, tighter manufacturing controls, and supply chain that delivers consistent high-quality products on an on-time, in-full basis.

How does Sigma-Aldrich's Enhanced Quality Program and Change Control Notification Program help customers deal with regulations related to raw materials? The Change Control Notification Program involves a series of steps that help prevent supply disruptions during any changes in the raw material manufacturing process for IVD products. The CCNP significantly minimizes disruptions for our customers when manufacturing changes require additional verification and validation, or when critical raw material availability causes changes to the process. The Enhanced Quality Program provides customers an opportunity to select raw materials that are suitable for their manufacturing needs and also meet their requirements for Change Control Notification. We've launched the ELITE brand of products for the IVD industry, and beginning next year we will gain ISO13485 certification for our manufacturing site in St. Louis. All of these shifts are designed to help customers stay on top of changing regulations and manufacturing processes.

Laboratory developed tests (LDTs) have been much in the news lately for clinical labs. How do your services address this subject? LDTs are here to stay. As bacteria continue to evolve and develop newer resistance markers and as we gain better understanding of disease states, I see a constant need for developing newer, better tests to improve diagnoses and patient management. Sigma-Aldrich's customer base consists of diagnostics manufacturers as well as clinical and reference laboratories developing LDTs, which require the use of high-quality raw materials and documentation. Sigma-Aldrich has several teams focused on developing solutions that can be used by our testing customers for developing LDTs. Because raw materials used for making LDTs go through the highest degrees of quality control, Sigma-Aldrich's testing customers always achieve the same level of quality and consistency in their clinical testing. We are actively participating in the continuing discussion on regulatory affairs, and with expert knowledge of our customers and the marketplace, we expect to be a leader in meeting the needs of the changing marketplace.

How does your long tenure with the organization and your immersion in its culture impact the way you fulfill your present responsibilities? My experience over the years at Sigma-Aldrich enables me to have a clear understanding of our capabilities. This insight helps me to bring together the necessary components to create solutions to solve our customers most difficult problems.

Frank Wicks

President, Applied Business Unit; EVP, Sigma-Aldrich

Professional

I currently serve as Executive Vice President of Sigma-Aldrich and President of the company's Applied Business Unit. I've been with Sigma-Aldrich since 1982, and have held a number of leadership positions, including President of the former Research Business Unit, Managing Director of North America and President of the former SAFC Business Unit.

Education

BS, Microbiology; PhD, Biochemistry from Oklahoma State University
Advanced Management Program, Harvard Business School

Personal

I've served as an Advisory Board Member for the International School of Business at Saint Louis University and a trustee of the Covenant Theological Seminary of the Presbyterian Church of America. I'm also a member of the Board of Directors of Cass Bank in St. Louis and have served as a member of the C&E News Advisory Board (American Chemical Society). I'm married with three adult daughters and nine grandchildren. I enjoy reading, and all forms of music.

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