PROGRAMMING IN R: A GATEWAY TO LABS’ DIGITAL FUTURE

The Right Call for Genomic Ethics
A New Sepsis Strategy
Patient Hypotensive? Febrile? Tachypneic?

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SSC Hour-1 Bundle calls for early lactate measurement of tissue hypoperfusion
Surviving Sepsis Campaign (SSC) has introduced the 2018 Hour-1 Sepsis Bundle for early recognition and management of sepsis. The SSC Hour-1 Bundle includes obtaining blood for lactate measurement within the first hour of sepsis recognition and to remeasure lactate if the initial lactate is >2 mmol/L.¹ The campaign suggests guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.¹

CMS SEP-1 quality metric includes early lactate measurement of tissue hypoperfusion
Consistent with the SSC Hour-1 bundle, US Centers for Medicare and Medicaid Services has introduced the Severe Sepsis and Septic Shock: SEP-1 Management Bundle to assess the quality of sepsis care in hospitals. The SEP-1 metric calls for lactate measurement to be completed within 3 hours of sepsis recognition.²


novabimedical.com
Variant Calls in the Genomic Medicine Era
Fast-changing information is prompting laboratories to review their duty to reinterpret and recontact providers and patients

Why Clinical Laboratorians Should Embrace the R Programming Language
A case for learning R as a gateway to laboratory medicine's digital future

The Battle for a Better Sepsis Test
Biomarkers and predictive analytics are combining forces for better diagnostics
NIH ANNOUNCES $1 MILLION COMPETITION FOR GLOBAL DISEASE DIAGNOSTICS

The National Institutes of Health (NIH) is partnering with the Bill & Melinda Gates Foundation to launch a $1 million Technology Accelerator Challenge that aims to spur development of non-invasive, handheld, digital technologies that will help combat diseases with high global and public health impact. The challenge is focused on sickle cell disease, malaria, and anemia. NIH is looking for technology that could rapidly screen large populations as well as provide physicians with a tool to personalize therapy for individual patients.

NIH will award up to $500,000 for a top finalist and several smaller awards to five semi-finalists. The Gates Foundation will separately review winners and honorable mentions and consider them for follow-on support, including a grant of up to $500,000.

Current tests for sickle cell disease, malaria, and anemia can be challenging to deliver in low-resource settings, particularly at the population level, due to cost, invasiveness, and the expertise required to administer them, according to NIH.

“While this challenge is not constrained to any specific technology, the inspiration for it comes from the widespread availability of mobile phones and the potential for mobile phone-linked sensor technologies to non-invasively detect changes in the blood and blood vessels associated with these treatable diseases,” said Bruce Tromberg, PhD, director of NIH’s National Institute of Biomedical Imaging and Bioengineering.

The challenge will accept applications through June 2, 2020.
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Implementing a quality management system (QMS) is an important indicator of a business’s dedication to quality for its product or results. Quality control (QC) is one component of QMS that clinical labs have been using for decades to evaluate the analytical quality of lab results, predominantly through testing QC materials and using Westgard Rules to assess whether the quality is met. However, the Six Sigma quality management method has emerged over the past 2 decades as a means for providing additional, valuable information to assess quality in clinical labs. One incredibly useful, but in my view underutilized, aspect of Six Sigma involves calculating the Sigma metric.

**DEFINING THE METRIC**

The Six Sigma methodology, developed by a Motorola employee in the 1980s, measures process capability relative to quality requirements with the goal of only 3.4 defects per million products or results produced. The Sigma metric is a simple calculation using the allowable total error (ATE) or total analytical error (TAE), bias, and imprecision for a particular process:

\[
\text{Sigma} = \frac{\text{ATE or TAE} - |\text{Bias}|}{\text{Imprecision (standard deviation or coefficient of variation)}}
\]

ATE/TAE, bias, and imprecision are in the same units, which is either the measurement unit or percent. Percent may be the easiest unit with which to work. A higher Sigma indicates a higher-quality process because it is achieved through lower bias and/or imprecision. The desired minimum Sigma metric for a clinical lab assay is 3.0. Lower values indicate a need for more QC materials or runs for proper quality monitoring or for assay or process improvement to reduce bias and imprecision.

**CHOOSING DATA**

Determining which data to use for the Sigma metric calculation might be the greatest barrier to incorporating Six Sigma into a QMS. Many methods can be used to calculate bias: comparing to a reference method, or assayed reference, QC, or linearity material; averaging bias compared to the peer group or all-methods means for multiple proficiency test surveys; or calculating deviation from the target concentration of spiked controls. Bias is different at different concentrations, so laboratorians have options like selecting the average bias to represent an average Sigma, using the range of biases to represent the range of Sigma, or calculating Sigma targeting medical decision limits.

Imprecision is usually determined from QC results, but as with bias, laboratorians will need to decide which imprecision value to use. Several resources are available to obtain evidence-based ATE/TAE values. For measurands without a reported ATE/TAE, selecting a close approximation using a similar measurand or a reasonable, arbitrary value may be needed. A lab’s quality goals can steer these decisions (See resources, next page).

Westgard has incorporated the Sigma metric for selecting a QC plan with associated Westgard Rules. Using either Power Function Graphs or OPSpec Charts, a QC plan suitable for the capabilities of a clinical lab assay can be chosen inclusive of the number of QC materials and runs, to achieve the desired probabilities of error detection (0.05 or lower) and false rejection (0.9 or higher). Power Function Graphs and normalized OPSpec Charts are available on the Westgard website.

**THE POWER OF THE SIGMA METRIC**

The Sigma metric empowers clinical laboratorians to better understand the quality in their labs and to select quality products. The Sigma calculation reveals whether bias, imprecision, or both are contributing to a lower Sigma metric for an assay or analyzer currently in use. With this valuable information, the associated processes can be thoroughly evaluated for improvements to reduce...
bias or imprecision, thus improving quality and subsequently reducing laboratory costs.

Additionally, calculating the Sigma for an assay or analyzer under evaluation for purchase can highlight products with better quality, enabling clinical laboratorians to make educated decisions on which purchases will maintain a high degree of quality for their labs. Moreover, clinical laboratorians making comparisons between products will likely motivate manufacturers to produce higher-quality products.

I urge clinical labs that haven’t already done so to embrace the Six Sigma metric, because it can be a powerful and valuable addition to any QMS and the start of a larger repertoire for quality improvement.

Resources

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Resources
Cancers’ Complexities, Commonalities Detailed in Extensive Genomic Analysis

A massive undertaking involving more than 1,300 scientists from 37 countries reported in 23 papers shows the results of analyzing 47 million genetic changes in 2,600 genomes of 38 different tumor types. The Pan-Cancer Analysis of Whole Genomes (PCAWG) presented what the researchers called “the most comprehensive study of whole cancer genomes to date.”

Taking advantage of the latest sequencing and computational informatics technologies, the researchers, divided into 16 working groups, opened doors to the genetic complexities and commonalities in cancer, and offered insights that could spur further discoveries and eventual treatments.

PCAWG analyzed whole genomes rather than the more common approach of sequencing only protein-coding regions. They produced 1,188 tumor transcriptomes to link RNA and DNA alterations and explored genetic drivers, tumor signatures, and virus DNA found in cancers. These analyses generated more than 800 terabytes of data, roughly equivalent to the storage required for 200,000 movies.

PCAWG found cancer-driver mutations for 95% of cases, and that on average each cancer genome has four or five drivers. Sizable minorities of cancers showed signs of chromoplexy (17.8%) or chromothripsis (22.3%), reflecting complex and chaotic rearrangement processes. The researchers found that genetic changes leading to cancer occur early on—sometimes decades in advance of diagnosis.

The investigation also uncovered genetic drivers in noncoding DNA, like noncoding regions of the tumor-suppressor gene TP53 and of the telomerase gene TERT. Another PCAWG team characterized mutational signatures using more than 84 million somatic mutations from 4,645 whole-genome and 19,184 exome sequences to describe 81 signatures including single- doublet- and clustered-base-substitutions as well as small insertion-and-deletion signatures, many not previously identified. In a first, another team identified 16 structural variants involving large rearrangements.

An analysis of viruses associated with cancer highlighted the prevalence of Epstein–Barr virus, hepatitis B virus, and human papillomavirus.

All the PCAWG papers, published in Nature and related journals, are open access at nature.com/collections/afdejafafdb. The researchers’ raw genome sequencing data and other resources also are available to researchers.

OPIOID POISONINGS WORSENING IN CHILDREN, ADOLESCENTS

About one-quarter of opioid poisonings occur in children and adolescents, and poisoning incidents have become more severe in recent years, according to an abstract presented at the Society of Critical Care Medicine’s annual congress. The retrospective study of more than 750,000 opioid poisoning cases reported to the National Poison Data System from 2005 to 2018 found that 27.5% (207,543) of cases occurred in patients younger than age 19.

Trend analysis over three eras (2005–2009, 2010–2014, and 2015–2018) showed that the percentage of patients admitted to critical care units and deaths increased over time; 6.6%,
EMERGENCY DEPARTMENTS OVER-TEST FOR SUSPECTED PULMONARY EMBOLISM

Computed tomographic pulmonary angiography (CTPA) is overused in the diagnostic workup of pulmonary embolism (PE), underscoring “the urgent need for dissemination and implementation of protocols to reduce low-yield CTPA scanning,” including D-dimer testing, according to the authors of a study examining emergency department (ED) practices involving PE-related testing (Circ Cardiovasc Qual Outcomes 2020;13:e005753).

The study, a cross-sectional analysis of electronic health record and billing data from 16 EDs in Indiana and 11 hospitals in the Dallas-Fort Worth area, identified ED patients who underwent any of the following, including D-dimer testing, CTPA, scintillation ventilation perfusion lung scanning, or pulmonary angiography. Out of 1.83 million patient encounters, 5.3% had a diagnostic test for PE. Nearly 60% of all patients who had tests for PE underwent CTPA without D-dimer testing. About 21% of CTPA took place in women younger than age 45, who are at greater risk of cancer from CTPA radiation exposure, according to the authors.

The pooled diagnostic yield of CTPA for PE was 3.1%, with a 1.3% rate in Indiana EDs, and a 4.8% rate in Dallas-Fort Worth facilities.

Patients in Indiana were less likely than those in Dallas-Fort Worth to receive D-dimer testing before CTPA (30% versus 52%, respectively), possibly reflecting the impact of a targeted quality improvement initiative that had taken place in Dallas-Fort Worth to increase use of D-dimer testing in low-risk patients.

The data imply that “D-dimer ordering correlates with an increased yield rate of PE on CTPA,” wrote the investigators. “This relationship suggests but does not prove a positive cause-effect relationship between rate of D-dimer ordering and PE yield.”
Fast-changing information is prompting laboratories to review their duty to reinterpret and recontact providers and patients in the Genomic Medicine Era.

Widespread implementation of next-generation sequencing, along with more patients undergoing such testing, has significantly increased the number of gene variants detected. Consequently, clinical laboratories are facing new quandaries. One is how often to reinterpret data to classify a variant, especially if the variant initially was found to be of unknown significance. Another is when to contact providers or affected patients with any new information.

To try to help, the American College of Medical Genetics and Genomics (ACMG) last year released two policy statements (Genet Med 2019;21:769-71; Genet Med 2019;21:1267-70). One recommended that clinical laboratories have policies and protocols for variant-level reevaluation and case-level reanalysis that keep pace with new developments in population databases and bioinformatics. A second suggested recontacting patients is a shared responsibility among ordering providers, laboratories, and patients.

Neither document put a definitive timetable in place for these actions, which was deliberate, said Josh Deignan, PhD, FACMG, a co-author of both and an associate director of the University of California, Los Angeles Molecular Diagnostics Laboratories.

“We didn’t want to hold anybody to a specific standard, like every variant or every case has to be reviewed every year, two years, or three years,” Deignan said. Instead, the authors felt laboratories should set their own policies without restrictions based on their size, resources, and scope of practice. Deignan and his co-authors also underscored that reclassifications should be expected, and that the reports that labs produce “are really only good as of the date on the report, which is based on our available resources and knowledge at the time,” he said.

IS EVERY 2 YEARS OPTIMAL?
Exactly how often findings should be reinterpreted is a matter of opinion. “A lot of people would argue that
Everybody agrees on the principle that if the lab knows new information that would impact how someone takes care of a patient, the provider wants to know that and tell that to the patient.

—Caitlin Chisholm, MS, CGC
investigating possibilities that might facilitate standard periodic reinterpretation of variants. In addition, the lab is developing pathways to more easily allow clinicians, in consultation with patients and families, to request a reinterpretation or reanalysis in so-called cold cases, where no diagnosis had been made.

**A DUTY TO CONTACT PATIENTS?**

None of the sources CLN interviewed contact patients directly—all share any new information only with the ordering provider or clinic. They recommended that both consent forms and direct counseling sessions inform patients that interpretations can change based on new information and encourage patients to update their contact information as appropriate.

“Everybody agrees on the principle that if the lab knows new information that would impact how someone takes care of a patient, the provider wants to know that and tell that to the patient,” Chisholm said, “but when you get into the nitty-gritty of how to make that work, it gets a lot more complicated.”

Chisholm tells patients who receive a VUS report the onus is on them to call the lab back in a year or two to trigger a reinvestigation. “That works out well for patients who are highly motivated and engaged, and sophisticated and savvy with the medical system, but the majority of patients never call us back.”

**CLEARING HURDLES**

Clinical laboratories face several challenges in both reinterpretations and recontacts. One is information. ClinVar is one of the only public databases for multiple labs, Park said, but not every lab submits material. In some cases, information available on a variant in a database has been reported by just one lab, which potentially causes diagnostic uncertainty. And, people from underrepresented minorities are much less represented in the databases, too, Lockwood noted. Efforts like the National Institutes of Health’s All of Us research program, which aims to gather data from 1 million diverse Americans, should help.

The Dutch laboratories surveyed cited workload as a factor impeding active, periodic reinterpretation, with the process seen as “laborious and unamenable to complete automation,” although El Mecky, Johansson, van Langen, and their co-authors suggested that reclassifying only variants for which clear, new evidence is present regarding a pathogenic or benign effect could benefit patients without exhaustive database searches.

Lack of reimbursement for the time and effort spent on reanalysis is another concern, Deignan said. “There’s a sense that we should make sure people have updated classifications and reports when possible, and to do what’s best for patient care, but other than a re-review of the entire case, for which there is a CPT code, a one-off variant reevaluation isn’t typically thought to be a reimbursable activity.”

Some labs are looking for advanced software tools to help. For example, a portal through which she could push variant updates automatically to providers or patients would be helpful, Chisholm noted. While no computational barriers exist to reinterpreting variants on a regular basis, getting the diagnosis correct can only be solved through clinical trials and better basic science research directed at disease models of those specific variants, Park cautioned.

Eventually, said Deignan, there will be enough information in ClinVar and other databases that labs will discover that variants new to them may already have been vetted by several others.

Whole-genome sequencing also is changing the field, Lockwood said. “We’re going from studying 1.5% of the genome to three billion base pairs—it’s a pretty significant jump,” she observed. “We still don’t know that much, but this isn’t a problem that’s going away anytime soon, and the more sharing we can do across the entire community, the faster we’re really going to be able to implement broad genomic medicine across different disease indications or healthy population screening.”

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Why Clinical Laboratorians Should Embrace the
A CASE FOR LEARNING R AS A GATEWAY TO LABORATORY MEDICINE’S DIGITAL FUTURE

BY SHANNON HAYMOND, PHD, DABCC, FAACC, AND STEPHEN MASTER, MD, PHD, FAACC
like many other industries, clinical laboratories are becoming more reliant on data analytics. Clinical laboratories generate, process, and store transactional data with high quality and efficiency. These data are required for patient care and quality assurance activities and increasingly are used for operational decisions. To analyze all these data, laboratories often rely on commercial spreadsheets or other specialized software applications. However, these programs can be functionally limited and often are not suitable for more complex statistical analyses and visualizations or for analysis of large or high-dimensional datasets. Importantly, the analysis and visualization workflows in these programs have limited reproducibility and transparency.

In contrast, R is a comprehensive, open source, platform-independent, freely available programming language, and it has a massive, worldwide user and contributor base. These characteristics make R ideally suited for clinical laboratorians. Applications of R in medicine—and specifically among clinical laboratorians—are growing due to increased visibility of R’s versatility and the availability of relevant, focused training.

Tools for almost any conceivable application have been written in R and publicly shared, enabling adaptation to a variety of user interests. Further, analyses carried out with R are highly customizable, reproducible, and can be automated. R is heavily utilized for its graphic and reporting capabilities, including the ability to render publication-quality figures with interactivity and to generate web-based dashboards and other reports in a variety of formats.

WHAT IS R, AND WHAT ARE ITS BENEFITS?
As a statistical programming language, R allows laboratorians and others to transform and analyze data and communicate results. It includes a wide variety of capabilities that provide greater functionality for working with data than Microsoft Excel and other commercial data analysis programs. R uses text-based commands to process data, and as such it functions as a full-fledged programming language for the advanced user.

Unlike Excel and many other graphical user interface (GUI)-based programs, R’s reliance on text-based structure makes it straightforward to review at any time the commands used in a data processing pipeline to ensure that the correct steps were taken. Furthermore, the ability to view the underlying commands facilitates transparency and reproducibility of analyses.

The same text commands are used regardless of the size of the dataset; thus, it is just as easy for the user to perform an analysis on 1 million test results as it is to perform that analysis on 10 results. This feature makes it simple to automate and scale any process with R. In addition, the graphing capabilities of R far surpass that of Excel and many other GUI-based programs, in both functionality and potential for customization and automation.

GETTING STARTED WITH R PROGRAMMING
 Though users can program with R from the command-line interface of a computer, it is common to use an integrated development environment (IDE) like RStudio. RStudio provides a cross-platform (i.e., works the same on Windows and Mac) graphical interface to write and execute code and to configure and manage components of R environments, including data, plots, results, versions, and packages. Similar to other IDEs, RStudio includes several features that make writing and debugging code easier and more efficient. And unlike some other IDEs, it offers smooth integration with tools for interactive documentation and dynamic report generation in a variety of formats (e.g., .doc, .pdf, .html).

FIVE KEY ATTRIBUTES OF R
Open Source
As R software is freely available and open source, clinical laboratorians can download it at no charge and deploy it widely in their labs or hospital systems without any licensing fees. Open source means that the underlying code for R can be downloaded and, in principle, edited if necessary. This is important because it ensures that R does not depend on a commercial entity for bug fixes and empowers a large population of developers who are able to audit the underlying code, minimizing the chance for security issues or other source code errors and ensuring ongoing development of the software. Open source software also allows any suitably skilled individual to examine exactly how the software works, rather than relying on it as a “black box.” While the continued evolution and enhancement of the code base can create compatibility issues over time, programmers offer packages and workflows designed to help with this issue.

A Broad-Based Community of Users
R is widely used and supported within statistical communities and data-driven industries. Given the rapid pace of development in analytical techniques, such as machine learning or artificial intelligence, it is important that software packages continually evolve. The two dominant choices for data science as of this writing are R and Python (also freely available), and in both cases it is now possible to adapt code developed on one platform to run on the other. Consequently, for almost any statistical method, new or old, there is likely
at least one freely available add-on package to implement it within the R environment. These packages are available on popular software-hosting sites, including the Comprehensive R Archive Network (CRAN; https://cran.r-archive.org) and GitHub.

As one example, Holmes and Buhr have recently published work related to extracting reference intervals from laboratory results (1). While they developed a corrected version of the traditional Hoffmann method that runs in R, they were also able to easily implement a statistically superior (and more algorithmically complex) approach using mixture modeling based on freely available code. The ability to use superior, more accurate statistical methods by taking advantage of the massive repository of available add-on packages is a significant advantage for laboratorians.

Importantly, the R community is recognized for its purposeful inclusivity, both in welcoming diversity among members and in fostering new members’ ability to learn the language.

Integrated Tools for Sharing Results
R provides a number of convenient tools for sharing and communicating results with dynamic reporting and the potential for interactivity. In particular, R supports the development of web-based dashboards and user interfaces and applications. There are several methods for creating graphics interfaces in R, including Shiny, a package for creating general web-based interfaces to R programs.

Among other things, these methods make it possible for a laboratorian to develop interactive business intelligence-style dashboards for operational management that would otherwise require commercial software, such as Tableau or QlikView. Custom R-based reports can be widely deployed for use by members of a laboratory who do not have any knowledge of R programming and do not have R installed.

With R, a laboratorian can also readily turn analyses into presentations or high-quality documents. Analysis and reporting can also be automated to occur on a user-defined schedule (i.e., every day at 8 a.m.).

A Perfect Fit for Clinical Laboratory Data
R is ideally suited for the type of data that clinical laboratories typically generate. Most lab datasets are structured in a rectangular format, meaning that variables are in different columns, and samples are in rows. For example, a typical laboratory information system data report might show a different patient result on each row, while columns would list test date and time, patient identification, test name, result, units, reference range, and other data. This format is routinely handled in R as a data frame, and many native tools have been provided in R for processing such data.

Even if raw data are not optimally formatted, R excels at transforming data from a variety of formats into rectangular data frames. In fact, some of the most prominent R packages developed over the past few years (the so-called tidyverse packages for dealing with tidy data) are optimized to import, structure, transform, summarize, model, plot, and communicate these types of datasets (2). As a result, laboratorians can more easily perform frequently-conducted laboratory data processing tasks, from generating turnaround time reports to looking at global distributions of results by assay. Moreover, they can share results in PDF reports, interactive dashboards, or other formats.

R is also heavily utilized in high dimensional data analyses, common to ’omics, because of its comprehensive and cutting-edge package library of statistical methods. This includes packages specifically built for genomics (e.g., Bioconductor project) and metabolomics (e.g., XCMS, MetaboAnalyst).

Reliable Scalability
R can be scaled for use across the entire healthcare enterprise—from one person downloading it on a personal laptop or workstation to a group of laboratorians, clinicians, or analysts who want to collaborate on a large project. Similarly, if an institution wishes to implement a bioinformatic pipeline or make Shiny dashboards available organization-wide, commercially supported tools and services can be purchased to enable these workflows.

R integrates seamlessly with many other popular data science technologies (e.g., Python, SQL, Spark, TensorFlow, Microsoft PowerBI,
of complete blood counts, and ignore other complete blood count elements, or even more complicated permutations). Such calculations in Excel could require manual processing prone to errors.

In contrast, R not only efficiently processes complex rules, but also does so in a reproducible way. If an individual makes a copy/paste error in Excel, it may never be detected; however, R code can be reviewed at a later time for correctness, and it can be reapplied to a new dataset in the same format without starting from scratch. This makes R ideal for recurrent tasks such as calculating turnaround times, assessing quality control compliance, tracking population statistics, and other operationally relevant data. Once data have been analyzed, R can be used to communicate the results in various formats.

In addition to operational work, R supports clinical laboratories’ needs for more advanced analytics and statistical modeling. There is growing interest in applying artificial intelligence/machine learning approaches to laboratory data in order to predict disease. R packages provide access to every major approach in this area, from straightforward logistic regression to random forests and even deep learning.

We have used R, for example, to analyze hematology analyzer results and build a random forest model that flags samples from patients with myelodysplastic syndrome (3). This required no proprietary software—only the freely available data processing tools from R to load and process data, create training and test datasets, build a random forest model, and plot receiver operating characteristic curves showing the performance of this model on independent datasets. Given the importance of predictive analytics for the future of laboratory medicine, R provides an ideal tool for clinical laboratorians to learn about or experiment with these new analytic techniques.
FOR LABORATORIANS TO EMBRACE AND THRIVE IN THIS FUTURE, WE WILL NEED IMPROVED TOOLS TO PROCESS THE RAPIDLY CHANGING STREAMS OF DATA THAT WE PRODUCE.

RESOURCES FOR NEW R PROGRAMMERS
The aforementioned user and contributor base has embraced the open source movement. This user community generously creates and shares resources for learning R in a variety of formats (Table 1). Though the available content is largely not specific to laboratory medicine, learners can quickly and easily find educational materials—many free—for most any application of R through an Internet search or exploration of a book.

Translating general R principles for data manipulation, analysis, and visualization to laboratory-related problems is usually straightforward. Though no prior programming experience is needed to learn R, those new to programming might find it challenging at first. That said, R is one of the fastest growing programming languages and is experiencing a surge of interest within pathology and laboratory medicine.

Learning R requires working with data and writing and executing code. The first steps in learning R involve gaining access to R and RStudio. There are several ways to accomplish this, including downloading and installing R and RStudio or initiating a free RStudio Cloud account (rstudio.cloud). R includes many built-in datasets that are commonly used for demonstrations of package functionality and in tutorials.

Self-paced education is available through several massive open online course formats and from websites focused on R education, examples of which are listed in Table 1. These resources encompass, for example, comprehensive curricula that teach the basics for using R to wrangle, analyze, and visualize data; modules with targeted instruction for performing a specific analysis in R (e.g., build and validate time series forecast models); and other, more focused tutorials on how to use a particular R package or function (e.g., convert datetime formats).

Help with R is not hard to find. For example, the R-bloggers website (r-bloggers.com) lists tutorials and news related to R. A popular source for troubleshooting and for finding example code is Stack Overflow (https://stackoverflow.com/questions/tagged/r), a question and answer site that is a rich resource for R-related information. Clinical laboratorians also can explore a number of books for learning R (Table 2). R for Data Science by Hadley Wickham comprises the foundation of many introductory level short courses and online resources. It is considered a contemporary must-read for those beginning to learn R.

Content geared specifically for laboratory medicine professionals is also available with more and more being developed over time. In recent years, AACC and other professional societies have offered short courses designed for learners with varying levels of R experience, and several are planned for the 2020 AACC Annual Scientific Meeting in July.

Content in these sessions often covers method validation, instrument interfacing, and test utilization reporting. More advanced topics on predictive modeling using laboratory results and database integration have also been presented.

DATA ANALYTICS IS IN YOUR FUTURE
We believe that clinical laboratories will require increasing use of data analytics to optimize operations, manage utilization, and provide improved interpretation of complex laboratory data in the context of patients’ medical records. For laboratorians to embrace and thrive in this future, we will need improved tools to process the rapidly changing streams of data that we produce. R provides an excellent format for learning about and, ultimately, implementing the types of computational tools required in a new era of laboratory medicine. Importantly, the skills and computational thinking that a laboratorian acquires by using R also readily translate to other programming languages and informatic approaches. R provides an ideal tool for clinical laboratorians to embrace our data-oriented future.

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THE BATTLE FOR A BETTER SEPSIS TEST

BY JEN A. MILLER
Laboratory medicine professionals know all too well that sepsis not only is a major problem but also that there’s no foolproof way to test for it. Current sepsis testing is “less than ideal,” said T. Scott Isbell, PhD, DABCC, associate professor of pathology at Saint Louis University School of Medicine in Saint Louis. “We don’t have a single biomarker that we can rely on to be able to say ‘if we measure this, it’s sepsis. If we detect it and it’s above this amount, it’s sepsis,’” he said. “That’s related to the fact that sepsis is a very complex, heterogeneous syndromic type of problem. It’s been very difficult for us to find one thing to latch onto.”

Some patients clearly are either at risk for sepsis or already septic, so there’s little guesswork in how to treat them. “For someone coming in the [emergency department] who’s obviously very sick, that’s easy: broad spectrum antibiotics, get the patient in the [intensive care unit], and ask questions later,” said Tim Sweeney, MD, PhD, co-founder and CEO of Inflammatix, a molecular diagnostics company developing tests for sepsis. “But for the vast majority of patients, it’s not obvious. There’s a big gap in what clinicians need and the tools that they’re offered, especially in diagnostics.”

Moreover, there is no one type of septic patient, Isbell added. “It can range from a young child with a small abrasion on a leg that turns into sepsis to a 90-year-old person in a nursing home with a urinary tract infection whom we fail to recognize is septic because she also has dementia,” he said.

**AN URGENT AND COMPETITIVE SEARCH FOR ANSWERS**

Even as health systems and clinical laboratories grapple with how best to deploy existing assays like lactate and procalcitonin, academic researchers and industry entrepreneurs remain engaged in a fierce competition to find the biomarker, combination of biomarkers, or perfectly tuned statistical algorithm that can reveal the actionable insights clinicians crave.

One such company exploring the use of a novel biomarker is Swiss medtech company Abionic, which developed abioSCOPE, a nanofluidic immunoassay technology that measures for pancreatic stone protein (PSP). “PSP is the only marker to identify sepsis from noninfection inflammation 24 hours before the current methods, giving physicians a clear signal when they start the antibiotic therapy,” said Abionic CEO Nicolas Durand, PhD.

Abionic first demonstrated the kinetics of this marker by studying patients with severe burns. The company started with these patients, Durand said, because they come into hospitals without an infection, and their chances for developing one and therefore sepsis are high. Abionic found that PSP “was rising fast, much earlier than any other existing sepsis marker,” he said.

Abionic has tested abioSCOPE in 14 hospitals in Europe on several hundred patients and confirmed that in more than 85% of cases, practitioners could have diagnosed sepsis more than 24 hours earlier than the standard of care. The company is currently in its first U.S. clinical trial to validate those results for the Food and Drug Administration (FDA), working in seven hospitals. Abionic plans to market the first PSP tests in Europe in the second quarter of 2020.

Another road to a better test might be a precise combination of markers. Inflammatix—winner of AACC’s Disruptive Technology Award at the 2019 AACC Annual Scientific Meeting—is using machine learning algorithms that look at the expression of multiple messenger RNAs in the blood that reflect the immune system’s response to infection. Sweeney said that this process identifies the presence of a bacterial or viral infection and determines if a patient has or is likely to develop sepsis. The test is designed to give point-of-care results in 30 minutes or less.

“We go ask the immune system,” he said. “If we can figure out what the immune system is reacting to, then we know how to treat the patient. We think this will be the first product to say: First, let’s figure out if you have an infection, and, second, let’s figure out if you have sepsis.”

In January Inflammatix secured $32 million in funding to power its commercial launches in Europe.
and regulatory submissions for FDA. The new financing follows a November 2019 contract worth up to $72 million with the U.S. Biomedical Advanced Research and Development Authority to develop its tests for acute infections and sepsis. Sweeney hopes to submit Inflammatrix’s HostDx sepsis test to FDA in 2021 and launch in Europe the same year.

In a third example aimed at the point of care, U.K.-based QuantuMDx and California-based Ontera are working together on a solution that they believe can determine, in one system, whether a patient has a bacterial or viral infection and then whether or not the organism is antibiotic resistant. QuantuMDx has developed a cassette-based device that separates and concentrates pathogen cells from a sample using electronic fields, while Ontera is known for its nanopore biosensor measurement system. “The combined system is a panel that allows [the operator] to do both in that first hour” rather than waiting 24 hours for a culture, said Ontera CEO Murielle Thiriau McLane. She expects the test system to be on the market at the end of 2022.

ANALYZING BYTES INSTEAD OF BLOOD
Even as promising research emerges on new biomarkers and instruments, health systems are also moving forward with big data approaches that aim to interpret existing data using machine learning. These data points include laboratory values as well as traditional vital signs and co-morbidities in patient records.

In May, HCA Healthcare, which has 185 hospitals and 2,000 sites of care in 21 states and the U.K., announced that it had developed an algorithm driven, real-time system called Sepsis Prediction and Optimization of Therapy (SPOT) Technology. According to HCA, in conjunction with the use of evidence-based clinical interventions SPOT has helped save about 8,000 lives in the last 5 years.

Other health systems have been evaluating a predictive analytics approach as well, taking advantage of new algorithms offered by electronic medical record (EMR) companies. At Saint Louis University Hospital, Isbell and the hospital’s sepsis committee implemented one such system available from Epic. The algorithm runs continuously in the background to check patient records every 15 minutes and sends clinicians an alert via the EMR if the algorithm’s score predicts a patient is at risk of developing sepsis. In addition to demographics, vital signs, and comorbidities, the algorithm also calculates the scores using hematologic parameters from the clinical laboratory, as well as creatinine, HbA1c, procalcitonin, and other results.

During a session at the 2019 AACC Annual Scientific Meeting in which Isbell presented initial results of using the algorithm, he noted that its specificity is suboptimal, especially in the emergency department. Isbell and the sepsis committee are working to fine-tune the system to determine how they can improve specificity and avoid any potential over-treatment with antimicrobials. There’s also the question of clinicians’ acting on the alerts: So far only about 60% respond by accepting the suggested order set.

Ultimately, experts expect the war on sepsis to continue on multiple fronts: new biomarkers, predictive analytics, and insight into immune system response. “The new tests focused on the immune response along with machine learning approaches are promising and move us toward the ultimate goal—prediction and prevention of sepsis,” Isbell commented.

THE TOLL OF SEPSIS

270,000 DEATHS
According to the Sepsis Alliance, sepsis kills about 270,000 Americans per year, making it more deadly than breast cancer, prostate cancer, and AIDS combined. Up to 30% of patients diagnosed with severe sepsis do not survive, and up to 50% of survivors suffer from post-sepsis syndrome. Mortality for sepsis increases by 8% for every hour treatment is delayed.

$24 BILLION
Sepsis is the most expensive inpatient cost in American hospitals. The average hospital stay for sepsis costs approximately double the stay for any another diagnosis, and the annual rate of growth of sepsis costs in hospitals is three times the rate for hospital costs overall, according to the Centers for Disease Control and Prevention.
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Disclaimer: AACC collected 60 mL of blood from volunteer donors attending the AACC Annual Meeting in Atlanta, GA in order to establish the 99th percentile for cardiac troponin in a healthy population. After collection, the blood was processed on site, divided into equal sample sizes and then transported to CDC for storage at -80°C. Samples were de-identified and no test results will be provided to donors. Sets of donor samples are being offered to IVD manufacturers of cardiac troponin assays for purchase. AACC has undertaken this activity as part of its mission to further scientific research. THE DONOR SAMPLES ARE PROVIDED "AS IS". AACC DISCLAIMS ALL WARRANTIES INCLUDING IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE.
Benchmarking: A Promising Practice for Lab Stewardship Toolkits

As clinical laboratories continue to experience pressures to lower costs and enhance performance in a resource-constrained environment, our need for data-driven tools to guide our operations is ever-increasing. In this setting, looking at solutions employed in other industries that face similar pressures to produce the highest-quality products at competitive price points can prove useful.

Benchmarking—the practice of measuring performance against a target using a specific indicator—is used broadly in other industries, especially manufacturing, to tackle these challenges. Indicators might include things like cost (how inexpensively can I deliver a product), productivity (how efficiently can I make something), or defect rate (how consistently can I make something). While benchmarking applications are relatively nascent in clinical laboratories, some studies have been published recently that highlight its promise (1,2,3). Given the similarities between clinical laboratories and the production of other goods, benchmarking represents a real opportunity for improving our stewardship activities.

Benchmarking Approaches

Benchmarking takes many forms. Process, or best practice, benchmarking is particularly relevant for clinical laboratory stewardship. In this model, one identifies processes and relevant best practices to establish target improvement goals. Performance in these processes is then measured against the target after the best practices have been implemented.

There are two main methods for establishing a target: absolute and relative. Absolute benchmarking makes comparisons based on guidelines. In this case, the indicator would be a lab’s performance relative to the standard of a guideline. This is a gold standard as guidelines provide accepted targets for performance comparison.

In contrast, relative benchmarking makes a performance comparison between groups and models the performance of industry leaders. In this case, laboratory managers might look for comparisons within their own organizations or between organizations. For the former, this might involve assessing variation in performance among providers in selecting the correct laboratory test for an indication.

Relative benchmarking is useful in the absence of accepted guidelines. However, while relative comparisons reveal variation, they might not shed light on the appropriateness of a given practice. One organization might use less of a given resource than another organization, but what drives that practice or whether the practice contributes to better care delivery might not be clear. Some clinical laboratory managers might have experience with relative benchmarking through initiatives like the College of American Pathologists’ Q Probes or a benchmarking service like Vizient.

Developing Benchmarking Targets

The process for developing and implementing a benchmarking initiative (Figure 1) shares a lot in common with the Plan-Do-Study-Act process improvement tool. The first steps are to select a process and identify a best practice, either in comparison to a guideline or some other group. From there, labs need to measure baseline performance for their current process and compare it to the target. When lab staff identify a gap, they can implement changes while continuing to measure performance. Multiple cycles of implementing changes and evaluating performance might be necessary to get to the target performance level. Once a lab reaches its goal, leaders can refocus resources and begin the cycle again with a new process.

Key Considerations

Several important considerations raise the likelihood of success when selecting a stewardship target amenable to benchmarking.

If Something Is Measurable, It Is Manageable

When a lab can measure its performance via an indicator, this gives the lab team a means to measure improvement. However, some things are inherently more measurable, and thus more manageable, than others. For example, the ABIM Foundation maintains useful guidelines for stewardship through its Choosing Wisely initiative (4). Recommendation 27 of the American Society for Clinical Pathology’s Choosing Wisely guidelines states, “Do not repeat hepatitis C virus (HCV) antibody testing in patients with a previous positive HCV test. Instead, order hepatitis C viral load testing for assessment of active versus resolved infection.” The volume of repeat HCV antibody testing is relatively straightforward to monitor and thus makes a good indicator for measuring improvement. Conversely, Recommendation
Exercise Caution When Basing a Target on Another Organization’s Performance

When comparing themselves to another group, clinical laboratories should choose peer organizations carefully. How similar or dissimilar one lab is to another might determine the appropriateness of modeling one’s performance against the other. For example, a lab seeking to benchmark its blood product utilization might want to choose organizations that have similar case complexity and similar scope of services, like running (or not) a transplant or extracorporeal membrane oxygenation program. In making comparisons against another organization, a lab would also need to ensure that both entities measure the same metric in the same way. For instance, if a metric involves units issued per day, both organizations need to measure patient days in the same way for a valid comparison.

Serve Patients Well and the Dollars Will Take Care of Themselves

This will be common wisdom to readers of Clinical Laboratory News, but labs’ first focus should be taking care of patients, with bottom line concerns following. Healthcare organizations optimize their value equation by increasing quality and decreasing costs. Clinical laboratories represent only approximately 3% of annual healthcare spending in North America (5). Accordingly, labs will do well to maximize our contribution to the quality of patient care instead of starting with the goal of reducing lab costs. Hospitals have relatively more opportunities to tackle the 97% of costs. Hospitals have relatively more opportunities to tackle the 97% of costs incurred outside laboratories.

Chances to Benchmarking Success

Chances to Benchmarking Success

Common challenges with implementing benchmark initiatives include data liquidity (i.e. data availability) and organizational expertise in working with laboratory data to generate insights. Data analytics is expensive, so finding ways to demonstrate the value of investing in this resource through measured performance improvement is a great way to build momentum and support for additional resources. Starting small and building on those wins is a good practice to secure more investment in analytics resources. Labs also face the challenge of hospital department budgets typically being managed in silos. Improved outcomes or cost savings through laboratory initiatives might create wins for stakeholders outside a clinical laboratory but not the lab itself. Don’t be afraid to share those wins with others while simultaneously promoting the lab’s contributions to those successes. Collaboration allows all parties to win while keeping patients at the center of the effort.

Final Thoughts

Benchmarking provides a powerful resource for labs to confront the performance and cost pressures they face today. Focusing on good clinical practices with measurable indicators of performance provides a solid practice to improve the value of laboratory services to our patients.

References


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This is a very exciting era in laboratory medicine as virtually every day new genetic tests and emerging laboratory technologies enter the market. With these advancements also comes the (fun) challenge of distinguishing clinical testing from research testing. Making this distinction matters in two key ways. First, from a regulatory standpoint, it would be financially irresponsible to bill patients and insurers for research testing. Second, in terms of clinical implications, we have to demonstrate the value of classifying variants (clinical validity), then show that variant classification impacts patient clinical outcomes (clinical utility). Laboratory test stewardship programs provide an important foundation for striking an appropriate balance between implementing new genetic tests and meeting standards for clinical validity and utility, paying particular attention to the size of genetic panels.

Since the 1980s, identification of genetic markers has supported tailored clinical diagnoses and therapies, and as such, genetic testing has become an attractive diagnostic tool. Single gene testing has progressed to more expansive gene panels, exome, and even genome sequencing. While novel technologies provide the potential for increased efficiency, more comprehensive analysis, and reduced invasive testing to guide clinical care, the financial impact and potential secondary findings of these methods necessitate a balanced approach to responsibly implement precision medicine in clinical practice.

A Question of Value
To be good laboratory testing stewards, we must address questions about the value of new and emerging technologies. Simply defined, value is the quality of a test divided by its cost. While mathematical equations are straightforward precisely because they are objective, the perspective of “value” varies for each stakeholder (patients, providers, laboratorians, and payers), and these perspectives often have competing interests.

A crucial consideration is the timeline in which novel technologies are implemented clinically and, perhaps even more challenging, the elements that distinguish research testing from clinical testing. Clinical testing (for all laboratory tests) encompasses analytical validity, clinical validity, and demonstrated clinical utility. In some cases, genetic tests are Food and Drug Administration (FDA)-cleared for specific clinical applications. Patients and insurers typically are responsible for the cost of clinical testing. As new assays appear on the market, they might demonstrate analytical validity, but lack evidence establishing clinical validity and utility.

Requiring patients or insurers to cover the cost of building this evidence for a new assay is contrary to laboratory stewardship principles. Clinical testing for all laboratory tests encompasses analytical validity, clinical validity, and demonstrated clinical utility. In some cases, genetic tests are Food and Drug Administration (FDA)-cleared for specific clinical applications. Patients and insurers typically are responsible for the cost of clinical testing. As new assays appear on the market, they might demonstrate analytical validity, but lack evidence establishing clinical validity and utility.

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The Troubling Issue of VUS
When adopting new genetic tests, a second consideration is the size of a panel. A bigger panel with more genes or genetic markers does not necessarily improve diagnostic clarity. With an increased number of assayed genes comes greater potential for variants of uncertain significance (VUS). These variants can be particularly challenging because genomics is still relatively new and we collectively lack sufficient data to confidently classify variants...
as pathogenic or benign. In the absence of evidence supporting these classifications, laboratories assign variants to a VUS “holding cell” category. Once sufficient evidence arises, variants originally classified as VUS will be upgraded (to pathogenic or likely pathogenic) or downgraded (to benign or likely benign).

One would predict that approximately half of all VUS would be upgraded and half downgraded. However, in what is termed the “VUS paradox,” there is significant discordance between the expected and observed reclassification of variants. It is much more common for VUS to be reclassified as benign or likely benign (downgraded) than to be upgraded (1). Given the large body of evidence demonstrating that VUS can cause patient harm, labs act irresponsibly if they inappropriately classify variants as VUS. As laboratory stewards, we need to ensure that any gene panel ordered is the best fit for the clinical question at hand instead of using an inappropriately large gene panel likely to result in challenging VUS.

From the perspectives of patients and insurers, it is critical to demonstrate how outcomes will improve as a result of using this new technology. From a consumer perspective, cell-free DNA prenatal screening is appealing—it’s less invasive than diagnostic testing like amniocentesis and can reveal a baby’s sex in the first trimester of pregnancy. However, this new modality remains a screening test and actually can complicate decision-making when used as a diagnostic test. This is because it tests both maternal and fetal cell-free DNA and uncovers findings that can be difficult to interpret.

For example, numerous cases have been reported of detecting unknown maternal cancer, which is called occult maternal malignancy. If a cell-free DNA prenatal screen identifies a potential maternal cancer, the affected patient necessarily will embark on a diagnostic hunt for a tumor during an already difficult period of pregnancy. This can be challenging from an insurer’s perspective as well because finding a tumor based on cell-free DNA prenatal screening results might necessitate expensive imaging studies.

While there is great promise in expanding the technology of cell-free DNA to detect single-gene Mendelian disorders, the American College of Obstetricians and Gynecologists has issued a practice advisory that, “there has not been sufficient information regarding accuracy and positive and negative predictive value … [and thus,] single-gene cell-free DNA screening is not currently recommended in pregnancy” (2).

**Conclusion**

The pace at which new technology is being developed and implemented in clinical settings will undoubtedly stay in the fast lane. As such, laboratorians need to consider how to best integrate novel technologies into clinical practice (or not), striking a responsible balance between true clinical research and ancillary testing.

Using alternate funding sources for clinical research, including risk-sharing partnerships with insurers, has proven successful and may pave the way for clinical research to become true clinical testing. Practice guidelines are extremely valuable but often lag behind advances in technology precisely because they require a high burden of published evidence. An institutional approach utilizing an oversight committee, such as a laboratory stewardship committee, is an effective vehicle for evaluating implementation of new technologies and shifting appropriately from research to clinical testing when sufficient evidence exists for clinical validity and utility.

The genomic testing era is very exciting, and responsibly implementing a collaborative stewardship program is critical for ensuring that we offer the right test to the right patient at the right time.

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**Tina Lockwood**, PhD, DABCC, DABMGG, is an associate professor in the department of laboratory medicine and director of the genetics and solid tumor diagnostics laboratory at the University of Washington in Seattle. +EMAIL: tinalock@uw.edu
Multiple Coronavirus Tests Receive Regulatory Approvals Worldwide

As the coronavirus disease (COVID-19) epidemic continues to grow, regulatory bodies around the globe have authorized numerous tests for the coronavirus SARS-CoV-2—which was formerly known as 2019 novel coronavirus (2019-nCoV). In the U.S., the Food and Drug Administration first issued an emergency use authorization (EUA) for the Centers for Disease Control and Prevention’s (CDC) 2019-nCoV real-time reverse transcriptase polymerase chain reaction (RT-PCR) diagnostic panel, and has since granted all high-complexity labs permission to develop and perform their own tests for COVID-19 prior to receiving an EUA. As CLN went to print, FDA had also granted EUAs to Roche for its cobas SARS-CoV-2 test, which runs on the cobas 6800 and 8800 systems, and to Thermo Fisher for a SARS-CoV-2 test that runs on the company’s Applied Biosystems 7500 Fast Dx real-time PCR instrument.

In China, the National Medical Products Administration has granted emergency use approval to the Chinese company BGI and its subsidiary MGI Tech for three coronavirus-related products: the PMseq metagenomics sequencing kit for coronaviruses, the ultra-high-throughput sequencer DNBSEQ-T7, which the PMseq runs on, and a real-time fluorescent RT-PCR kit for COVID-19. In particular, the PMseq and DNBSEQ-T7 could aid with epidemic control by not only identifying patients with COVID-19, but also by dynamically tracking the mutation of SARS-CoV-2 via sequencing.

Other regulatory authorizations for COVID-19 tests include emergency use approvals granted by the Korea Ministry of Food and Drug Safety to Seegene and KogeneBiotech for the COVID-19 Real-time PCR assay and PowerChek 2019-nCoV Real-time PCR kit, respectively. Seegene’s test also received the CE mark, along with a molecular test for COVID-19 developed by Novacyt’s molecular diagnostics division, Primerdesign, and the Logix Smart Coronavirus COVID-19 test developed by Co-Diagnostics.
FDA OKS FIRST TEST FOR FRAGILE X SYNDROME
A suragen has earned de novo Food and Drug Administration authorization for the AmplideX Fragile X Dx and Carrier Screen kit, making this the first commercially available test that detects fragile X syndrome. Healthcare professionals can use the test’s results in conjunction with a patient’s family history and symptoms to diagnose this genetic condition. In individuals with fragile X syndrome, a segment of the X chromosome gene FMR1, known as a CGG trinucleotide repeat, is repeated in excess. The AmplideX Fragile X Dx and Carrier Screen kit analyzes blood to measure the number of repeats of the CGG segment in the FMR1 gene. This determines whether a patient has a number of CGG repeats that is considered either normal, intermediate, premutation (which increases the risk of having a child with fragile X), or full mutation. In addition to aiding in the diagnosis of fragile X and identifying carriers of fragile X-associated mutations, Asuragen’s test aids in the diagnosis of fragile X-associated disorders, including fragile X-associated tremor/ataxia syndrome and fragile X-associated primary ovarian insufficiency.

QIAGEN GETS CE MARK FOR BREAST CANCER CO-DIAGNOSTIC
The CE mark has been granted to Qiagen for its therascreen PIK3CA Rotor-Gene Q polymerase chain reaction (PCR) kit, which identifies breast cancer patients with activating mutations in the phosphatidylinositol-4,5-biphosphate 3-kinase catalytic subunit alpha (PIK3CA) gene. In collaboration with Novartis, Qiagen developed the test as a companion diagnostic for Piqray (alpelisib) using a worldwide co-exclusive license from Johns Hopkins University for PCR-based companion diagnostics that detect mutations in the PIK3CA gene. The test detects 11 clinically actionable PIK3CA mutations, which are estimated to occur in approximately 40% of hormone receptor-positive, human epidermal growth factor receptor-2 negative advanced breast cancer cases. It also analyzes DNA from both formalin-fixed paraffin-embedded tissue or plasma specimens. Qiagen’s receipt of the CE mark for this test follows on the heels of the Food and Drug Administration approving the test in 2019 as a companion diagnostic for Piqray in the U.S.

YOURGENE HEALTH EARN AUSTRALIAN APPROVAL FOR CHEMOTOXICITY TEST
Australia’s Therapeutic Goods Administration has approved Yourgene Health’s chemotoxicity diagnostics assay, Elucigen DPYD, which identifies cancer patients who are at risk of experiencing adverse effects from chemotherapy. Specifically, this genotyping test diagnoses cancer patients with dihydropyrimidine dehydrogenase (DPD) deficiency, which can cause severe and sometimes lethal side effects in patients taking the chemotherapeutic drug 5-fluorouracil (5-FU). This drug is commonly used to treat colon, esophageal, stomach, pancreatic, breast, and cervical cancers, and is metabolized by the DPD enzyme encoded by the DPYD gene. Researchers estimate that globally, more than 2 million people are treated with 5-FU every year, and of these, up to 20% will be hospitalized due to DPD deficiency and up to 1% may die.

Yourgene’s Australian distribution partner, Southern Cross, will market the Elucigen DPYD test in Australia. The test also previously received the CE mark in Europe in September 2019.

GENETRON HEALTH RECEIVES CHINESE APPROVAL FOR LUNG CANCER PANEL, SEQUENCING PLATFORM
The China National Medical Products Administration has approved two products from the Beijing-based company Genetron Health: a lung cancer panel called the 8-gene Lung Cancer Assay, and the high throughput next-generation sequencing platform, Genetron S2000.

The 8-gene Lung Cancer Assay detects PIK3CA plus seven genes that the 2018 National Comprehensive Cancer Network guideline recommends as biomarkers for non-small cell lung cancer: EGFR, ALK, ROS1, BRAF, KRAS, HER2, and MET. The test is based on Genetron Health’s One-Step Seq technology, which enables labs to complete the library construction process in one step of reaction, thereby minimizing manual operation and the chance of contamination. The test is compatible with both the Genetron S5 sequencing platform and the Genetron Chef system.

As for the Genetron S2000, this platform is designed for comprehensive genomic testing in high-throughput settings such as large hospitals and regional medical testing centers, with data output ranging from 55 to 1,440 gigabytes.

NEW YORK STATE APPROVES ENZO BIOCHEM’S MOLECULAR TESTS FOR STIS
Enzo Clinical Labs, a wholly owned subsidiary of Enzo Biochem, has received New York State approval for its CT/NG/TV tests, which detect Chlamydia trachomatis (CT), Neisseria gonorrhoeae (NG), and Trichomonas vaginalis (TV). The tests use liquid-based cytology sample collection and run on Enzo Biochem’s proprietary GenFlex instrument, a high-throughput molecular diagnostic platform that includes sample collection, sample processing, amplification, and detection. In addition to the CT/NG/TV tests, Enzo is currently developing assays for other sexually transmitted diseases for the GenFlex platform. GenFlex builds on Enzo’s proprietary Ampiprobe detection technology and is designed to overcome challenges with existing molecular diagnostic platforms, such as the need for multiple independent instruments for extraction, polymerase chain reaction setup, and detection. Enzo also projects that the GenFlex platform will help labs to achieve 30%-50% more cost savings than the closed molecular diagnostic systems currently on the market.
Walmart Launches Second Low-Cost Health Clinic
The multibillion-dollar retail company Walmart has opened its second full-service primary care health clinic, in Calhoun, Georgia. The Calhoun Walmart Health Center is partnering with various healthcare providers including Tivity Health to provide easily accessible, low-cost patient care without a strong focus on patients’ health insurance status. The health center offers medical consultations, procedures, and diagnoses all at one facility that Walmart is pitching as an alternative to doctors’ offices. In a separate facility adjacent to the Walmart Supercenter, patients also receive services such as primary and urgent care; lab tests, X-rays, and other diagnostics; counseling; dental; optical and hearing services; and health education classes.

The health facility employs qualified medical professionals and will operate just like any other medical center that allows patients to create new and recurring appointments. As part of the grand opening, the company announced a donation to Susan G. Komen to increase women’s health services for underserved patients in Georgia. Walmart launched its first health clinic in September 2019 in Dallas, Georgia, and expects to expand to other locations in the future. “The issues of healthcare affordability and accessibility are two of the greatest and most prevalent concerns in our country today,” said Sean Slovenski, senior

Shriners Hospitals, Jackson Lab Collaborate on Pediatric Conditions
Shriners Hospitals for Children and The Jackson Laboratory (JAX) have teamed to advance research on orthopedic conditions in pediatric patients. With the opening of Shriners Hospitals’ Genomic Institute, Shriners Hospitals and JAX aim to focus on conditions such as clubfoot, scoliosis, and osteogenesis imperfecta.

Under the terms of the agreement, Shriners Hospitals will implement next-generation sequencing of DNA samples collected from children diagnosed with one of the specific conditions throughout all hospital locations in North America. In addition, the JAX team will analyze each sample and develop mouse models carrying the same genetic variations as patients to further new research. Through genetic research, the parties envision a future in which clinicians will be able to immediately diagnose and treat each rare condition and prevent a lifelong medical struggle.

“Harnessing the power of genomics to understand the basis for orthopedic and other pediatric diseases is of the utmost importance,” said Charles Lee, PhD, FACMG, scientific director and professor at The Jackson Laboratory for Genomic Medicine. “This research can bring hope to countless families, and we’re looking forward to working with Shriners Hospitals to help children around the world.”
vice president of health and wellness at Walmart U.S. “We have been prioritizing how Walmart can be a leader in promoting better health outcomes for people in their communities, on their schedules, and within their budgets.”

**QUEST ACQUIRES BLUEPRINT GENETICS, PARTNERS WITH SIEMENS HEALTHINEERS**

In an all-cash agreement, Quest Diagnostics acquired Blueprint Genetics to improve testing and pharmaceutical drug research and development for rare and genetic diseases. Quest is hoping to improve its next-generation sequencing (NGS) capabilities by leveraging Blueprint Genetics’ expertise with interpreting gene variants in NGS data. Ultimately, Quest’s goal is to continuously develop new Food and Drug Administration-approved tests for a number of genetic diseases that currently affect an estimated 30 million Americans.

“Teaming up with Quest will allow us to extend our capabilities in the United States as well as in Canada and other countries where we already have strong and growing client relationships,” said Tommi Lehtonen, vice president and general manager of Blueprint Genetics. “While we considered joining forces with several organizations, Quest’s genetics leadership, national infrastructure, and strong cultural fit made it the perfect partner from which to extend our reach to new providers and patients.” Quest plans to deploy Blueprint’s genetic testing in pediatric and academic hospitals.

Following the deal with Blueprint Genetics, Quest announced another deal, this time a collaboration with Siemens Healthineers on immunoassay testing. Siemens was chosen by Quest to be its main supplier for immunoassay testing using Siemens’ Atellica Solution analyzer. The system will allow Quest to significantly increase its volume of immunoassay testing, the companies said, as well as the turnaround time for results. Per the agreement, both companies plan to launch up to 120 Atellica Solution immunoassay analyzers in 19 core laboratories across the U.S. They also plan to open a Quest lab in New Jersey that will feature the testing system beginning in 2021.

**FIRMS SEEK FDA APPROVAL FOR INTEGRATED PRODUCTS**

In a regulatory cooperation agreement, Biodiesix and Streck are seeking Food and Drug Administration (FDA) approval for combined molecular diagnostic testing and specimen collection products. The agreement is intended specifically for Biodiesix’s companion diagnostic tests for lung cancer and Streck blood collection tubes. By integrating the blood collection tools into Biodiesix’s collection protocols, company experts believe the partnership will facilitate sample transportation and therefore could decrease turnaround time.

Currently, the only FDA-approved sequencing tests are those that use tissue samples rather than blood-based samples. To improve the timeliness and accuracy of results, both companies are committed to receiving FDA approval and increasing the use of blood-based testing in labs. “Partnerships like this one between Streck and Biodiesix allow patients to receive critical results that can impact their quality of life and improve health outcomes for those most vulnerable,” said Connie Ryan, CEO of Streck. “We are excited to work with Biodiesix as we are both passionate about bringing this cutting-edge technology to the forefront of patient care.”

**THERMO, NANOPIN AIM TO REDUCE TURNAROUND TIMES**

Thermo Fisher Scientific is collaborating with NanoPin Technologies to advance blood-based infectious diseases detection technology. Under the partnership, the companies intend to develop clinical assays for infectious diseases that will ultimately reduce the turnaround time for results. “Time is critical when it comes to the diagnosis and treatment of patients suffering from infectious disease, and current methods do not facilitate prompt diagnosis and rapid evaluation of treatment response,” said Bradley Hart, senior director of clinical research, chromatography, and mass spectrometry at Thermo Fisher Scientific.

The partnership will combine NanoPin’s diagnostic platform with Thermo Fisher’s advanced liquid chromatography-mass spectrometry (LC-MS) technology and develop highly sensitive LC-MS-based workflows. Through study of disease-related antigens derived directly from patient blood samples, the parties hope to improve clinical decision-making and personalized patient care. “Through our agreement with Thermo Fisher, our unique diagnostic platform has the potential to change how infectious diseases, such as tuberculosis, are detected, treated, and controlled by solving the unmet needs of healthcare providers managing patient care throughout the world,” said Thomas Tombler, PhD, CEO of NanoPin Technologies.
What is the biggest challenge that labs face with sweat chloride testing?

A: The sweat test involves transdermal administration of pilocarpine by iontophoresis to stimulate sweat gland secretion, followed by collection and quantitation of sweat onto gauze, filter paper, or into a Macroduct coil and analysis of chloride concentration. Appropriate performance of the sweat test is crucial for accurately diagnosing cystic fibrosis.

The Cystic Fibrosis Foundation requires laboratories to maintain an annual quantity not sufficient (QNS) rate for this test of 5% or less for children older than 3 months and an annual QNS rate of 10% or less for neonates and infants 3 months or younger. This requirement aims to prevent repeat testing triggered by insufficient sample volume, which in turn increases the wait time for a definitive diagnosis, delays initiation of therapy, and reduces sweat testing’s overall cost-effectiveness. However, attaining sufficient sample volume remains a major challenge with sweat chloride testing.

When should labs perform sweat testing in newborns to avoid QNS situations?

In asymptomatic newborns with a positive newborn screening result or positive prenatal genetic test for cystic fibrosis, labs should evaluate sweat chloride when the infant is at least 10 days old, greater than 36 weeks gestation, and weighs >2 kg. In symptomatic newborns (for example, those with meconium ileus), labs can evaluate sweat chloride as early as 48 hours after birth if they are able to collect an adequate sweat volume.

Prior to testing, labs or clinicians should also provide parents of patients with a verbal explanation of the testing procedure as well as a written take-home explanation. This helps to ensure that infants are well hydrated prior to testing (and should be done in the case of adult patients as well).

What else can labs do to minimize QNS for sweat chloride testing?

First and foremost, labs should validate the sensitivity of their chloride detection method before putting it in place. Essential validation procedures include studies of accuracy, precision, and upper/lower limits of the analytic measurement range. In particular, the method should accurately detect sweat chloride at the lower end of the normal range (10 mmol/L).

Next, labs should specially train select staff members to collect and analyze samples, making sure to assess these individuals’ competency before they start working with patients. I recommend limiting the number of staff who do sweat chloride collection/testing so that the lab can easily monitor performance.

Labs should do a weekly review of QNS rate per person so that they can deal with deficiencies in training promptly. Establishing monthly meetings between laboratory staff and cystic fibrosis clinical team members can also improve sweat testing by increasing communication about pain points. If QNS rates are very high, labs should call in consultants to regularly review the sweat test procedure for areas that need attention.

Throughout sweat collection, transport, and analysis, lab staff need to take every precaution to minimize evaporation, contamination, and condensation of the sample. Steps that can help with this include avoiding the use of electrolyte-containing solutions during the testing process; following proper procedure for the filter paper/gauze or Macroduct coil; and limiting collection time to 30 minutes, as going beyond this can lead to sample evaporation. Ideally, labs should process the sample immediately, but if this isn’t possible, it should be stored appropriately. Experts also suggest bilateral testing to ensure that at least one adequate sweat sample is obtained.

Of course, even if labs implement all of these recommendations, a low rate of QNS situations will still inevitably happen. Whenever insufficient samples occur, labs should make sure not to analyze them and should never pool them for analysis.

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