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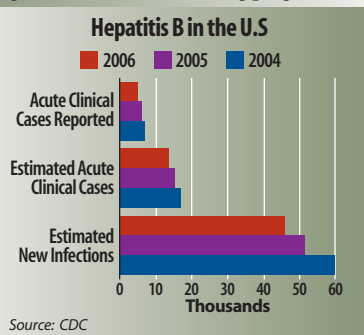
RECOMMENDATIONS REVISED FOR CHRONIC HBV TESTING

Based on a new look at epidemiologic data, CDC recently expanded its testing recommendations for chronic HBV infection, an effort to stem the rising incidence of the disease. A panel of researchers, physicians, and public health officials suggested the changes in light of data showing a high rate of HBV in certain populations.

Recent statistics show that the overall incidence of acute HBV has declined substantially since 1985, yet CDC estimates that 800,000 to 1.4 million Americans have HBV and that many are unaware of their disease.

While the rising incidence is not good news, drug therapy for the disease has improved. The advent of several effective antiviral drugs has made it possible to prevent or delay liver disease associated with HBV, underscoring the importance of identifying infected patients early in the disease process, when many are asymptomatic.

Serologic testing for hepatitis B surface antigen is the primary way to screen for HBV. Previous CDC guidelines called for testing pregnant



women, infants born to HBsAg-positive mothers, household contacts and sex partners of HBV-infected persons, people born in countries with HBsAg prevalence $\geq 8\%$, individuals, like healthcare workers, exposed to blood or body fluids, and people infected with HIV. In the revised guidelines, CDC expanded the testing recommendations to include people born in countries with HBsAg prevalence $\geq 2\%$, people with behavioral exposures to HBV, including men who have sex with men and injection drug users, individuals receiving cytotoxic or immunosuppressive therapy, and those with liver disease of unknown etiology.

While the overall prevalence of HBV in the U.S. is an estimated 0.3% to 0.5%, up to 3% of men who have sex with men, 6% of injection drug users, and between 1% and 2.6% of those born in foreign countries are estimated to have HBV. The recommendations also for the first time give health professionals guidance for effective management of HBV patients.

The full report is available online at <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5708a1.htm>.

ISO Accreditation Comes to America

Are Labs Ready to Embrace an International Quality Management System?

BY BILL MALONE

In September, Norway-based DNV Healthcare became officially recognized as a national accreditation organization for hospitals, the first new player in hospital accreditation in 40 years. On top of breaking into the venerable circle of accrediting bodies, the organization also brought something new to the shores of the U.S.: hospital accreditation based on compliance with the ISO 9001 quality management standard. Meanwhile, CAP, the second largest lab accrediting organization, recently rolled out an optional accreditation program based on the ISO 15189 standard for medical labs, creating a buzz among industry observers that the U.S. healthcare system—including labs—should brace for an ISO invasion. Governments and industries around the world have been using international standards for more than half a century to facilitate trade, establish a technical base for regulation, and safeguard consumers. Now it appears that more clinical labs will start looking toward medical lab-specific ISO 15189 accreditation, hoping to take advantage of a customized quality management system (QMS) that carries the prestige of the ISO label.

Glen Fine, executive vice president, Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS), which holds the secretariat through 2009 for the ISO committee that develops standards for labs, thinks the time has come for labs to take notice of quality management systems like the ISO standards. "The world is

See **ISO Accreditation**, continued on page 3



C. difficile Infections on the Rise

Is it Time to Return to Culturing?

BY GINA ROLLINS

A prevalence study of *Clostridium difficile* released in November by the Association for Professionals in Infection Control and Epidemiology (APIC) heralded grim news for the healthcare industry. The increasingly potent pathogen is 6.5 to 20 times more common than previously identified, with 13 per 1,000 inpatients either infected or colonized. Extrapolating that rate to the average number of patients hospitalized in the U.S., the study estimated that *C. difficile* infection (CDI) affects 7,178 inpatients on any given day and causes the deaths of about 301 patients per day. The care provided to these individuals results in an extra 40,197 days of hospitalization on average, at a cost of about \$32.1 million. At the same time, detecting CDI remains a challenge because available diagnostic methods all have drawbacks and there isn't an industry-wide diagnostic algorithm.

"CDI is an escalating issue in our nation's healthcare facilities," said William Jarvis, MD, the study's principal investigator and president of Jason and Jarvis, a healthcare epidemiology consulting firm. "Clearly, preventing the development and transmission of it should be a top priority for every healthcare institution."

The Bad News

The APIC analysis amplified prior incidence studies and highlighted the most troubling aspects of *C. difficile*. This spore-forming, gram-positive, anaerobic bacillus, first identified in the 1930s, has become a leading cause of healthcare-acquired infections and is adapting quite

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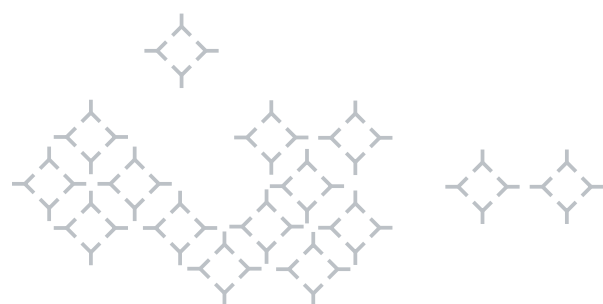
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ISO 15189 Raises Expectations

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getting smaller, and it's hard to ignore it," said Fine. "The IVD industry that supports labs adopted quality management system principles years ago. So you have industry which has adopted it, you have an international groundswell moving in this direction, and you have CMS which positively views labs that adopt a QMS approach to meeting CLIA requirements. In the worst case, organizations don't want to be left behind. In the best case, they want to be early adopters."

The ISO Umbrella

While at the helm of Beaumont Reference Laboratory in Detroit, Joseph Skrisson was one of the early adopters of ISO standards for clinical labs. In the late 1990s, he was looking for a way to organize his staff under a quality management system (QMS) that went beyond the lab's traditional CAP accreditation and covered areas like documentation control, billing, and couriers. At that time, the lab-specific 15189 document hadn't been written, which meant more work on his lab's part to apply the more generic ISO 9001 standard to its particular needs. However, Skrisson knew that because ISO standards were well known in other industries in the Detroit area, more of his customers would recognize an ISO certification as a stamp of quality. This could mean a competitive advantage. "In Detroit, a city heavily into the automotive industry and manufacturing, the Big Three automobile manufacturers send a lot of patients to physician offices," said Skrisson. "A lot of the auto suppliers and many of the manufacturing companies used ISO already. So when you can say you're ISO accredited, that means something to them. It means quality in a language they understand."

Now the CEO of Piedmont Medical Laboratories (Winchester, Va.), Skrisson recently headed up his lab's effort to become the first lab to complete the new CAP 15189 program that accredits clinical labs to the ISO standard. Skrisson explained that when he came to Piedmont in 2004, the lab didn't have a good quality management system in place. Based on his experience in Detroit, Skrisson believed that using ISO would again be a good way to implement quality management and process improvement, and get documentation under control. Now having become the first U.S. lab to fully implement and be accredited under the CAP

15189 program, Skrisson said Piedmont is already seeing significant achievements and positive customer feedback that he credits to adhering to the ISO standard.

The core benefit of using ISO 15189 comes from following its comprehensive and highly structured approach for quality management, while also allowing labs to employ tools like Lean or Six Sigma, explained Cordelia Sever, MD, FACP, chair of CAP's new accreditation program. "The management requirements are quite broad, and it's really suited to be an umbrella for any kind of quality system that you want to plug in there," she said. "That's one of the things that's very sketchy in the CLIA standards—some components are there, but it's not as rigorous and systematic as the ISO standards."

Getting Accredited

ISO 15189 involves an across-the-board review of the clinical lab, with 15 management requirements and eight technical requirements aimed at areas like continual improvement and technical competency. At only 40 pages, ISO 15189 might appear to be a do-it-yourself program (See Table, above). However, Sever made it clear that it's not always easy to understand what the standard is asking the lab to do. "Because it is a very cut-and-dry document, it's not really rich in explanatory language," Sever explained. "Reading the standard and understanding what it really means are two different things. So having the actual assessment by the certified assessors makes people understand what the expectation is and what the intent is of the standard."

Sever also emphasized that an accreditation program like CAP's helps keep labs on track through coaching to sustain gains and keep from losing ground. She believes that an ISO accreditation program strengthens a lab's commitment to the process. "It gives some urgency and value to the whole thing and infuses discipline into the processes. It also accelerates your progress, because if you don't have any established goals and external checkpoints, with everybody busy all the time, it's easy to slip back."

Under a 15189 accreditation program, one of the most important steps is the gap analysis. This takes place after the lab has purchased the 15189 document from ISO and has conducted a preliminary internal audit of its processes. During a gap analysis,

ISO 15189 Overview

The ISO 15189 standard, designed specifically for medical laboratories, covers 15 management requirements and 8 technical requirements. The standard is concise and to the point, with each section consisting of anything from a few sentences up to several pages of explanation.

Management requirements

- ▶ Organization and management
- ▶ Quality management system
- ▶ Document control
- ▶ Review of contracts
- ▶ Examination by referral laboratories
- ▶ External services and supplies
- ▶ Advisory services
- ▶ Resolution of complaints
- ▶ Identification and control of nonconformities
- ▶ Corrective action
- ▶ Preventive action
- ▶ Continual improvement
- ▶ Quality and technical records
- ▶ Internal audits
- ▶ Management review

Technical requirements

- ▶ Personnel
- ▶ Accommodation and environmental conditions
- ▶ Laboratory equipment
- ▶ Pre-examination procedures
- ▶ Examination procedures
- ▶ Assuring quality of examination procedures
- ▶ Post-examination procedures
- ▶ Reporting of results

assessors look in detail at where the lab falls short of the ISO standard and reveals what the lab needs to work on most. "The labs we have worked with so far say that a gap assessment is really quite critical," said Sever. "They say the gap assessment should be a requirement for accreditation. However, because it's not required by the ISO standard, it's still an optional cycle."

After the gap assessment, Sever also recommends a pre-assessment from CAP, which takes place within 90 days of the final accreditation assessment. The pre-assessment is a trial run that gets the lab ready for its own final internal audit, followed by the final accreditation assessment. The pre-assessment usually follows up on gaps that were previously identified and is a fairly short visit, Sever explained. Once the lab passes the final accreditation assessment, a 3-year cycle begins. In the first and second years, two surveillance assessments are scheduled; during the third, onsite reaccreditation is required (See Figure, below).

Challenges and Benefits

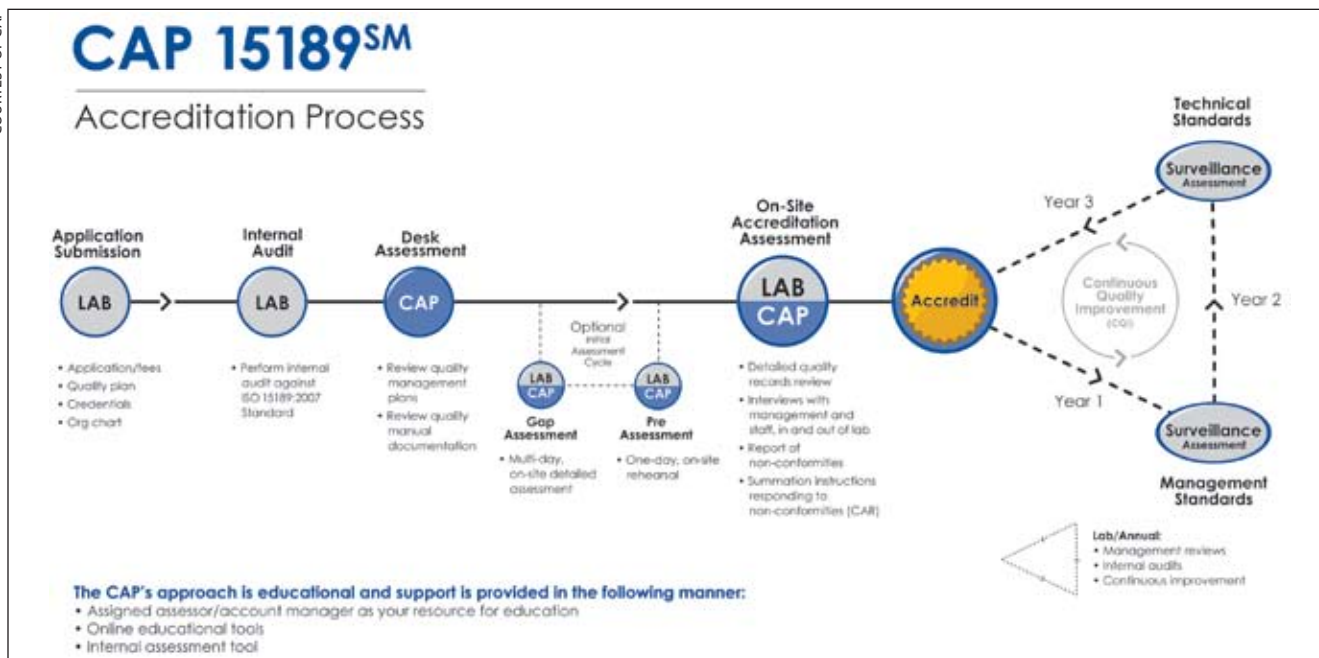
According to Sever, those labs working toward their ISO 15189 accreditation with CAP usually point to the document control requirement as the most onerous. Basically, every process and procedure must be written down, properly organized, and followed to the letter. "In other words, with ISO, if you

don't have it documented, if you don't have a procedure, you don't do it," said Skrisson. "There are no verbal procedures or hand-me-downs. But that's one of the real strengths of the system." Skrisson stressed that once his lab got this right, it was able to reap some of the greatest benefits from this area. To streamline the process, he chose to go with electronic documentation, because it made it easier to update procedures any time there was a change and stay in compliance with the ISO requirements. "That was a great improvement because you could go online at any time and access the policy or procedure for a particular workflow or operating standard in the lab," he said.

Another challenge comes from the requirements aimed at process improvement, which is really the center of the ISO approach. The 15189 ISO standard not only requires that a lab seek continuous quality improvement, but also take proper corrective and preventive actions, which boils down to root cause analysis, according to Sever. "Root cause analysis is still surprisingly shallow in the standard lab arena, and the ISO standard really mandates a more in-depth and appropriate level." One tool useful in targeting preventive action is "five why analysis," which pushes a lab to investigate progressively deeper into the cause of a problem or a non-conformity to the standard. "This idea of corrective and preventive actions, and a scheduled review of effectiveness of those actions, all feeds into continuous risk assessment embedded in the system," said Sever. Skrisson found that the bottom line of process improvement is getting staff to consistently look ahead for pitfalls and implement corrective measures. For example, instead of using a staffing shortage as an excuse, the lab worked on developing a plan that made sure that if someone was out, the operation could carry on without interruption. "What ISO really drives you toward is making certain that the product you deliver every day to your customer is consistent, high-quality, and never changes no matter what challenges you have in operations," Skrisson said.

Experts in ISO 15189 accreditation emphasize that getting buy-in from managers and staff is key. "You have to convince the top administration that ISO accreditation

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is worth the effort,” said Daniel Périgo, RPh, the integrated management system coordinator at Fleury Diagnostics (São Paulo, Brazil). He is also responsible for the lab’s Sustainability department (quality, environmental, and social projects), and frequently presents programs on the ISO certification process. “I think perhaps the greatest difficulty is resistance to change. In implementing a quality system and standardizing processes, we have to change the way people are used to working. And that can have some resistance if not everyone is convinced this is a good thing for the lab.”

Périgo also said that labs frequently wrestle with defining indicators, as required under ISO 15189’s continual improvement section. The standard states that “laboratory management shall implement quality indicators for systematically monitoring and evaluating the laboratory’s contribution to patient care. When this program identifies opportunities for improvement, laboratory management shall address them regardless of where they occur.” Often the lab can define indicators that are good for monitoring a process, but not as good for management purposes, said Périgo, which can make it hard to prove that implementing the ISO standard is useful to achieve financial, customer satisfaction, and market share goals.

Skrisson said that while it did take some time to get his staff trained for ISO 15189 accreditation, the program also got his staff asking questions about why they did things they way they did, and then started pushing for improvements on their own. “People at the bench level really drive most of the changes,” said Skrisson. “Every day they see the flaws in the system. As the staff starts buying into it, you hear comments like, ‘Wow, I’m glad we finally changed this, because it never made any sense but we did it this way for years.’”

Périgo also reiterated Sever’s view that ISO 15189 gives a lab a more complete picture of its operations. “Our experience in Brazil is that the main advantage of the ISO standard is that it looks at the process as a whole. You don’t only look at the technical aspects of the work, at the bench level. It also makes the quality system more visible to managers, to the top administration of the lab, or to the hospital administration for a hospital lab.”

The Alternative Approach

Since 1995, CLSI, a U.S.-based international lab standards organization, has served as the ANSI-designated executive secretariat to the ISO technical committee TC212, Clinical Laboratory Testing and In Vitro Diagnostic Test Systems. The committee includes representatives from 33 countries, and, over the last 15 years, it has produced 19 international standards, including ISO 15189, on subjects such as point-of-care testing, quality management, and safety in medical laboratories. Other committees produce standards for reference laboratories and medical devices. In fact, IVD manufacturers have been using ISO standards for decades, as most companies market their products in Europe and around the world, where ISO “carries great clout,” said CLSI’s Fine. “As soon as you cross borders, you’re likely to run square into 15189.”

In addition to its support of the ISO standards process, CLSI has developed its own quality management system, a program that is also internationally ap-

plicable for different countries. Similar to ISO 15189’s 15 management requirements and eight technical requirements, the CLSI QMS is built on 12 Quality System Essentials. There is some overlap between the two systems, but each has its own distinct take on implementing the QMS. “If your lab fully adopts a quality management system approach, either system will get you to a good endpoint,” said Fine. “The difference is that the ISO model is very general, whereas the CLSI system tends to be more specific and implementable.” The CLSI system is based on two documents: HS1, A Quality Management System for Healthcare and GP26, Application of a Quality Management System Model for Laboratory Services. Unlike the ISO 15189 standard, labs can acquire CLSI’s complete QMS in a bundle called “The Key to Quality,” a package intended for labs implementing a quality management system on their own. Broadly, HS1 discusses CLSI’s 12 Quality System Essentials, while GP26 covers the path of workflow approach. In addition, all of CLSI’s libraries of more than 200 standards and guidelines have a degree of interrelatedness with these two primary QMS guidelines.

According to Fine, many U.S. labs will likely identify with the CLSI model more readily than ISO’s. “The CLSI system is easily understood and it’s something you can take and layer into your CLIA requirement,” said Fine. “As an internationally applicable standard, ISO 15189 is intentionally very broad and overarching, and it’s a document intended to be adapted to fit national or regional lab needs.”

Part of the reason the CLSI standard is more specific arises from the way CLSI develops its guidelines. CLSI gathers experts from government, industry, and professionals with the aim of “putting the best minds in the room,” said Fine, and the process is open to all interested parties, regardless of their geographic location and with no limitations on the number of people from a single country. With ISO, only one officially designated member body from each country can participate in the voting process. This comes from ISO’s primary mission to reduce trade barriers, explained Fine. “ISO’s primary focus is on standardizing industry, commerce, and trade, whereas CLSI is focused exclusively on developing best practices in the clinical and laboratory fields for practicing professionals, industry and government.” As to whether CLSI’s model is competing with the ISO 15189 standard, Fine said he looks at it as “The two systems are complimentary. I don’t necessarily see it as choosing one over the other. Factors including regulatory requirements, complexity of the lab setting, and culture all play a factor in the decision process.” Regardless, a lab clearly has some homework to do before it decides to go with one system or the other.

CLIA Still Rules in the U.S.

Even though many countries around the world have adopted ISO standards as the national basis for regulatory and accreditation of clinical labs, at this point, CMS is not ready to make ISO standards a required part of lab accreditation under CLIA. According to Judith Yost, MA, MT (ASCP), director of CMS’s division of laboratory services, ISO 15189 requirements are too general and, in some cases, not as strin-

gent or specific as CLIA regulations. For example, ISO 15189 requires that the lab have a competent laboratory director, but CLIA spells out explicit education, training, and experience requirements, as well as clear-cut responsibilities for this position that aren’t part of the ISO 15189 standard. “Certainly you can see principles and concepts of CLIA within the quality standard of ISO 15189, but it’s so broad-based that in many cases it’s just not equivalent to our regulations,” said Yost. “You have a standard that’s written for 35 different countries, so to be able to articulate that specificity isn’t an easy task, which is why they leave it up to individual countries to determine what they want to do with it.”

A member of TC212 technical advisory committee that wrote ISO 15189, Yost stressed that while CMS can’t accept ISO standards as a stand-alone measure to satisfy CLIA requirements, the agency does support and encourage labs to take a quality management system approach. “I think there are plenty of examples of labs that have used the CLSI documents and ISO standards who’d tell you that they now work smarter, not harder, and that they produce a higher quality work as a result of implementing those standards in their laboratory,” Yost said. She also noted that because CLIA covers more than 200,000 labs, smaller or less sophisticated organizations would have a hard time applying something as comprehensive as ISO 15189.

More Changes Coming

In the same way that DNV has shaken things up by breaking onto the hospital accreditation arena and requiring ISO 9001 adherence, the American Association for Laboratory Accreditation (A2LA, Frederick, Md.) hopes to make waves when it earns deemed status to accredit labs in the first quarter of this year by offering ISO 15189 in addition to accreditation to CLIA. A2LA has already begun accrediting medical labs to ISO 15189 internationally, beginning with a lab in Aruba. According to Roxanne Robinson, vice president of A2LA, the organization knows of a number of medical laboratories that have been waiting for A2LA to achieve deemed status under CMS and switch from another accrediting body. “We do have labs waiting in the wings for this,” said Robinson. “They’ve expressed a lot of interest in ISO 15189, and they know that we’re internationally recognized as having worked with ISO standards for a very long time.”

Robinson stressed that she feels U.S. labs are lagging behind the rest of the world in adopting the ISO 15189 standard. “Business is becoming global, and the U.S. cannot be U.S.-centric anymore,” she said. “I think the medical community is finally understanding this, that if they want to compete internationally, at the same level as their peers, they have to look at a global process for determining competence.”

Skrisson also emphasized that he hopes ISO standards will become a way for leaders from labs around the world to sit down and be able to share best practices around a common set of ideas. “I’m looking forward to one day getting together with colleagues from Australia, Japan, China, Africa, and talking about lab challenges and emerging technologies, and putting it all under a universal program where we’re all talking the same language regarding quality and competence in our laboratories.”

Hypervirulent Strain Characterization Difficult

C. difficile, continued from page 1

hardily to its environment. Of particular concern, a hypervirulent, antibiotic-resistant strain has developed within the past 8 years. As it has taken hold, laboratorians and infectious disease professionals have discovered to their dismay that diagnostic techniques and protocols are inadequate in terms of providing rapid and accurate diagnosis, typing the strain, and testing its antibiotic susceptibility. Of particular concern, the most sensitive test, anaerobic culture, with reported sensitivity of 95% or higher, is rarely performed. Indeed, the APIC study found that just 4.2% of participating institutions routinely performed cultures for *C. difficile*, and less than 2% of *C. difficile*-infected patients were identified by culture. Other available tests, though faster and less labor intensive, have a wide range of reported sensitivities, with most between 70% and 80%.

“It’s pretty clear the most sensitive test was available 30 years ago,” said Dale Gerding, MD, associate chief of staff for research and development at the Hines Veterans Affairs Hospital in Hines, Ill., and professor of medicine at Loyola University in Chicago. “Since then we’ve sacrificed sensitivity for rapid testing and less use of technician time. The development and use of a rapid, accurate diagnostic is a major goal for improved *C. difficile* surveillance and treatment.” Gerding is on the forefront of *C. difficile* research; his lab contains a library of between 7,000 and 8,000 isolates and was instrumental in identifying the hyper-

virulent outbreak strain.

Aside from the sensitivity of culture in detecting *C. difficile*, other information to be gained from culture, namely having isolates available for antibiotic susceptibility and strain identification, also has been lost in the shuffle. That circumstance was reflected in the APIC study, according to Jarvis. “With the higher-than-expected prevalence, we’re missing something, not only in terms of epidemiology but also in testing susceptibility. We’re totally dependent on someone [at an organization] suspecting there’s a problem,” he noted.

The Hypervirulent Strain

The *C. difficile* strain causing the most concern is BI/NAP1/027, which is referred to differently based on the type of analysis used to characterize the bacterium. By pulsed-field gel electrophoresis (PFGE), the strain is called North American Pulse-field type 1 (NAP1), by PCR-ribotyping, as 027, by restriction endonuclease analysis (REA), as BI, and by toxinotyping as toxinotype III. Ribotyping and the 027 moniker are more common in Europe; in the U.S., PFGE and REA predominate, as do the names NAP1 and BI.

Nomenclature aside, the outbreak strain has several properties that have made it a force to be reckoned with. NAP1 strain produces both the toxins TcdA (an enterotoxin) and TcdB (a cytotoxin), which are encoded on a pathogenicity of locus within the chromosome of the organism. Of note, it produces more of both toxins than other

strains: 16 times higher concentration of TcdA and 23 times higher concentration of TcdB in comparison to toxinotype 0, historically the most predominate toxinotype of *C. difficile* and the source of about 75% of infectious strains. The mechanism of this accelerated production is thought to be deletion at position 117 of the *tcdC* gene that results in a non-functional TcdC protein, which normally downregulates expression of TcdA and TcdB. Without the gene, there is less suppression of toxin production, resulting in higher levels in the stationary phase of growth. There also are *C. difficile* strains that lack TcdA but are TcdB positive. Originally these were thought to be benign, but recent analyses suggest these strains can cause severe disease too, according to Gerding.

Another unique property of the NAP1 strain that may play a role in its virulence is the presence of a binary toxin, consisting of CdtA and CdtB, which is present outside the pathogenicity locus and has been associated with increased disease severity. This formerly uncommon toxin is similar to other binary toxins like the iota toxin, which is responsible for virulence in some types of *C. perfringens*. NAP1 also has a propensity to hypersporulate and this may be the reason it establishes itself so quickly and successfully during outbreaks. “My personal opinion is that’s what increases the quantitative contamination,” noted Robert Owens, Jr., PharmD, co-director of the antimicrobial stewardship program at Maine Medical Center in Portland. “It’s not surprising why it’s so hard to get out of an environment. With the hypersporulation it really anchors itself in your hospital.”

More Virulence Factors

Perhaps of most concern, the NAP1 strain is highly resistant to fluoroquinolones such as gatifloxacin and moxifloxacin. This characteristic of the strain developed sometime between the early 1990s and 2000, according to Gerding. His laboratory tracked its existence in a less virulent form to 1984. Canadian researchers noted a marked increase in the incidence of CDI in 2004, and the strain was first reported in the literature in 2005 based on analysis of isolates dating back to 2000 (NEJM 2005; 353: 2433-2441). A complete picture of the strain’s evolving pathogenesis in the 1990s is not available because of lack of isolates from this period, an issue that continues today. “It’s very challenging in the U.S. to know what’s going on because no one is culturing,” noted Jarvis.

Another factor thought to impact the spread of *C. difficile* is the use of alcohol-based hand hygiene products instead of soap and water handwashing, as these solutions are not sporicidal and don’t remove spores effectively from the hands. Likewise, the most common hospital cleaning agents, like quaternary ammonium-based solutions, also appear ineffective in eradicating spores.

The Infection and Its Spread

CDI causes a spectrum of illness from mild diarrhea to toxic megacolon. The NAP1 strain is associated with increased mortality and morbidity, including higher rates of pseudomembranous colitis and colectomies. Mortality from CDI increases with increasing age, but old age is not the only risk factor for the disease. Antimicrobial usage, especially over prolonged periods, is a definitive cause of susceptibility; proton-pump inhibitors and H2 antagonists are putative causes. Recently there have been reported cases of particularly severe CDI in the peripartum period, among women who took prophylactic antibiotics during delivery (Am J Obstet Gynecol 2008; 198: 635). Other analyses have found the disease to be present in community-based patients without recent antibiotic exposure, and in a variety of animals, with toxinotypes common to humans.

Following outbreaks in North America, the NAP1 strain now has a presence in at least 16 European countries, although molecular subtyping is demonstrating divergence of the North American and European strains over time, according to Ian Poxton, PhD, DSc, professor of microbial infection and immunity at the University of Edinburgh College of Medicine and Veterinary Medicine. Poxton also is chair of the European Study Group for *C. difficile*. Already, aggressive efforts in the Netherlands to rein in the strain, though successful, have been followed by the emergence of another strain, Ribotype 078, which is now the prevalent strain in that country, according to Poxton. In the U.S., NAP1 is known to exist in 40 states and “we have every reason to believe it’s in all states,” said Brandi Limbago, PhD, team lead in bacterial characterization, typing and identification in the division of healthcare quality promotion at CDC.

CDC and Gerding’s lab collaborated to identify the NAP1 strain originally and continue to provide assistance in strain typing and resistance testing to organiza-

See **C. difficile**, continued on page 6

Table 1

Detection Properties of *C. difficile* Diagnostic Assays

Assay	Target	Advantages	Limitations
Imaging	Disease pathology	Can assess disease severity and extent	Cannot be used to specifically determine <i>C. difficile</i> infection
Anaerobic culture	<i>C. difficile</i> presence	Directly measures presence of organism with highest sensitivity	Slow turnaround; labor intensive; low specificity due to detection of non-toxicogenic isolates
Toxigenic culture	<i>C. difficile</i> presence and toxin B presence	Highest sensitivity	Slow turnaround; labor intensive
CTX assay	<i>C. difficile</i> toxin B presence	Directly measures toxin presence; highly sensitive	Slow turnaround; labor intensive
Toxin A or Toxin A/B (ELISA or EIA)	<i>C. difficile</i> toxins A and B presence	Ability to batch samples; same day results	Toxin A-only EIA will not detect A-/B+ isolates; lower sensitivity with higher variability reported compared to other diagnostic tools
GDH or Common Antigen	GDH protein presence	GDH constitutively produced at high levels; has high NPV; same-day results	May cross-react with other organisms; GDH is not a virulence factor, but is a constitutively produced protein; positive samples require further testing to identify toxin producing strains
Polymerase Chain Reaction (PCR)	Presence of target gene (usually toxin)	Ability to batch samples, same-day results; comparable sensitivity to CTX assay	Does not detect toxin presence; may be limited by nucleic acid extraction

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Detection Methods Limited by Sensitivity

C. difficile, from page 5

tions hit with outbreaks. There is a *C. difficile* module in CDC's National Healthcare Safety Network, but it is not a reporting requirement of all states. At the present time, there is no standardized nationwide method of *C. difficile* surveillance.

Detection Methods: Pros and Cons

The arsenal for detecting *C. difficile* has grown over time, but all methods have pros and cons, so there is no single ideal test and no industry-wide testing protocol (see tables, pages 5 and 7). Basic bacterial culture detects the presence of *C. difficile*, with a reported sensitivity of 95% or higher, but it does not distinguish between toxigenic and nontoxigenic strains, takes 2 or more days for results, is labor intensive, and requires effort to maintain proficiency with specialized growth media.

Toxigenic culture, which measures both *C. difficile* and toxin TcdB presence, has acceptable sensitivity and specificity and is considered a reference standard for new diagnostic assays. However, it also takes days to process. "Culture is not fast enough for routine patient care," said Limbago. "It takes 2 days to culture and up to another 2 to get the toxinogenicity, so the entire process can take up to 4 days."

Cytotoxicity assay, which detects toxin TcdB, is both sensitive and specific, and has reported sensitivity in the range of 74% to 90%, although some studies have found lower sensitivity compared with toxigenic culture. It also is somewhat slow and de-

pendent on the lab's proficiency in maintaining cell lines.

EIA, which detects both toxins TcdA and TcdB using antibodies, is the test of choice today, mainly because it is readily available through easy-to-use kits, and can be run in a matter of hours, and batch-processed. The APIC study found that nearly 90% of participating institutions use EIA to detect *C. difficile*. But the test is not as accurate as culture or cytotoxicity assay and has reported sensitivity ranging from 44% to 99%, and specificity from 75% to 100%.

With this relatively low sensitivity, clinicians tend to repeat-order the test during outbreaks when results don't match their suspicions about a patient. For instance, during Maine Medical Center's original NAP1 outbreak in 2002, clinicians panicked. "It was chaos. We were doing tests three times per day per patient," recalled Owens. Aside from over-taxing already busy labs, that type of repeat testing only "increases the probability of false-positives. It becomes a confounder," noted Gerding.

Another immunoassay, glutamate dehydrogenase (GDH), uses antibodies to detect the enzyme from *C. difficile*. Like EIA, the GDH assay offers speedy results and ease of use, but it too has a wide range of reported accuracies. Significantly, since it detects both toxigenic and nontoxigenic organisms and the antibody against *C. difficile*, and also can detect GDH from other organisms, GDH assays generally have been used as a first step to rule-out *C. difficile*, followed by another test, such as EIA, to determine if there

is a toxigenic strain. Two-step, GDH-EIA assays are available and have been reported to have high sensitivity, but not outstanding specificity. Other research indicates that the sensitivity of the GDH portion of at least one assay is only 76%, making it "far too low for use as a screening test for negative specimens," according to Gerding.

New on the scene are commercial PCR assays, which are available in Europe and expected soon to enter the U.S. market. These assays detect the presence of toxin genes. However, they don't all detect the same gene or use the same primers, so sensitivities and specificities vary, but reported sensitivities have been in the 86% to 100% range. Like EIA, PCR offers the advantages of fast results and batch processing. Once adopted widely in the U.S., results from the assay will support epidemiologic efforts in identifying strains, but will not provide information about antibiotic susceptibility.

Some PCR assays are being touted to detect characteristics of *C. difficile*, such as presence of the binary toxin and deletion of the *tcdC* gene, but the benefits of that type of data are unclear, at least for clinical labs. "A lab's concern is whether *C. difficile* is present and whether it is a toxin-producer. I'm not sure how useful it is to know about specific characteristics because there aren't specific infection control guidelines around a specific strain," noted Limbago.

Gerding predicts PCR eventually will become the standard *C. difficile* assay. "Clinical labs have become familiar with the technology because of MRSA, so they can just drop in a new cassette to test for *C. difficile*," he explained.

New Guidelines Forthcoming

Both the European Study Group for *C. difficile* and a joint effort of the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) are in the process of updating diagnostic and treatment guidelines for *C. difficile*. Current IDSA-SHEA guidelines, issued in 1995, recommended EIA or stool culture in symptomatic patients only. The new guidelines are expected next summer, according to Steve Baragona, communications and public affairs officer for IDSA. The European Study Group for *C. difficile* is closer to finalizing its revision, with new guidelines expected early in 2009, according to Poxton. He indicated that "a lot of different algorithms are under consideration," but that the guidelines committee may recommend the GDH assay as a front-line test, followed by another to establish whether a toxigenic strain is present.

For now, typing of the strains continues for the most part to be the domain of only selected labs. A recent analysis compared the discriminating ability and typeability of seven techniques, along with their agreement in grouping isolates by allele profile A through F, which are defined by toxinotype, presence of binary toxin gene, and deletion in the *tcdC* gene. The methods included PCR-ribotyping, PFGE, REA, surface layer protein A gene sequence typing, multilocus variable-number tandem-repeat analysis, amplified fragment length polymorphism, and multilocus sequence typing. All were found to be capable of detecting outbreak strains, but only REA and MLVA had enough discrimination to distinguish



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strains from different outbreaks (J Clin Microbiol 2008; 46:431-437).

What Should Labs Do Now?

Even without updated guidelines, there are a number of measures laboratorians can take to improve *C. difficile* diagnostic capabilities and help clinicians stay on top of any outbreaks. First and foremost, is to “know the limitations of the assay you’re using,” advised Limbago. With that in mind, if one of the methods known to have less-than-ideal sensitivity produces a negative result, “if there is any concern based on clinical symptoms, use another test, including culture,” said Poxton.

Jarvis suggested that laboratorians, infection control, and infectious diseases staff collaborate closely to “flag and do additional follow-up on patients that are unusual—that is, who do not have known risk factors for *C. difficile*—or who have more severe disease or have had treatment failures.” Such a group’s focus should be on developing a testing and treatment algorithm that is based foremost on clinical criteria, said Owens. “If you’re using a test with 80% sensitivity, you want to make sure you’re only testing people who are clinically appropriate for testing. Clinicians just want confidence so that if a test comes back yes or no, they can trust the result,” he observed. That type of multidisciplinary approach was essential in Maine Medical Center’s ability to get a grip on its NAP1 outbreak, according to Owens. Even so, CDI rates at the institution seem now to have settled into a new “normal”, at about 15 patients per day, down from 30-to-50 per day at the height of the outbreak.

Table 2
Properties of *C. difficile* Diagnostic Assays

	Directly detects <i>C. difficile</i> presence	Measures pathology	Detects toxin A	Detects toxin B	Differentiates toxigenic vs. non-toxigenic infection	Can bundle samples	Same-day results	Directly measures toxin presence	Easy use
Imaging		X							
Anaerobic culture	X								
Toxigenic culture	X			X	X				
CTX assay				X	X			X	
Toxin EIA			X	X	X	X	X	X	X
GDH						X	X		X
PCR				X	X	X	X		X

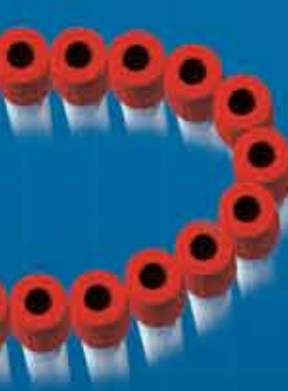
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Regardless of which of the newer assay methods are used, Limbago suggested that laboratorians develop a system for routinely culturing for *C. difficile*, by, for example, performing a certain number each month as a matter of course. “It will help maintain proficiency with the culture, which is not necessarily easy, and ensure that isolates are available should an outbreak develop,” she explained. Culturing for *C. difficile* has

made a comeback in Western Europe, such that many facilities now are performing it “quite routinely,” according to Poxton.

Time invested now in systems and protocols will position labs to respond well to *C. difficile* outbreak strains as the organism continues to evolve. “NAP1 is the strain currently of interest, but that won’t be the case in the future. There will be another,” Gerding predicted. **CLM**

Disclosures: Gerding holds patents for the treatment and prevention of CDI licensed to ViroPharma, and is a consultant for BD GeneOhm, Genzyme, GOJO, Optimer, Salix, Merck, Cepheid, Schering-Plough and ViroPharma. He holds research grants from the US Dept of Veterans Affairs, Cepheid, GOJO, Massachusetts Biological Laboratories, Optimer, and ViroPharma.



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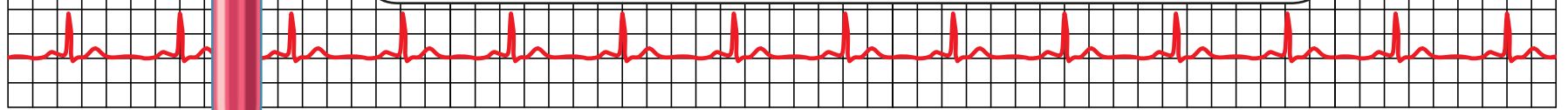
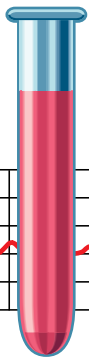


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Fatigue and Error

An Interview with Matthew B. Weinger, MD

What is the relationship between fatigue and lab error, and what can lab leaders do to minimize problems caused by fatigue? This interview with Dr. Matthew B. Weinger addresses the relationship between fatigue and error. Dr. Weinger is the director of the center for perioperative research in quality, the Norman Ty Smith chair in patient safety and medical simulation, and professor of anesthesiology, biomedical informatics and medical education at the Vanderbilt University School of Medicine. He also practices at the Middle Tennessee VA Healthcare System.

Michael Astion, MD, PhD conducted this interview.

Q: What is fatigue?

A: Fatigue is a global term encompassing the effects of acute sleep loss, chronic sleep loss, and physical and mental exhaustion. Obviously, these factors interact. In addition, fatigue is exacerbated by personal factors like emotional stresses, as well as other negative work factors, such as high work volume and cumbersome processes.

Q: What errors are particularly prone to fatigue?

A: Fatigue is particularly dangerous in situations where a rare, but very salient signal has to be detected; multitasking and prioritization are key elements of work; there is a time gap between when information becomes available and when it has to be used; and creative thought is required. More than one of these circumstances can exist concurrently. Table 1 lists some examples from clinical labs.

Q: What are some of the multitasking/prioritization errors we might expect from a fatigued worker?

A: A couple of patterns are observed. The first is called load shedding. Here, the worker has two or three priorities to take care of. The highest priority task is addressed, but the secondary and tertiary tasks, though they have to be completed, are neglected, delayed or performed less diligently. For

example, the worker's main priority might be a high-volume, random-access analyzer used for stat chemistry tests, the secondary priority might be a batch analyzer running concurrently, and the tertiary priority might be manual, kit-based testing that can be performed anytime during the shift.

Q: Please describe the second pattern.

A: In the second pattern, workers choose the first priority correctly, but problems develop when addressing lower priority tasks. After moving to the lower priority task, they tend to get stuck there, often on relatively trivial issues, and forget to return to the high priority.

Q: Can you give us some insight regarding why fatigued workers are at higher risk for failing to follow through on critical value calls?

A: Critical values are often handled by the same lab personnel performing testing. Therefore, a critical value requires multitasking and prioritization, tasks that are more susceptible to fatigue. In addition, for some critical values, there is a time delay between when information is available to the technologist and when it is communicated to the care provider. This time gap is the period the technologist may wait for a call back after paging the physician. During this gap, the technologist will return to



Dr. Weinger teaches and conducts research in patient safety, human factors, and clinical decision making.

work on other priority tasks. Sometimes the call back never comes and the technologist forgets about the call. In addition, the call back represents an interruption of the intervening task and an opportunity for fatigue-induced omission errors.

Q: Are there certain tasks that are more resistant to fatigue?

A: Pattern recognition tasks are fairly resistant to fatigue. Essentially, automatic responses are well preserved, as long as they are activated. For example, "textbook" diagnoses and guideline-based therapeutic decisions are relatively well preserved in sleep-deprived doctors.

Q: Are there times when pattern recognition tasks will fall victim to fatigue?

A: Yes, when there are lots of patterns to look at or when there is an uncommon pattern requiring creative thinking. Creative thought suffers in a fatigued worker.

Q: What is the relationship between fatigue and age?

A: In general, fatigue adversely affects people above age 60 more than it does younger people; however, this is mitigated somewhat by experience. For pattern recognition tasks, more experienced workers have more deeply ingrained heuristics or mental schema that will be less susceptible to fatigue.

Q: What is the relationship between fatigue and morale?

A: Chronic fatigue tends to have a negative effect on morale and mood.

Q: What is your view on automation as a solution to fatigue?

A: Automation is an important solution to the problem of fatigue provided the automation is well designed and reliable. Automation tends to produce fewer errors; but when errors do occur, the results can be more disastrous especially if the worker has been "out of the loop" and must figure out what has gone wrong. Therefore, it is important that automated systems provide informative monitors and alarms regarding the state of the system and its likelihood for failure.

Q: Obviously, we want to have well rested workers and work processes that are less susceptible to fatigue-induced errors. But, in cases where lab workers are fatigued, are there temporary interventions besides coffee that can help a person stay alert and decrease the probability of error?

A: On a temporary basis, bright lights, physical activity, conversation, and avoiding junk food are all helpful. The use of pharmacologic interventions is more controversial and has not been well-studied in the healthcare setting. Current research has been focused on the drug Provigil

Sleep Deprivation and Impairment

"Most studies of recurrent partial sleep deprivation have suggested that sleeping only 5 to 6 hours a night can lead to impairment. These decrements in performance accumulate with continued partial sleep deprivation as may be seen in individuals with chronic insomnia (defined as difficulty sleeping on a frequent basis) or in physicians working regularly recurring call or night shifts. In the early morning hours, after nearly 24 hours without sleep (e.g., at the end of a difficult night on call), psychomotor performance can be impaired to an extent equivalent to or greater than is currently acceptable for alcohol intoxication" (from reference 2).

Table 1

Lab Work That Is Particularly Prone to Fatigue-associated Errors

Work situation	Example(s)
Rare, but salient signal needs detecting	<ul style="list-style-type: none"> Unusual error flag in automated system Detecting a low-abundance, pathogenic organism on a microscope slide
Multitasking/prioritization	<ul style="list-style-type: none"> Responsibility for operating multiple instruments on the same shift Operating instruments while handling phone calls
Time gap between when information appears and when it is used	<ul style="list-style-type: none"> Critical value calls requiring a physician call back.
Work requiring creative thought	<ul style="list-style-type: none"> Managing a crisis caused by a physical threat like a spill or power failure Troubleshooting uncommon errors Manually validating an infrequently encountered result

(modafinil). The claims for this drug are that it reversibly blocks fatigue, is not habit forming, and avoids some of the over-activation associated with caffeine.

Q: What are some of the current controversies related to fatigue and medical errors?

A: One important issue is whether our approach to reducing work hours is causing more problems with transitions of care, for example, handoff errors. Another topic of debate is whether residents receive sufficient exposure to clinical medicine now that work hours have been reduced.

Q: Can you elaborate on the handoff errors?

A: If physicians and other healthcare workers work less, especially avoiding very long shifts, they will be more alert, and this could decrease many kinds of errors. There is, however, a tradeoff. With shorter and fewer shifts, there are more transitions in care where data and system status information must be handed off from the off-going to the on-coming worker. This means there are more opportunities for communication failures, which are one of the most common types of medical errors. Essentially, by shortening work hours, we are trading off fatigue-related errors for handoff-related errors. It is likely that the best approach to this is to develop strategies to improve handoffs, since it is unlikely that there will be a return to the days where clinicians work greater than 80 hours per week.

Q: What are some approaches to minimizing fatigue without creating too many handoffs?

A: One of the best approaches is to use innovative scheduling of shifts. For example, a complete shift changeover at 8a.m. is a significant opportunity for lost information due to multiple handoffs. A better approach would be to use staggered shifts in which a few people come to work or leave work at 4a.m., a few at 6a.m., etc. Staggered shifts lead to better transitions of care because there is always a cohort of workers

who are immersed in the system status and are aware of current and ongoing issues. Staggered shifts also allow the option of using the well-rested workers for the most difficult tasks.

Q: Many reference labs run a majority of their tests on the night shift so that the results are available to physicians in the morning. Is the night shift particularly prone to errors?

A: There are insufficient data specific to healthcare; however, studies of shiftwork in other professions consistently find that night-shift workers are at higher risk for making errors. Night-shift workers are also more prone to injuries, such as needlestick injuries, and have poorer occupational health.

Q: From the perspective of reducing errors, is it better for workers to consistently work the night shift, or is it better to work the night shift occasionally as part of a rotation of many workers?

A: Workers who consistently work the night shift are less error prone than those working nights intermittently. The ability for a night worker to optimize performance is based on the ability to establish a new circadian rhythm. This adaptation varies from individual to individual but nonetheless requires the ability to sleep consistently during the day. This is not an easy task for most people, especially given the demands and expectations of most people's family and personal lives.

Q: In the clinical lab, workers are sometimes asked to work a second shift due to labor shortages. What are the vulnerabilities in working two shifts?

A: In general, for workers who normally work a day shift or an evening shift, for example 4 p.m. to midnight, a double shift involving days or evenings is not as bad as one involving the midnight shift. When the midnight shift is involved, the effect of sleep deprivation comes strongly into play and the risk of errors increases significantly as the second shift progresses.

Q: Besides optimizing the amount of staffing, what can be done to reduce the risk associated with two shifts?

A: I think you can do a lot with innovative scheduling. For example, try to put the least amount of work where workers are most vulnerable, which is at the end of the second shift. Staggered shifts can also be helpful here. For example, to cover for a missing night shift worker, you can have one evening shift employee stay for 4 hours extra and another come in 4 hours early. Although this is not ideal, the effects of sleep deprivation and fatigue may be less for both workers. The worker who stays 4 hours more will be tired but not as tired as if he or she stayed for the full 8-hour shift. The worker who comes in early will not get as much sleep as they normally do, but they should get enough sleep, and this lowers their risk of making an error.

Q: What do you think about breaks and naps?

A: Breaks are a good idea for reducing fatigue, and for many people a short nap during a break is helpful. Naps during a work break are a complicated issue. For most people naps of either less than 15 minutes or greater than 2 hours are helpful and will reduce fatigue-related errors. Naps between 20 minutes and 2 hours can be problematic because of sleep inertia, which refers to the significant impairment occurring immediately upon waking from a nap. This disorientation is worse for intermediate length naps. Another problem with naps is the variability between people regarding an optimal nap length. Some people sleep for 15 minutes and feel great and can get right back into a work task, while others

are significantly impaired and need time to acclimate before they are again working optimally.

Q: Do you have some practical advice regarding napping?

A: Napping is not a good idea if you are the only person working on the shift. But if you have people who cross cover, and you are obviously sleepy, a nap of less than 15 minutes during a required work break may be a good idea.

Q: You are an anesthesiologist. What are some interventions that are being used in your field regarding reducing fatigue?

A: Where I work, we are decreasing shift lengths. For example, a faculty shift can not exceed 16 hours. In addition, residents are under work-hour restrictions and cannot work more than 24 hours at one time, nor can they work more than 80 hours per week. Anesthesiologists are also openly talking about fatigue risks and are monitoring ourselves and our colleagues for fatigue. I am hopeful that other physicians and healthcare workers will come to realize that it is not unprofessional to admit that they are tired, and they will take appropriate actions to minimize the effect of their fatigue on patient care.

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Breaks, even naps, can help reduce fatigue.

Engineers in the Clinical Laboratory

An Interview with Patrick Fasse, BSME, Industrial Engineer, ARUP Laboratories, Salt Lake City, Utah, and Brian Nass, MSME, MSIE, Director of Process Improvement, Mayo Clinic, Rochester, Minn.

Engineers routinely use disciplined problem solving methods, like Lean and Six Sigma, to improve processes. In recent years, interest in these engineering methods has soared in the clinical lab industry as evidenced by the availability of educational events and materials related to these topics. However, a gap exists between discussion of engineering methods and the actual use of those methods in labs. To close the gap, some health systems and larger labs have employed engineers to lead process improvement initiatives. In this interview, two engineering leaders, Patrick Fasse from ARUP, and Brian Nass from Mayo Clinic, discuss the engineering approach to improving clinical lab performance.

Michael Astion, MD, PhD, conducted this interview.

Q: What is your educational and work background?

Fasse: I am a mechanical engineer. Before coming to ARUP, I was part of a consulting group that worked on a variety of material handling issues. The main focus was to apply world class Lean techniques to eliminate waste in the warehouse distribution industry. During my tenure there, we implemented automated conveyor/sorting systems and improved overall material handling throughout all operations. I have no formal healthcare education.

Nass: I have master's degrees in mechanical engineering and industrial engineering. Before coming to Mayo, I worked for many years in computer hardware and software design and manufacturing. I specialized in applying the Toyota production system in this setting. I have no formal healthcare education.

Q: Is your background a natural fit for the clinical lab?

Fasse: Yes, the movement of specimens, reagents, people, and information around a lab is analogous to the engineering problems I worked on before joining ARUP. Problems in clinical labs are amenable to engineering solutions.

Nass: It is a very good fit. The clinical lab is a great area in which to begin applying Lean in healthcare. The end-to-end testing process—from specimen receipt, sorting and preparation, through analysis and reporting—is relatively linear, and the process issues are the same as those commonly encountered by engineers in other industries. These include rework, mismatch between staffing and workload, batching, unplanned equipment downtime, calibration problems, and lack of standardization.

Q: What are some of the projects you have worked on?

Fasse: My original project with ARUP was to reduce the time it took for a specimen to move from the delivery truck to specimen processing and then to the bench. Most of my other projects involve using Lean methods to reduce waste and build in more capacity to our system.

Nass: Most of the projects I have worked on involved applying Lean techniques to improve turnaround time, quality, and cost. At Mayo Clinic, we have since spread the application of Lean to radiology, surgery, nursing, the emergency department, cardiovascular diseases, and several outpatient procedural areas.

Q: What is your approach to working with lab staff to redesign a process or workspace? How do you gain buy-in?

Fasse: I mainly see myself as a facilitator. I start each project with a teaching session regarding Lean techniques. I go over some common types of lab waste (see insert) and let them know that I am open to the possibility of lab redesign. I then observe the work in the lab where the project will occur and talk to individual techs. My main goal is to help them generate ideas that will improve quality.

Nass: Before starting on a project, I ensure that the lab leadership supports the initiative and are open to having me observe the processes directly. After making initial observations and a preliminary assessment of the situation and opportunity, I serve mainly as a teacher of Lean and as a guide to help the staff apply Lean thinking to all aspects of the lab. When I started in this position, I taught using examples from manufacturing. But now that we have had a number of successful projects at Mayo Clinic, I use those examples instead. My overall objective is that lab staff will not need me once they have completed a few Lean projects with me or my team's assis-

stance. In addition, I try to get the different lab divisions to learn from and help each other. This involves using staff who have successfully participated in a Lean project outside of their own area. This provides new project teams an outside set of eyes, and the prior Lean project's expertise helps spread the teaching into new areas.

Q: Mr. Nass, you were involved in a project that improved work flow in the molecular diagnostics lab that performs virology testing. What was your approach to that project?

Nass: In that particular case, high demand was causing increased delays and rework. First, I observed the work in the lab. I then worked with a small team of lab supervisors and techs to create a current state value stream map (see insert). The map allowed us to see how specimens flowed through the lab and how the final work product—the test result—was created and delivered, all from the point of view of the customers, who are physicians and their patients. The value stream map, in conjunction with observing the lab work, allowed us to identify critical problems which were corrected rapidly.

Q: What were the areas for improvement?

Nass: The analysis of the specimens was the rate limiting step. Within that rate limiting step, there were several correctable problems causing delays. The batch sizes were too large, so we reduced them. There were insufficient signals to identify the end of a batch run, and this meant instruments were sitting idle, waiting for a technologist to identify a completed batch. Similarly, there were insufficient signals to identify problems that either slowed or halted analysis. We put in visual and auditory signals so that instruments were used nearly continuously. By using small batches and enhanced "pull signals" to pull the next batch onto the analyzer, we removed nearly all the waste within the rate limiting step.

Q: What was the outcome?

Nass: In one week of intense work, we reduced turnaround time in that lab by 50% and improved the capacity to handle additional volume. Schedules became more predictable, the amount of overtime decreased, and morale improved.

Sources of Waste in the Lab

- ▶ Waiting
- ▶ Transportation
- ▶ Over-processing
- ▶ Inventories
- ▶ Motions
- ▶ Defects
- ▶ Overproduction
- ▶ Reprioritization
- ▶ Misutilization of skills



Value Stream Mapping to Identify Waste

As it applies to lab testing, value stream mapping is a Lean method to analyze the work required to bring the test result to the physician and patient. The test result in the hands of physician and patient is viewed as the ultimate product of the clinical laboratory. This product is the result of a group of processes. Each process falls into one of three categories:

- ▶ It is waste, and should not occur.
- ▶ It does not add value to the product, but it must occur (e.g., fulfillment of certain regulatory requirements).
- ▶ It adds value to the product.

The main idea in re-engineering work processes is to get rid of the waste. Below are some examples of waste in lab testing.

Common Types of Waste in Clinical Labs

Waste Categories	Examples
Delays	<ul style="list-style-type: none"> ▶ Batching in any part of the lab testing process ▶ Delays related to using serum (requires clotting) rather than plasma ▶ Delays between test order and sample draw, sample draw and arrival in lab, receipt in lab and specimen processing, specimen processing and analysis ▶ Analytic delays ▶ Postanalytic delays in reporting results ▶ Delay in retrieving results by care provider ▶ Transport delays between different lab sections
Duplication	<ul style="list-style-type: none"> ▶ Duplicate specimen collection and test orders
Correction/Rework	<ul style="list-style-type: none"> ▶ Redraw due to suboptimal specimens (e.g., line contamination, hemolysis, quantity not sufficient, clot, wrong temperature) ▶ Redraw due to mislabeling ▶ Repeating tests because of analytic error ▶ Any other error leading to a corrected report
Motion/Steps	<ul style="list-style-type: none"> ▶ Positioning the most commonly used analyzers far away from specimen processing ▶ Using a multi-step manual assay, when an automated assay with fewer steps is available. ▶ Reagents and materials for testing placed too far from technologist
Inventory mismanagement	<ul style="list-style-type: none"> ▶ Insufficient inventory ▶ Too much inventory (e.g., reagents outdating before use)

Modified from reference 1.

Q: Why do you aim for rapid improvement?

Nass: Staff find it highly motivating because it sends a clear message that meaningful change is within reach.

Q: Does lab leadership always have to be involved?

Nass: The supervisors have to be there from the outset of the project. In general, their presence, participation, and buy-in are necessary for the project to succeed.

Q: Mr. Fasse, can you describe the work you have done related to decreasing wasted motion in the lab?

Fasse: We sometimes waste a fair amount of motion performing lab tests that leads to delays in testing and inefficiency in allocation of labor. Specifically, if you watch techs perform during the analytic phase of testing, sometimes you see disorganized work areas that lead to wasted movement and unnecessary travel to obtain reagents, ice, and other supplies.

Q: Can you give us a specific example?

Fasse: There was one area where tests were done with the aid of an automated pipetting system. In this area, techs were traveling a

great distance to retrieve vats of distilled water from a water dispenser. After I provided some Lean training, we decided to redesign the process. We ended up bringing a water dispenser right next to the bench where the test was being performed. This decreased the distance traveled to perform the tests by 40%. In general, our approach is to have techs move less by working closer to their instruments in uncluttered work spaces. This leads to decreases in the analytic time and makes the work environment more pleasant.

Q: Why are work areas disorganized, when many techs are highly organized?

Fasse: One interesting source of clutter that leads to unnecessary motion as techs travel around it is excess inventory of testing kits, reagents, ice, and other supplies near the work bench. The oversupply is driven by fear of having insufficient materials to carry out testing, which makes sense because insufficient supplies block the tech from completing their main mission: delivering quick and accurate test results to our clients. To overcome this fear and reduce clutter, reliable systems for delivering inventory to the bench must be developed. Once techs have confidence in the delivery

system, they will not hoard supplies, and the benches become uncluttered. The main goal of all this is to produce more space for work within the existing lab footprint.

Q: When analyzing a lab process, do you find that your objective differs from that of lab technologists and technicians?

Fasse: We usually view the objective as the same, but we may have a different view on the path to achieve that objective.

Nass: My main objective is knowledge transfer; therefore, setting goals for turnaround times, quality, etcetera, come from the lab staff.

Q: Have you found that a lack of clinical lab training impeded your ability to contribute to the lab?

Fasse: It has not been an impediment. I bring a complementary set of tools to the team. Engineers are able to see the unnecessary layers that have been added to work, and are used to redesigning processes. Engineers are also comfortable with a green field approach, by which I mean we rip all the layers off a process and take a fresh look.

Nass: Lack of lab training has actually helped, because I have been able to ask the naïve questions without being burdened by the past. As outsiders to the lab, we can see things that insiders cannot see.

Q: Large labs have the resources to employ an engineer. However, most clinical labs are smaller operations that cannot afford an engineer, or even engineering consultants. How can smaller labs implement an engineering approach?

Fasse: It does not have to be an engineer. It can be as simple as choosing somebody in the lab who is interested in becoming an expert in Lean/Six Sigma. These people can get some special training and then can be a local expert in process design in a smaller lab. They can accomplish a great deal, especially related to removing waste in processes.

Nass: I like the idea of a lab champion who receives special training, perhaps at a local community college, or university. Another approach is to gain expertise by partnering locally with somebody in an industry where Lean and Six Sigma are routinely used. Industry experts are often quite willing to share expertise in a meaningful way, and this can be less expensive than consultants.

Q: What types of lab projects can benefit most from an engineer's involvement?

Fasse: Clinical lab experts are in the best position to develop and implement policies and procedures for lab testing. Engineers can help in important ways that are not necessarily reflected in the test's policy

and procedure. These include decreasing distances traveled by techs, decreasing other forms of unnecessary movement, and reducing excess inventory. In general, engineers are useful for developing custom tools to complement a process, such as automated conveyor systems to improve specimen transport within the lab, spatial redesign of a lab, or customizing the workspace where instruments are located.

Nass: All projects can benefit. The lab faces several classic engineering issues: poor layout; batching; swings in demand/capacity; quality problems; and non-optimal use of equipment. All of these are amenable to engineering approaches, specifically Six Sigma and Lean. In addition, I would mention that as I work throughout Mayo Clinic, the engineering approach is particularly good for a number of procedural areas, including surgery, radiology, gastroenterology, cardiovascular labs, and the emergency department. These areas have relatively linear processes consisting of a check-in, preparation, a procedure, and post-procedure work, including analysis and reporting of results and/or outcomes and follow-ups.

Q: From an engineering perspective, what are the greatest opportunities for the future that a lab should embrace?

Fasse: We still have a great deal to learn from manufacturing, especially applying Lean to all parts of our operation. Through engineering methods, we have a great opportunity to build more capacity into our systems while creating better working environments.

Nass: There is an opportunity in the lab, and throughout the healthcare system, to become more proactive about patient safety issues by introducing engineering tools such as fault tree analysis. These tools could let us predict serious events, like lab errors, medication errors, or life-threatening sepsis, before they happen, and intervene so that they do not occur.

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HIV Screening

A Look at the CDC Guidelines and HIV Rapid Tests

BY PATRICIA SLEV, PHD

In 2006, approximately 25% of the 1 million individuals infected with HIV in the U.S. were unaware of their HIV-positive status. In an effort to increase awareness and promote early diagnosis of HIV infection, the CDC responded to this public health epidemic by releasing revised recommendations for HIV screening of adolescents, adults, and pregnant women. The guidelines, published in September 2006, not only expanded HIV screening to individuals age 13–64 in all routine healthcare settings, they also eliminated the need for special consent forms or prevention counseling (1).

Identifying infected individuals is critical for two reasons. First, undiagnosed individuals miss the opportunity to receive timely, highly active antiretroviral therapy that now allows people to live with HIV as a chronic disease (2). In addition, undiagnosed individuals are disproportionately responsible for new infections. According to CDC reports, 25% of individuals who are unaware of their infection are responsible for 54%–70% of new HIV infections (3). This is important because studies show that individuals who are aware of their infection status reduce behaviors that contribute to HIV transmission (4). Despite these statistics, the most common reason that people seek testing for HIV on their own remains overt illness. Surprisingly, most of these individuals have sought medical attention multiple times for unrelated complaints in a variety of healthcare settings prior to being tested and diagnosed with HIV.

While implementation of the CDC guidelines across the U.S. is still limited, studies have emerged that provide important data on the benefits of expanded HIV

high-risk groups, such as blacks and men that have sex with men, the face of the epidemic is changing. Today, increasing numbers of cases are found in the follow-

portant, has limited success in identifying persons infected with HIV.

Overview of the CDC Guidelines

The 2006 CDC guidelines for HIV screening represented a shift from targeted screening of individuals at high risk or in high prevalence areas to routine screening of all individuals between the ages of 13–64 in all healthcare settings (1). Specifically, the recommendations allow for HIV screening under opt-out regulations, implying that consent to medical care and routine medical testing includes HIV testing. In addition, the guidelines recommend that individuals engaging in high-risk behavior should be screened at least annually. Similar provisions apply to pregnant women. CDC advises that routine prenatal screening include HIV testing and that repeat screening be performed in the third trimester in high HIV-prevalence populations.

Some Early Results

Although the release of the 2006 CDC guidelines offered the promise of widespread HIV screening, two years later, HIV screening is still limited and far from routine. Drawbacks include lack of funding for screening programs, limited ability to refer patients to subspecialty care, and laws in many states that prohibit opt-out testing. In fact, it would appear that few institutions have implemented the revised guidelines. A recent study revealed that only 57%, or 58 academic EDs surveyed, offer HIV screening with rapid tests. The majority of these offer HIV screening only for some special conditions such as occupational exposure (5).

Nevertheless, there are success stories from institutions that have made an effort to offer universal, opt-out HIV testing. One such example is the experience at George Washington University Medical Center (GWU) in Washington, D.C. (6). This academic institution offered HIV test-



screening. This article will describe some of those studies, as well as the performance characteristics of rapid HIV tests and proposed testing algorithms for diagnosing HIV infection.

The HIV Epidemic in the U.S.

Studies show that a substantial proportion of HIV-infected persons, approximately 40%, are diagnosed late in the course of infection and develop AIDS within a year of their HIV diagnosis. While the majority of AIDS cases are still concentrated among

ing populations: individuals <20 years old, women, members of non-black racial minority groups, individuals who do not live in urban areas, and heterosexual men and women who believe they are not at high risk for contracting HIV.

Data from early CDC-sponsored HIV screening programs that were implemented in hospital emergency departments revealed a 2–7% positivity rate compared to 2% at STD clinics that tested high-risk individuals (1). This suggests that screening only high-risk individuals, although im-

ing in accordance with the new CDC recommendations to patients being treated in the ED for a period of 3 months. During the study period, more than 4,000 patients were offered POC HIV screening and almost 2,500 (59.7%) accepted. There were 26 preliminary positives, of these 13 were lost to follow-up, 9 were confirmed positive and 4 were confirmed negative by Western blot. The authors estimated the cost at approximately \$4,900 per confirmed positive case of HIV infection and concluded that routine, opt-out testing in EDs was cost-effective. The group also noted that they relied on the laboratory for QC and oversight of the POC testing and strongly encouraged other institutions to involve the laboratory in HIV screening programs.

A Look at Rapid HIV Tests

With the advent of rapid HIV tests, the options for screening have increased dramatically, as well as accessibility to screening and testing. In fact, many experts agree that expanded HIV screening would not be possible without rapid tests. These tests are now widely used in a variety of traditional and non-traditional healthcare settings, such as STD clinics, state health departments, community outreach programs, and labor and delivery settings (7). Furthermore, as hospitals around the country attempt to comply with CDC's recommendations, rapid tests have become increasingly common in EDs (6, 8, 9).

Rapid HIV tests are screening tests, and therefore, any reactive result is considered a preliminary positive that must be confirmed with a Western blot or IFA for HIV-1 infection (10). While releasing preliminary HIV-positive results remains a concern, the potential benefits of increasing awareness of HIV status has resulted in widespread acceptance of this testing strategy.

Rapid HIV tests are extensively regulated in the U.S. and quite reliable. FDA insists that all rapid tests have >98% sensitivity and specificity for HIV infection. Currently, there are six FDA-approved rapid tests for HIV (Table 1). In general, the tests consist of single-use devices that cost approximately \$20 and produce results in 30 minutes. Four of the FDA-approved rapid tests, OraQuick ADVANCE Rapid HIV-1/2 Antibody Test, Clearview HIV-1/2 STAT-PAK, Clearview Complete HIV-1/2, and Multispot HIV-1/2 Rapid Test detect antibodies to both HIV-1 and HIV-2, but only the Multispot HIV-1/2 Rapid distinguishes HIV-1 from HIV-2 infection. Sample types include whole blood (fingerstick or venous), serum, plasma, and oral fluid. Four of the rapid tests use whole blood or oral fluid samples that do not need processing and are CLIA-waived. The remaining two tests, Multispot HIV-1/2 Rapid Test and Reveal G-3 Rapid HIV-1 Antibody Test, use plasma and serum exclusively and are therefore classified as moderately complex under CLIA and must be performed in a lab. Sensitivity ranges from 99.3% (OraQuick ADVANCE, oral fluid) to 100% (Multispot HIV-1/2 Rapid Test, serum and plasma and Uni-Gold Recombigen, serum and plasma). The specificity ranges from 98.6% (Reveal G3, plasma) to

Table 1

FDA-Approved Rapid HIV Antibody Tests

Test	Manufacturer	Sample Type	Sensitivity	Specificity
OraQuick ADVANCE Rapid HIV-1/2 Antibody Test	OraSure Technologies (Bethlehem, Pa.)	oral fluid	99.3%	99.8%
		whole blood (fingerstick or venipuncture)	99.6%	100%
		plasma	99.6%	99.9%
Clearview COMPLETE HIV-1/2	Inverness Medical Professional Diagnostics (Louisville, Colo.)	whole blood (fingerstick or venipuncture)	99.7%	99.9%
		serum and plasma	99.7%	99.9%
Clearview HIV-1/2 STAT-PAK	Inverness Medical Professional Diagnostics (Waltham, Mass.)	whole blood (fingerstick or venipuncture)	99.7%	99.9%
		serum and plasma	99.7%	99.9%
Reveal G-3 Rapid HIV-1 Antibody Test	MedMira, Inc. (Halifax, Nova Scotia)	serum	99.8%	99.1%
		plasma	99.8%	98.6%
Uni-Gold Recombigen HIV	Trinity Biotech (Berkley Heights, N.J.)	whole blood (fingerstick or venipuncture)	100%	99.7%
		serum and plasma	100%	99.8%
Multispot HIV-1/2 Rapid Test	Bio-Rad (Redmond, Wash.)	serum	100%	99.9%
		plasma	100%	99.9%

100% (OraQuick ADVANCE Rapid HIV-1/2, whole blood) (Table 1) (11).

As these rapid tests have become more widely available, more information regarding their performance in different contexts has also become available. The overall performance of these assays is good; however, some problems have surfaced (12). For example, researchers determined that the specificity in their study population of the OraQuickADVANCE assay using oral fluid was 96.9%, in contrast to the manufacturer's claim of 99.8% for this specimen type. Although these researchers found the use of rapid tests for HIV screening useful, with a reactive rapid test indicating an 8 to 32 fold increased odds of having HIV infection, they cautioned that specificity in real clinic settings may be lower than expected (8).

Episodic, unexplained increases in false-positive rates have also been observed with oral fluid samples. The original reports of increased rates of false-positive results occurred in 2005 at multiple sites including New York and Minnesota (13, 14). Although an investigation followed, a cause was never found (15). In late 2007, STD clinics operated by the New York City Department of Health and Mental Hygiene once again experienced an increased incidence of false-positive test results, prompting cessation of testing oral fluid samples (14). Unexplained clusters of false-positive results and lower-than-expected specificity with oral fluid samples in some clinical settings is a particular concern because this is the sample type preferred by both patients and testing staff. Moreover, oral fluid is the predominant sample type in many settings, including EDs.

Another concern is sensitivity of the tests. Although the sensitivity of the rapid tests is comparable with standard EIA tests, true sensitivity data may be somewhat lim-

ited in certain settings. For example, patients who test negative for HIV infection with a rapid test in EDs generally are not followed upon release from the hospital. In one study, a group of researchers evaluated four rapid tests for detecting acute infections: the OraQuick ADVANCE Rapid HIV-1/2, Clearview HIV-1/2 STAT-PAK, UniGold Recombigen HIV test, and the Multispot HIV-1/2 Rapid Test (16). The UniGold Recombigen appeared to be the most sensitive of all the tests studied, possibly because it is the only test that detects both IgG and IgM antibodies. In addition, the test requires a larger sample volume (50 µL) compared to the OraQuick and Clearview tests, which require only 5 µL of sample. Another possibility for the difference in sensitivities is inherent differences between kits and the different antigens used for antibody detection.

Although the exact cause of the Uni-Gold Recombigen test's increased sensitivity is not clear, overall the results indicate that the four rapid tests differ in their ability to detect acute infections. While this is not a surprising finding, it has important implications. Discordance between rapid tests, which actually represent acute HIV infection rather than negative serologic status, may impact recent proposals by some researchers to develop alternative testing algorithms composed solely of rapid tests for screening and confirmation.

Alternative Algorithms: No Western Blot?

Although rapid tests are strictly screening tests, recent proposals have suggested that two or more rapid tests or a combination of a rapid test and nucleic acid amplification test (NAAT) could be used in various testing algorithms to both screen and confirm HIV infection. One group of researchers evaluated 13 different assays that

consisted of four rapid tests, at least one 1st, 2nd and 3rd generation EIA, and a variety of NAAT assays to address this issue (17). All tests were evaluated using a panel of known positive and negative samples for HIV infection and a seroconversion panel. Dual test algorithms using the tests in different combinations were either optimized for sensitivity or specificity. A three-test algorithm that used the results from the third test as a tiebreaker was also evaluated. The three-test algorithm provided the highest sensitivity and specificity, regardless of the test combination studied. Other findings of this study suggested that NAAT testing was most useful for acute infections, but less sensitive for long-standing HIV infection than antibody testing.

Compared to the traditional two-step EIA followed by Western blot confirmation, the researchers suggest that the alternative algorithms may cost less. In addition, they propose that these algorithms may be more feasible in outreach community programs. As an additional benefit, the alternative test algorithms do not appear to compromise sensitivity and specificity and may even reduce the ambiguity observed with indeterminate Western blot results. In fact, a San Francisco group recently developed and implemented a multiple, rapid HIV test algorithm (RTA) for distinguishing false, rapid-test results from true positives, using a three, rapid-test algorithm. The results suggest that such an algorithm can function and expedite referral for infected clients (18).

Other studies have focused on diagnosing acute HIV infections and have suggested algorithms that include rapid tests and NAAT (19, 20). The first FDA-approved NAAT for diagnosis and confirmation of HIV infection came on the market in 2006, the APTIMA HIV-1 RNA Qualitative

Assay (Gen-Probe Incorporated, San Diego, Calif.).

Remaining Challenges

There is no doubt that the CDC guidelines have expanded and streamlined HIV testing using rapid tests. The expanded use of these tests in a variety of settings, both low and high risk, has provided critical information about their performance characteristics. These data are very useful for constructing new algorithms that may further decrease the time from screening to confirming HIV infection, with the ultimate goal of decreasing time to diagnosis and access to treatment.

In late 2007, CDC researchers, clinicians, and scientists met to evaluate the evidence for a number of alternative algorithms for screening and confirmation of long-standing and acute HIV infections. To date, no recommendations have been made. However, proposed alternative algorithms that rely heavily on the use of rapid tests and other technologies such as NAAT may someday replace the standard algorithm of EIA followed by Western blot that has been in place for the last 20 years.

Revised estimates of new HIV infection cases were published in 2008 based on results from a new antibody test, BED HIV-1 capture enzyme immunoassay, that

can distinguish between long-standing and recent HIV infections (21). These data suggest that the previous estimate of 40,000 annual cases of HIV was an underestimate and that the real numbers may be as high as 56,000 cases annually, a 20% increase over previous estimates.

These figures reinforce the need to diagnose HIV-infected individuals and the rationale behind the CDC recommendations for universal HIV screening. More recently, CAP published a guidance statement that supports the CDC's routine HIV screening recommendation (22). However, even the CDC admits that serious obstacles remain that prevent widespread implementation of the expanded HIV screening set forth in 2006. These include limited funding for HIV screening programs, controversy regarding the elimination of preventive counseling, and legal challenges to opt-out testing (23). Although progress is being made in tackling these obstacles, less than half of academic EDs expect to implement the CDC guidelines for routine HIV screening in the next 2–3 years (5).

In conclusion, HIV remains an important public health issue that continues to demand evolution of testing technologies and testing algorithms, as well as sustained funding and involvement of laboratorians. CLN

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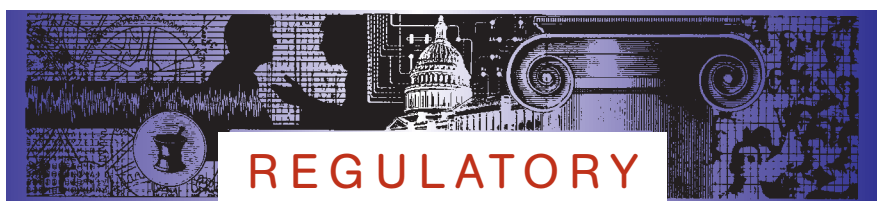
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Senators Call for GAO Best Practices Study

Senate Budget Committee Chairman Kent Conrad (D-N.D.) and Senator Sheldon Whitehouse (D-R.I.) have asked the GAO to study best practices used by state, hospitals, and other countries to reduce healthcare costs and improve quality. In their request to the GAO, the Senators note that many states have their own programs underway aimed at generating savings. For example, Michigan's Keystone Project was able to reduce hospital-acquired infections and other complications in ICUs. The project saved over \$165 million in a 15-month span between March 2004 and June 2005. Rhode Island embarked on a similar project that was able to decrease infections in patients with catheters by 36% in 2006. The Senators' letter asks GAO to advise Congress on how such programs could be applied nationwide. The letter is available on Senator Whitehouse's website, <http://whitehouse.senate.gov/>.

Quality Measures Inventory Released

HHS announced its first-ever inventory of quality measures for reporting, payment, and quality improvement, for use by its agencies and divisions. The HHS inventory is intended to advance collaboration within the quality measurement community and to help synchronize measurements. While several government and non-government groups, such as NCQA, publish reports on the quality of healthcare in the U.S., this is the first time the federal government has initiated a program of its own to make sure its agencies are on the same page. Measures for the inventory were contributed by the Administration on Aging, AHRQ, CDC, CMS, NIH, and other agencies. HHS Secretary Leavitt is calling on national and state policymakers, healthcare executives, and clinicians to use the HHS quality measure inventory and work toward a uniform set of measurements that can provide clear reports about the quality and value of healthcare in the U.S. The inventory is available from the National Quality Measures Clearinghouse on the AHRQ website, www.qualitymeasures.ahrq.gov.

Final Rule on Patient Safety Organizations Issued

A final rule issued by HHS lays out policies and procedures for patient safety organizations (PSOs), the legal entities that give clinicians and healthcare providers a framework to collect, aggregate, and analyze patient safety data without incurring new legal liability. Using a special secure environment of privilege and confidentiality protections, the law is meant to encourage hospitals and other healthcare organizations to embark on voluntary initiatives

for reporting safety information, sharing their findings, and speeding the pace of improvement. The final rule includes several changes from the proposed rule, including expansion of the types of entities excluded from being PSOs, revisions to how PSOs should disclose relationships with healthcare providers, more flexibility in how PSOs can store data, automatic expiration after 3 years unless continued by the HHS secretary, and quick delisting of a PSO under serious circumstances. More information is available on the AHRQ website, www.pso.ahrq.gov.

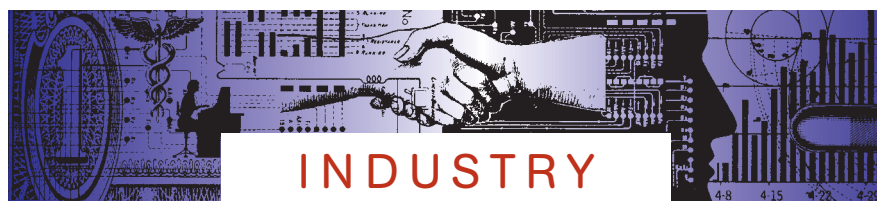
Congress Details Healthcare Reform Ideas

Prominent members of Congress from both the House and Senate are ramping up pressure on the new administration to tackle healthcare reform, with universal coverage as a central tenet of two plans recently put forward. Senate Finance Committee Chairman Max Baucus (D-Mont.) announced a plan that promotes universal coverage, reduced costs, and higher quality of care. The Senate Finance Committee, which oversees Medicare, Medicaid, CHIP, and tax policy changes, held nine hearings in 2008 on the subject of healthcare reform, and these hearings in part lead to Baucus's plan.

The central aim of the plan, universal coverage, would be achieved by creating a nationwide insurance pool called the Health Insurance Exchange. People who already have health insurance would keep their current plans, and those without it would get help to purchase insurance through the Exchange, which would offer premium subsidies and preclude discrimination based on preexisting conditions. The Baucus plan also includes ideas to cut costs and allow for the expansion of public programs by refocusing payment incentives on quality and value, rather than the current system, which Baucus says rewards providers for "delivering more care rather than better care."

On the House side, outgoing House Energy and Commerce Committee Chairman John Dingell (D-Mich.) outlined his proposal in a letter to President-Elect Obama. Similar to Baucus's plan, Dingell is also pushing for changes in the insurance market, more investment in research and preventive care, and universal coverage. Dingell recently joined with Senator Edward Kennedy (D-Mass.) to propose a bill offering universal coverage in the Medicare for All Act, but didn't go into details of how he would implement universal coverage in his letter to Obama. The letter is available on Dingell's website, <http://www.house.gov/dingell/>.

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Fluidigm Licenses Methods for Detecting Fetal DNA in Plasma

Fluidigm announced that it has acquired co-exclusive licenses to Stanford University inventions used in detecting fetal genetic characteristics in maternal plasma, including digital PCR and high-throughput sequencing. These licenses cover a method that counts chromosomes by finding trace amounts of fetal DNA in a pregnant woman's blood, a technique originally published by the Stanford researchers. Researchers believe this less invasive technique could be used to diagnose aneuploidy earlier.

Affymetrix to Acquire Panomics

Affymetrix has entered into a definitive agreement to acquire Panomics, a privately held company that offers assay products for a variety of genetic, protein, and

cellular analysis applications. This acquisition is intended to strengthen Affymetrix's position in high-growth validation and routine testing market segments, while also enabling whole-genome Affymetrix microarray studies that focus on genes and proteins of interest within Panomics products.

DxS and Amgen to Provide KRAS Companion Diagnostic

DxS, a personalized medicine company operating out of Manchester, England, has signed an agreement with Amgen to provide a KRAS companion diagnostic for Vectibix (panitumumab) in the U.S. The drug is used to treat metastatic colorectal cancer patients with wild-type KRAS status. DxS intends to use its TheraScreen: KRAS Mutation Kit as a companion diagnostic in conjunction with Vectibix, pending FDA approval.

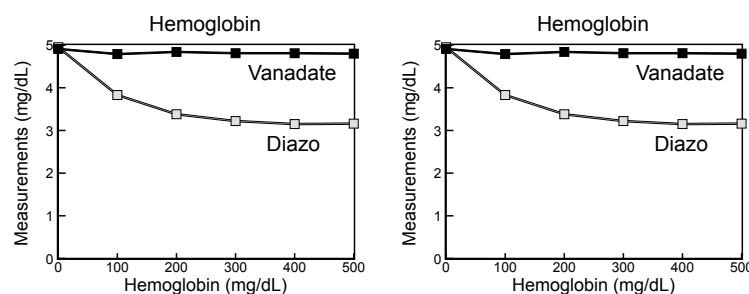
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New Panel of Fecal Protein Biomarkers for CRC Identified

A novel combination of fecal protein biomarkers demonstrated higher sensitivity and specificity than iFOBT alone in detecting colorectal cancer. If validated in further studies, use of these markers could help improve compliance with and accuracy of colorectal cancer screening programs (Clin Gastroenterol Hepatol 2008; 6:1122–1128). The goal of the study was to improve early detection of CRC in stool samples. iFOBT assays are more effective than guaiac-based FOBT, but still miss about one-third of cancer cases.

Researchers had found through previous research that the fecal marker S100A12 had increased expression in colorectal cancer. In this study, they evaluated the diagnostic performance of S100A12, along with five other stool markers, including hemoglo-

bin, hemoglobin-haptoglobin, calprotectin, carcinoembryonic antigen (CEA), and tissue inhibitor of metalloproteinase-1 (TIMP-1), alone and in combination, in a collection of 551 stool samples, divided into three groups based on clinical classification. Using univariate analysis researchers found that S100A12 had the best discrimination for CRC, followed by TIMP-1, hemoglobin-haptoglobin, hemoglobin, and calprotectin. CEA did not demonstrate diagnostically significant discriminatory power. Using multivariate analysis, the best sensitivity of 82% and specificity of 98% resulted from a combination of S100A12, hemoglobin-haptoglobin, and TIMP-1. This combination had the highest increase in sensitivity in early tumor stages. The results demonstrate a “significant improvement” in the early diagnosis of CRC, according to the authors. They plan to further evaluate the use of combined S100A12, hemoglobin-haptoglobin, and

TIMP-1 results as a threshold to trigger follow-up colonoscopy, in a multicenter study.

Biomarker Panel Could Help Identify Progression of Esophageal Dysplasia

An analysis of genes differentially expressed in high-grade esophageal dysplasia (HGD) versus nondysplastic Barrett’s Esophagus (NDBE) revealed that 131 genes are over-expressed by at least 2.5 fold in HGD versus NGDE, and 16 genes are under-expressed by at least the same amount (Clin Cancer Res 2008; 14:6440–6448). This innovative study is the first to employ laser capture microdissection (LCM) of HGD and BE epithelial cells followed by microarray analysis specifically designed to analyze material from formalin-fixed, paraffin-embedded (FFPE) samples. It lays the groundwork for identifying a panel of biomarkers that would help identify patients most likely to progress from NDBE to esophageal adenocarcinoma, and that

would aide physicians in better distinguishing between grades of dysplasia.

Researchers used LCM to isolate epithelial cells from areas of both HGD and NDBE in FFPE tissues from 11 patients. They extracted and amplified mRNA from laser-captured cells, then reverse-transcribed the mRNA and applied it on Affymetrix cDNA microarray chips customized for formalin-exposed tissue. Researchers employed real-time PCR and immunohistochemistry analyses to confirm differential gene expression. This process identified 157 differentially expressed genes from various gene function categories.

Some of the genes found to be either over- or under-expressed had been shown in previous analyses to be modified in the progression from BE to EAC, but this study identified several novel markers. Researchers plan to extend the study by including additional cases and examining whether any of the markers predict progression for NDBE to esophageal adenocarcinoma.

CDC Program Aims to Develop Genetic Testing Reference Materials

Clinical labs now offer more than 1,300 genetic tests, but for the vast majority of these tests, no publicly available, characterized reference or QC materials are available. Consequently, labs must improvise to obtain these reagents and, in some cases, develop and run assays without adequate controls. DNA from leftover patient samples, synthetic DNA, or DNA isolated from cell lines are often used for this purpose.

“Without adequate standards, it is difficult for laboratories to develop and validate genetic tests and to maintain the quality of these tests over time,” said Lisa Kalman, PhD, health scientist in the division of laboratory systems, at CDC’s National Center for Preparedness, Detection and Control of Infectious Diseases.

To address this need, CDC initiated efforts to develop appropriate and well-characterized reference materials for labs that perform genetic testing, and in 2004, the agency established the Genetic Testing Reference Materials Coordination Program (GeT-RM) in partnership with the genetics community. The goal of this program is to coordinate a self-sustaining community process to improve the availability of characterized genomic DNA materials for QC, PT, test development/validation, and research, said Kalman, who is the program’s coordinator. GeT-RM also aims to facilitate information exchange between users and providers of reference materials.

Although the program is coordinated by CDC, all of the actual work, including decisions about reference material priorities, specimen collection, material development and characterization occurs through voluntary collaborations with labs, Kalman explained. Based on the input from numerous stakeholders, cell lines with confirmed genotypes were identified as the preferred source of control DNA for genetic testing because they most closely resemble an actual patient specimen.

Recently, GeT-RM completed characterization of DNA reference materials from more than 90 cell lines for a number of genetic disorders, including fragile X, disorders on the Ashkenazi Jewish panel (Bloom syndrome, Canavan disease, Fanconi anemia, familial dysautonomia, Gaucher disease, mucopolidosis IV, Neimann Pick disease and Tay Sachs disease), cystic fibrosis, Huntington disease, MTHFR-related homocysteinemia, alpha1-antitrypsin deficiency, multiple endocrine neoplasia, and BRCA1 and BRCA2-related cancers. Each of these genomic DNA materials was tested in three to 10 clinical genetic labs using a variety of genetic assays, including DNA sequence analysis. Information about these materials is available on the GeT-RM website (<http://www.cdc.gov/dls/genetics/rmmaterials/default.aspx>) and labs may obtain these materials from the Coriell Cell Repositories (<http://ccr.coriell.org/Sections/Collections/NIGMS/?SId=8>). The program’s website provides a comprehensive source of reference material information. Information is grouped into three subject areas: inherited genetic diseases and pharmacogenetics; molecular oncology; and infectious disease. Information about available reference materials, including applicable characterization studies and results are also provided.

GeT-RM’s current efforts include characterization of DNA reference material for Duchenne muscular dystrophy, as well as a large-scale study of DNA from 100 cell lines for polymorphisms in five pharmacogenetic loci. According to Kalman, the program also intends to deal with the need for reference material in other areas of molecular genetic testing, including molecular oncology, cytogenetics, infectious diseases, and biochemical genetics.

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NEWS FROM THE FDA

C-Path Expands Partnerships Of New Drug Therapies

The Critical Path Institute (C-PATH), a non-profit that works to streamline the development of new medicines by acting as a mediator between the FDA and private industry, has been awarded a \$9 million investment grant from Science Foundation Arizona (SFAz). These funds will be used to improve testing methods that accelerate the development of treatments for major diseases, such as lung cancer, stroke, Alzheimer's, and Parkinson's disease. The grant is expected to have a continued impact on Arizona's rise as a major state for biomedical and pharmaceutical research.

Genedata Extends Collaboration with FDA

Genedata announced a renewed agreement with FDA's National Center for Toxicological Research for use of the Genedata Expressionist biomarker platform. Genedata Expressionist is a computational platform for biomarker discovery, which integrates transcriptomics, proteomics, and metabolomics data within a single software

system. The platform provides a single point of access for all experimental data. Weida Tong, Director of the Center for Toxicoinformatics at the FDA said, "We have successfully applied Genedata Expressionist in a number of FDA projects, including the Critical Path project and the Liver Toxicity Knowledge Base project. Expressionist is an excellent system for monitoring the quality of gene expression data."

MOU Signed Between FDA and USAMRIID

The FDA and the US Army Medical Research Institute of Infectious Diseases (USAMRIID) signed a memorandum of understanding agreeing to share information related to biological threats and diagnostic tests for biological agents in order to assist both parties in preparing for emergencies. As part of their agreement, USAMRIID will provide information on research and development efforts for diagnostics tests, as well as information and expertise on biothreat agents. The FDA agreed to provide feedback to USAMRIID in support of Department of Defense efforts to obtain FDA premarket approval,

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premarket clearance, or emergency use of authorization, for applications being developed by the Army.

FDA Teams Up with WebMD

The FDA has teamed up with WebMD in an effort to expand consumers' access to the agency's health information. Consumers will now be able to access safety

information on FDA-regulated products, receive public health alerts through the WebMD website, and learn how to report safety issues directly to the FDA. The FDA will also contribute Consumer Updates to WebMD The Magazine, a bimonthly publication reaching nearly nine million consumers. These new online resources can be viewed at www.webmd.com/fda and www.fda.gov/consumer.

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