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From the Desk of R. Lewis Dark...

THE DARK REPORT

RELIABLE BUSINESS INTELLIGENCE, EXCLUSIVELY FOR MEDICAL LAB CEOs / COOs / CFOs / PATHOLOGISTs

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COMMENTARY & OPINION by...

R. Lewis Dark

Founder & Publisher

Congress Seems Ready to Tackle LDT Regulation

RECENT DEVELOPMENTS SIGNAL THAT THE FIGHT over FDA regulation of laboratory-developed tests (LDTs) is about to intensify. Last month, two Congressional representatives announced a new bill about LDTs that they said was a "discussion draft." The bill is titled the "Diagnostic Accuracy and Innovation Act (DAIA)." *(See page 15.)*

It was a big deal in 2014 when the **Food and Drug Administration** issued draft guidance on a proposed framework for regulatory oversight of LDTs. If it were put into place, this draft guidance would mark the end of the FDA's historical policy of not applying the medical device regulations to LDTs. Instead, the FDA would implement a risk-based approach for regulation of moderate- and high-risk LDTs.

News of the FDA's plans to regulate LDTs was met with immediate opposition from the clinical lab industry. Since 2014, FDA officials took measured steps to advance their plan to regulate LDTs. Then, in January, the FDA issued a discussion paper and said it was prepared to work with all stakeholders on how to accomplish its goal of LDT regulation.

FDA regulation of LDTs would be a major development for the clinical laboratory industry. In the past two decades, the number of LDTs that commercial lab companies offers for use in clinical settings has exploded. A large proportion of these LDTs lack adequate clinical data to support the accuracy of the biomarkers they measure and to demonstrate that the test results contribute to improved patient care.

Molecular assays and genetic tests are the fastest growing segment of laboratory testing and large amounts of money are involved. The power players in the lab industry would prefer to maintain the status quo for LDTs. At the moment, any lab company can offer any lab test that meets the current definition of an LDT and the user, meaning the ordering physician, must trust that the reported results are accurate and those results are useful in diagnosing the patient and selecting effective therapies.

From that perspective, today's LDT marketplace can be described as caveat emptor—"let the buyer beware!" Given the money involved in genetic testing, it is likely that there will be bitter fights over any bill, such as the DAIA, that would authorize the FDA to bring LDTs under full or partial regulation. TDR

FDA Clears Digital Path for Primary Diagnosis

Philips IntelliSite Pathology Solution becomes first digital pathology system to win FDA clearance

CEO SUMMARY: Proponents of digital pathology systems and whole slide imaging achieved a milestone on April 12 when the FDA cleared the Philips digital pathology system for sale in the United States. Now pathologists can use the system to perform primary diagnoses and get paid for those professional services. It is expected that this regulatory clearance will encourage more pathology group practices to consider acquiring their own digital pathology systems.

DIGITAL PATHOLOGY AND WHOLE SLIDE IMAGING just cleared one of its toughest regulatory hurdles in the United States. On April 12, the **Food and Drug Administration** cleared the **Philips** IntelliSite Pathology Solution (PIPS) for sale in the United States.

In announcing its decision, the FDA said that the Philips product is a "whole slide imaging (WSI) system that allows for review and interpretation of digital surgical pathology slides prepared from biopsied tissue. This is the first time the FDA has permitted the marketing of a WSI system for these purposes."

Alberto Gutierrez, PhD, Director of the Office of In Vitro Diagnostics and Radiological Health in the FDA's Center for Devices and Radiological Health, said, "The system enables pathologists to read tissue slides digitally in order to make diagnoses, rather than looking directly at a tissue sample mounted on a glass slide under a conventional light microscope."

The FDA's decision is significant because it gives Philips the first digital pathology system cleared for use in the primary diagnosis of tissue specimens, a significant milestone for digital pathology technology in the United States.

Two things can be expected to happen in response to the FDA's action. First, other manufacturers of digital pathology systems will file applications for market clearance and use the application Philips submitted as a guide. Within a year or two, other digital pathology systems will likely gain FDA clearance.

Second, it is widely believed that pathology groups and pathology lab com-

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panies have held off buying digital pathology systems until federal regulators cleared the technology for use in the primary diagnosis of biopsied tissue and resection cases. Now that Philips has won such clearance, there is likely to be a surge in demand for these systems.

This FDA clearance comes almost 20 years after the first telepathology and digital pathology systems entered the market. Most of those systems were used for research and internal purposes, such as teaching, tumor boards, and consults.

For Philips, this regulatory decision comes after seven years of development work and market engagement. "This FDA decision has been a long time coming and it feels good to make a difference in the industry by making the promise of digital technology applicable to what pathologists do every day," stated Russ Granzow, General Manager of Philips Digital Pathology Solutions. "The Philips IntelliSite Pathology Solution (PIPS) was demonstrated for the first time at USCAP 2010 and Philips signed the first contract for the system in 2011. That is well before it was possible for pathologists to get paid for using the system for primary diagnosis."

A Complicated Question

While recognizing the importance of the FDA's decision, Granzow was not ready to say that pathologists will do away with microscopes any time soon. "Will digital pathology systems replace the microscope?" he asked. "The transition towards a full digital workflow is a significant effort for the lab. The fact that the FDA approved the use of digital pathology for primary diagnosis is certainly an important milestone.

"The FDA's decision truly is a watershed moment for pathologists who now have the power to do primary diagnosis with any histology tissue type and any stain using digital pathology equipment," he noted. "Bringing digitization to the industry means we can leverage all the benefits that result when images are digitized. This includes enhanced logistics, and easier collaboration, as well as the future use of artificial intelligence and all the other digital tools and data to help pathologists be more effective in this new complex world of healthcare."

Faster Diagnoses

The FDA recognized these benefits as well. "Because the system digitizes slides that would otherwise be stored in physical files, it also provides a streamlined slide storage and retrieval system that may ultimately help make critical health information available to pathologists, other health care professionals, and patients faster," Gutierrez said in the FDA announcement.

The use of digital imaging will require labs to make significant and costly changes in workflow. "Some labs are very keen to make those changes because they believe that digital pathology systems mean they can improve quality and ultimately outcomes—we believe," Granzow said. "Those workflow changes will take time and money, which means some labs will adopt whole slide imaging right away and others will not.

"But regardless of how fast pathologists adopt digital workflow systems, the FDA approval is truly a watershed moment for all pathology groups," he added. "One reason this is true is because pathologists now have an easier path to realize a return on investment from their use of a digital pathology system.

"This is the important point about the FDA's decision: It means that pathologists can charge and get reimbursed for the professional component of doing a standard diagnosis for H&Es, IHCs, and special stains," emphasized Granzow. "The reimbursement codes already exist.

"ROI was beginning to become attractive just from the workflow improvements that pathologists would get and that was without being able to charge for and get paid for primary diagnosis," he said.

FDA Reviewed Clinical Study Data to Assess the Value of Digital Images Versus Glass Slides

WHEN IT ANNOUNCED THE CLEARANCE FOR MARKET of the Philips IntelliSite Pathology Solution (PIPS) for whole slide imaging (WSI), the FDA said the system can scan and digitize conventional surgical pathology glass slides prepared from biopsied tissue at resolutions equivalent to 400 times magnification. Pathologists then can view the digitized images for interpretation.

The FDA based its approval of the PIPS for primary diagnosis on a clinical study of approximately 2,000 surgical pathology cases using tissue from multiple anatomic sites. "Results of the study found that clinical interpretations (diagnoses) made based on the PIPS images were comparable to those made using glass slides," the FDA said.

Philips sponsored the study at the **Cleveland Clinic**, the **University of Virginia**, **Advanced Pathology Associates** in Rockville, Md., and **Miraca Life Science** in Irving, Texas.

The fact that the researchers concluded that clinical interpretations of digital images were comparable to those that a pathologist would make while viewing glass slides is the significant factor in the decision. To the researchers, the term "comparable to" meant pathologists could make interpretations that were "not inferior to" those made using glass slides.

When the researchers described the study in a poster presented at USCAP 2017, they said, "Before substituting the time-honored, familiar, and versatile microscope with digital microscopy, several valid concerns need to be addressed. The most critical issue is whether pathologic diagnoses rendered using WSI are comparable to (i.e. non-inferior to) pathologic diagnoses made with optical microscopy."

While several smaller and single-site studies were done previously, the research Philips sponsored was more robust. "This large, multi-center, non-inferiority study compares microscopy to WSI reads of 2,000 surgical pathology cases from 20 different organ systems (54 subtypes) with 16 reading pathologists from four institutions," the study by Feldman, Rubin, et. al, showed.

In their conclusions, the researchers wrote, "Manual digital is non-inferior to manual optical for primary diagnosis for surgical pathology. Manual digital is non-inferior to manual optical across a wide range of organ systems and pathologists."

"Now, with FDA clearance of our digital pathology system, it is possible for pathologists to get both workflow improvements and the big benefit of getting paid for using imaging for primary diagnosis. Those two factors will cause more pathologists to consider adopting digital pathology.

"Payment is important, of course, but don't overlook the fact that workflow is also a significant factor in any pathologist's decision to adopt an imaging system," Granzow added. "Our solution has always been focused on very efficient clinical workflow. You load the system, close the door, and there is no other human interaction after that. Slides are scanned and go to your image management system. It is designed for hands-off, very high throughput clinical workflow. That's what pathologists are looking for today."

Philips would not say how many pathology groups have installed the PIPS system in the United States. Granzow said, "It's in the hundreds of users and is significant," adding that the PIPS system is used by major academic medical centers, comprehensive cancer centers, and reference laboratories. **TDR**

—By Joseph Burns

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Digital Pathology Makes Group More Competitive

➤Community path group says DP helps level the competitive field with academic centers

➤➤CEO SUMMARY: One 15-member pathology group said adopting digital pathology will give it more competitive advantage. Advanced Pathology Associates (APA) in suburban Maryland, was one of four sites that participated in the clinical study of the Philips IntelliSite Pathology Solution application for FDA clearance to use the system for primary diagnosis. The experience was of such value to the pathology practice that APA is interested in buying and installing the Philips system.

One private practice pathology group in Maryland is enthusiastic about how it can use the **Philips** digital pathology system to gain competitive advantage, now that the FDA has cleared this system for use in the primary diagnosis of biopsied and surgically excised tissue.

This confidence is contrary to the popular wisdom, which says that digital pathology is best suited for academic medical centers, large reference labs, and comprehensive cancer clinics.

Advanced Pathology Associates is a 15-member community pathology practice in Rockville, Md. "We began using the Phillips IntelliSite Pathology Solutions (PIPS) in April 2015," stated Nicholas Cacciabeve, MD, APA's Managing Partner. APA participated in the clinical study that produced the data Philips submitted to the FDA in its premarket application.

"I was glad Philips recruited a community pathology practice to be part of its study of PIPS because I don't think digital pathology is for academic centers only," he noted. "It's for everybody, including community practices."

Advanced Pathology Associates was one of four sites that tested the PIPS for research done from October 2015 through May 2016. Philips then submitted that research to the FDA in October 2016 to support its application to use PIPS for primary diagnosis. The FDA granted that approval on April 12. *(See pages 3-5.)*

➤Leveling the Playing Field

Academic medical centers will certainly use the PIPS for primary diagnosis, but for Cacciabeve, the FDA approval means APA and other community practices can adopt whole slide imaging and get paid for the review and interpretation of digital surgical pathology slides prepared from biopsied and excised tissue.

"Digital pathology systems will help level the playing field between smaller pathology groups like ours and academic medical centers," he said. "This study shows that we have the ability to transmit digital images to drive the diagnosis of specific types of tissues into the hands of experts.

"As a community practice, I don't want to cede my ability to remain in the middle of clinical practice to academic medical cen-

ters," he added. "Within my own group, I want to have expert pathologists who can provide real-time consultations. But at the moment, we are a relatively small group practice of 15 pathologists using glass slides.

"We're about to begin discussions with Philips to acquire the PIPS so that we can offer our services with digital imaging to smaller hospitals that have maybe one or two pathologists," he said. "When we do that, we can support those pathologists seamlessly into our practice through consultation with digital imaging.

The Promise of Technology

"This means small hospitals with one or two pathologists can appear to have the same kind of sub-specialty pathology expertise as an academic medical center," continued Cacciabeve. "That's because the local pathologists and their referring physicians can consult in real time with us.

"The ability to share digital images means there will be no delay in the turnaround time," he said. "That hospital can send the digital image to our specialist pathologists, who have expertise here in breast pathology, hematopathology, and other areas, and we can provide real-time consultations.

"That's why I say that adopting digital pathology will become a necessity for community pathology groups like ours," he explained. "It's one reason why our practice was an early adopter in the PIPS research for the FDA submission. Being an early adopter has already given us a competitive advantage against other practices that will not adapt to digital pathology.

"We will also gain an even more significant competitive advantage when digital pathology systems start using computer algorithms to read slides," he said. "Consider what happened with the Pap smear. Like most labs, we don't do many conventional Paps because the technology is inferior to the new thin-prep methodology.

"That example tells me that if we don't adapt to the newest technology in reading tissue—which is going to be a digital image with a computational pathology computer application added to it—then we are not going to remain competitive in the marketplace. And we won't be providing the best of care," he said.

To gain that experience, Cacciabeve participated in the clinical trial Philips ran. "In our model, we have multiple pathologists at seven different hospitals, and, in this study, we used materials from two of the hospitals," he explained. "It was important for each of our pathologists to gain expertise, including some specialty expertise, with digital pathology.

Suburban Pathology Group Sees Advantages with WSI

AS THE MANAGING PARTNER of Advanced Pathology Associates, Nicholas Cacciabeve, MD, views digital pathology systems as the beginning of a new era in pathology. Digital pathology systems will replace microscopes, which pathologists have used for 150 years, he said.

"There's no question that microscopes are on the way out," he commented. "I've thought so for several years now.

"It's a big step for the FDA to clear the first system for use in the primary reading of digital images, and that's just the beginning of what digital pathology systems can do," noted Cacciabeve. "Digital technology will evolve to include computational pathology, which is one of the most exciting advancements to come from digital imaging.

"Today, it's very challenging for pathologists to read cases all day long and have a continuous focus on each case," he continued. "If you get distracted for a second or you get interrupted for something, you can miss a portion of a slide. But machines and computers don't get interrupted. They will be able to scan the entire slide looking for abnormalities. As that happens, it will make us more efficient and improve our accuracy and precision as diagnosticians."

"We believe this helps level the playing field in ways that benefit our community pathology group," noted Cacciabeve. "Traditionally, when the patient went to an academic medical center for diagnosis and treatment, there would be sub-specialists in many different fields in pathology. Depending on what biopsy or piece of tissue was taken from the patient, an expert would read it.

Leveraging Expertise

"With digital pathology, we can now share a digital image seamlessly with that expert on those tough cases that need an expert to help us render a diagnosis," he added. "It's the same thing with consultations.

"In many hospitals, just one or two pathologists are working by themselves," Cacciabeve explained. "Now that we have digital images, we can share those images quickly with consultant pathologists and have real-time discussions. That means there would be no delay in getting the diagnosis of the case.

"In addition, performing peer review and presenting cases at conferences can be done digitally," he said. "For all those reasons, it's a big advantage for a community pathology practice like ours to use a digital pathology platform."

Of the four pathologists at APA who participated in the PIPS study, two had 20 or more years of experience and two had less than four years of experience. "It did not surprise me that the two younger pathologists adapted to the digital workflow quickly," he explained. "They were comfortable with the software and with viewing images on a screen.

"The more experienced pathologists were a little slower to adapt to it, at least at the beginning," recalled Cacciabeve. "By the end of the study, all four were very comfortable with the technology and were efficient and confident in their reads."

For the pre-market approval study, Philips installed the PIPS system at no cost. APA used it as part of the study to have the four pathologists read 500 patient cases both digitally and optically. "So, basically we had 2,000 digital reads," he said. "That was valuable experience for us. Then once the study was over, they removed the equipment.

"One reason I wanted to participate in the project is I'm a strong believer that digital pathology is maturing rapidly," he said. "I saw it as a way to get our pathologists some experience using it in a safe, controlled setting.

"That's just what we got: 2,000 digital reads under somewhat real-life conditions," he added. "They read the slides as if it was the first time they were seeing the slides. We then submitted the diagnoses that were matched against a control standard, which was the original microscopic diagnosis done at least a year earlier.

"Four of our pathologists acquired valuable experience over the nine months of the research study (April 2015 to February 2016)," he said.

"We were assigned to read breast cases, gastric cases, respiratory cases from the lungs and larynx, and the oral cavity," he explained. "These 2,000 reads gave us experience with those organ sets.

Pathology Is A Business

"When you think about it, medicine is a business and pathology is a business," he added. "And someone said once that if you're not participating in the business, you're a victim of the business. Look at how clinical laboratories consolidated rapidly in the 1990s and look at how anatomic pathology groups are consolidating rapidly now.

"That consolidation suggests that the older model of one- or two-person practices will go by the wayside," concluded Cacciabeve. "At the same time, the digitalization of pathology will completely change the way we do the work today." TDR

—Joseph Burns

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Lab Mergers/Acquisitions

Aurora Diagnostics Acquires Pathology Groups, Posts Loss

Even as one of the nation's largest pathology firms buys more groups, it reports significant losses

ONE OF THE MORE CURIOUS SITUATIONS IN THE LAB INDUSTRY TODAY is the story of **Aurora Diagnostics** of Palm Beach Gardens, Fla. Even as it loses money, it continues to acquire pathology group practices.

Aurora recently issued its earnings report. For 2016, it disclosed a net loss of $29 million, with revenue of $284 million. This continues a multi-year losing streak of net losses of $83 million in 2015, $55 million in 2014, $73 million in 2013, and $161 million in 2012. Thus, in the five years of 2012 to 2016, the company has collectively lost $401 million.

Meanwhile, Aurora Diagnostics continues to scoop up private pathology groups. On April 3, the company announced that it would acquire **University Pathologists**, in Warwick, R.I., followed by another announcement on April 18 that it would purchase **Pathology Associates** of Princeton, N.J.

Additional Disclosures

In its annual 10-K filing with the SEC, the company said it expected to continue to operate as a going concern, that it had outstanding debt of $200 million of senior notes maturing on Jan. 15, 2018, and that it owed $197 million under its senior secured credit facility.

In addition, Aurora warned that, management believes it has enough cash and funds in a revolving credit facility to fund working capital requirements for 12 months. This belief assumes that the company will be able to conduct and close a proposed debt exchange offer and therefore avoid acceleration of the maturity date of the senior secured credit facility.

Financial Agreement

In its 10-K filing, Aurora Diagnostics also said that, in March, it amended a financing agreement for the sixth time with **Cerebus Business Finance**. The agreement was initiated on July 31, 2014, and has since been amended. Basically the amendment would have increased the applicable margin on the loan to 7.125% or 8.125% if Aurora Diagnostics failed to deliver audited financial statements within a specified time. By delivering the statements on March 31, the company did not expect to pay the increased rate.

Aurora Diagnostics said it owns "27 community-based pathology laboratory practices with more than 200 board-certified pathologists." Founded in 2006 it is one of the larger pathology companies in the United States.

The curious element in this story is why private practice pathologists are willing to sell their groups to a national pathology company that has, in the past five years, reported losses approaching one-half billion dollars. If this story turns out well, it will justify the optimism of the pathologists who sold their groups to Aurora in recent years. TDR

—Joseph Burns

Study involved patients referred to Mayo Clinic

Diagnostic Error Rate Of 21% Revealed By Mayo Clinic Study

➤➤ CEO SUMMARY: Researchers at the Mayo Clinic showed that only 12% of patients referred to Mayo physicians for a second opinion got a confirmation that their original diagnosis was complete and correct. In 21% of the cases, the diagnosis was completely changed. Among patients who got additional work ups for a second opinion, some 80% to 94% of them got additional lab tests. The research also showed that pathologists and radiologists take steps to ensure diagnostic accuracy by confirming findings with colleagues.

DIAGNOSTIC ACCURACY is once again in the news. This time, a research study performed at the **Mayo Clinic** in Rochester, Minn., determined that, among other findings, in a sample of 286 patients referred to the clinic, 21% had their diagnosis completely changed.

This and other findings from the study have important implications for pathologists and lab administrators. It is evidence of the substantial value that laboratories could contribute by collaborating more closely with clinicians to improve diagnostic accuracy and reduce or eliminate recurring sources of diagnostic errors.

"One of the most challenging errors to improve in healthcare is diagnostic accuracy," commented James Naessens, ScD, a health policy researcher with the Mayo Clinic. One of the authors of a recently-published article on misdiagnosis, Naessens' research showed that only 12% of the patients who were part of a study got a confirmation that their original diagnosis was complete and correct.

One significant finding of the study is that more than one in five patients (21%) got a completely new diagnosis. As well, in 66% of the cases, the patients received a refined or redefined diagnosis.

Previous research on diagnostic errors shows that these mistakes contribute to about 10% of patients' deaths and account for 6% to 17% of adverse events in hospitals.

An important finding from the research—and this finding was not in the published paper—is that during the 30 days when a patient was getting a second opinion at Mayo, some 80% to 94% of those patients got additional medical laboratory tests, Naessens said in an interview with THE DARK REPORT. "About 55% to 67% of these patients also got X-rays or other radiology exams, and 20% to 40% got CT scans," he added.

"Clearly, these ancillary services were needed to supplement the information the Mayo Clinic providers had gathered initially to figure out what was going on with these patients," explained Naessens. "To do that, our laboratory and radiology specialists were brought into play on the teams that were addressing the patients' complaints.

"The point is that these patients not only got a second opinion, but also there was a rereading of the medical records, face-to-face meetings with patients, and there was a need for the additional work up of lab and imaging tests," he added. "That additional information helped to change the diagnosis."

The findings from Naessens' research were published online on April 4 in the *Journal of Evaluation in Clinical Practice.* The paper is titled, "Extent of Diagnostic Agreement among Medical Referrals."

➤ Value in Second Opinions

For years, the patient safety movement has put an emphasis on the value of getting a second opinion. Now Naessens' research has confirmed the need for a confirmatory diagnosis because, as the research shows, physicians don't always have the answers. Often, unusual or complex symptoms will lead a physician to recommend a second opinion, or a patient may request one. Regularly, Naessens found, physicians rendering second opinions find that the original diagnosis was in error.

For the research, Naessens and colleagues examined the records of 286 patients referred from primary care providers to Mayo Clinic's General Internal Medicine Division between Jan. 1, 2009, and Dec. 31, 2010. The referring diagnosis was compared to the final diagnosis.

The original diagnosis was confirmed in only 12% of the cases (34). In 21% of the cases (60), the diagnosis was completely changed; and in 66% of the cases (189), the patients received a refined or redefined diagnosis.

"Effective and efficient treatment depends on the right diagnosis," Naessens

said in an article published by the Mayo Clinic news department. "Knowing that more than 1 out of every 5 referral patients may be completely [and] incorrectly diagnosed is troubling, not only because of the safety risks for these patients prior to correct diagnosis, but also because of the patients we assume are not being referred at all."

Other Research

The results of Naessens' research align with other research on diagnostic errors. Further, as Lenny Bernstein reported in *The Washington Post*, Naessens' work provides evidence that the healthcare system still could improve its level of diagnostic accuracy.

For the Post's article, Bernstein quoted Mark L. Graber, MD, the founder of the **Society to Improve Diagnosis in Medicine**, who said, "Diagnosis is extremely hard. There are 10,000 diseases and only 200 to 300 symptoms."

In the article published in the *Journal of Evaluation in Clinical Practice*, Naessens wrote, "Unlike tangible errors involving systems and processes—such as medication administration errors, prescription errors, and wrong site surgery—diagnostic errors have avoided the spotlight because they are less easily understood, not viewed as a system problem, and not perceived as problematic by physicians."

In September 2015, the **National Academy of Medicine** issued a report on diagnostic errors, "Improve Diagnosis in Health Care." The report was a continuation of the landmark **Institute of Medicine** reports: "To Err is Human: Building a Safer Health System" (2000) and "Crossing the Quality Chasm: A New Health System for the 21st Century (2001)."

Inattention to Errors

In the academy's report, experts showed that the occurrence of diagnostic errors has largely been unappreciated among many other efforts designed to improve healthcare quality and patient safety. "The result of this inattention is significant: the committee concluded that most people will experience at least one diagnostic error in their lifetime, sometimes with devastating consequences," the academy said.

"Improving diagnosis will require collaboration and a widespread commitment to change among healthcare professionals, healthcare organizations, patients and their families, researchers, and policy makers," commented the academy.

This point is one Naessens made in his interview with THE DARK REPORT. Pathologists and clinical laboratory scientists have an opportunity and a responsibility to work closely with other healthcare providers to ensure that patients get the correct diagnosis, he said. Also, he confirmed another point from the academy's report: diagnostic error is a relatively under-measured and understudied aspect of patient safety.

A Call for More Research

"Diagnostic error is an area where we need more research and more information," Naessens said. "I've been working in the quality measurement field for the last two decades here at Mayo, and diagnostic error is one of the areas that hasn't gotten much attention, partly because it's hard to measure. And, of course, we tend to focus on what you can measure.

"Yet, it's an important area that underlies the issue of whether a patient is getting the right treatment," he continued. "If we are going to determine if patients are getting the right treatment, then the first step is to ensure that they get the right diagnosis. If you get the wrong diagnosis you're certainly not going to get the right treatment."

Research published by Elizabeth McGlynn and others in 2003 in the *New England Journal of Medicine* showed that only 54.9% of the participants in the study

Understanding the Findings from Research Study Of Diagnostic Errors at the Mayo Clinic

RESEARCHERS AT THE MAYO CLINIC UNDERTOOK A STUDY TO DETERMINE the number and types of diagnostic errors seen in patients referred to the clinic. The sample was 286 patients who had been referred to the Mayo Clinic General Internal Medicine by primary care practices from January 1, 2009 to December 31, 2010.

The study was published online on April 4 in the *Journal of Evaluation in Clinical Practice*, with the title, "Extent of Diagnostic Agreement among Medical Referrals." The table below shows the categories of referral and final diagnosis. Researchers determined that in 12% (36/286) of cases, final diagnoses confirmed the diagnoses presented at the referral. Final diagnoses were better defined/refined in 66% (188/286) of cases. However, in 21% of cases (62/286) final diagnoses were distinctly different than referral diagnoses.

Examples of Referral and Final Diagnosis by Categories

	Referral Diagnosis	Final Diagnosis
CATEGORY 1 No Change Diagnosis	Question fibromyalgia	Fibromyalgia
	Low back pain	Mechanical low back pain-chronic
	Feelings of anxiety	Generalized anxiety
	Polymyalgia rheumatica	Polymyalgia rheumatica
	Dizziness	Imbalance/Vertigo
CATEGORY 2 Diagnosis Better Defined	Endocrine abnormalities	Secondary adrenal insufficiency; suspect opioid endocrinopathy
	Multiple constitutional symptoms over the last year	Acute CMV infection
	Syncope	Syncope secondary to doxazosin
	Weakness	Drug-induced rhabdomyolysis
	Elevated PSA; spinal mass	Metastatic prostate cancer to spine and lung
CATEGORY 3 Different Diagnosis	Anemia	Autoimmune hepatitis
	Weight loss	Malignant lymphoma suggestive of Hodgkin's lymphoma
	Body Aches	Acute Myelogenous leukemia
	Weight loss and abdominal pain	NSAID-induced gastropathy; irritable bowel syndrome
	Chronic fatigue	Heart failure

Source: "Extent of Diagnostic Agreement Among Medical Referrals"; J Eval Clin Pract, 10.1111/jep.12747, Van Such, Lohr, Beckman, Naessens.

received the recommended standard of care for their condition. *(See TDR, July 7, 2003.)*

All of which may indicate the need for systemic changes. "One of the things we wanted to point out in the study is that there seems to be an attempt by health insurers seeking to reduce costs to use narrow networks," he said. "When payers do that, some of those narrow networks might put burdens on patients or they may create barriers for patients seeking to get second opinions or to get another work up for their conditions.

"In those instances when a provider has some doubt, there should be a way for those patients to get further information and second opinions," he said. "Any restrictions on the ability of patients to get the additional information they need could be detrimental to diagnostic accuracy and to their health.

One in Five Patients Affected

"Primary care providers should be able to make sure their patients get any additional diagnostic work up when they feel that they don't have all the expertise and they need to call in additional help," he added. "Not every primary care visit has a 20% error rate, but the 20% rate means there should be plenty of opportunity for patients to get a confirmatory diagnosis. In fact, for some subgroups of patients, the rate could be higher than 20%."

One of the most surprising aspects of the research, Naessens said, was that he did not think the rate of changed diagnoses would be as high as it was: 21%. "I thought it would be about 5% or maybe 10%. I wasn't so surprised by that middle category, meaning where the diagnosis was refined or redefined, because we expected that a number of people were going to be referred as patients who had complex symptoms. For those patients, physicians often don't know what's going on and so, to figure it out, they need to work with experts in diagnosis such as we have here at the Mayo Clinic.

"The other surprising result was that there was no real concentration of problems in any particular diagnosis category except maybe for musculoskeletal issues," added Naessens. "These patients were coming to Mayo from different sorts of areas and yet there were no particular diagnostic areas that stood out. They were all well represented."

Model of Collaboration

For clinical lab scientists and pathologists, Naessens commented that they have a model of collaboration designed to eliminate diagnostic errors. "We use laboratory and pathology as examples of how they do a lot of double checking on their work and rereading of pathology slides," he said. "This method of operating your practice can go a long way toward minimizing errors.

"In part, that's why we suggest that other providers should use pathology and radiology as examples of how secondary reviews are beneficial, from a learning perspective, to improve your approach in selected cases to the point where it would be beneficial to patients," he added. "More of medicine should follow their lead. But physicians should also seek out pathologists and radiologists for second opinions, especially when the original physician is in doubt.

"In other words, physicians should not be afraid to work in teams because those different perspectives bring value, particularly in the more complex situations," concluded Naessens.

Study Of Diagnostic Errors

This study of diagnostic errors shows the growing interest some clinicians have in measuring the actual rate of errors in medical care. Pathologists and lab administrators may want to collaborate with physicians in their hospitals to conduct similar studies. **TDR**

—Joseph Burns

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Legislative Update

Federal Regulation of LDTs Subject of Proposed Bill

Two federal lawmakers release draft of a bill that would deal with laboratory-developed tests

THERE'S A NEW BATTLE over laboratory-developed tests (LDTs) looming on Capitol Hill. In response to the FDA's draft guidance to regulate LDTs, a bill has been proposed by two members of the house that would shape LDT regulations in different ways than proposed by the FDA.

The Diagnostic Accuracy and Innovation Act (DAIA) was made public on March 21 by U.S. Reps. Larry Bucshon, MD (R-Ind.) and Diana DeGette (D-Colo.). They called it "a discussion draft" of the DAIA and asserted that this law would provide a predictable and timely path to market for innovative diagnostic tests.

Bucshon and DeGette also said that the DAIA builds on previous work, meaning that of the Diagnostic Test Working Group (DTWG). This is a group that represents large clinical laboratories and companies that develop diagnostic tests. The DTWG was created in response to the FDA's 2014 proposal to regulate LDTs.

FDA's New Stance

The FDA proposal stirred up a firestorm of opposition across the clinical laboratory industry. It was a proposal that seemed to have few friends within the house of laboratory medicine. For example, both of the national lab companies went on the record as opposing the FDA's proposed LDT guidance.

In November 2016, after the federal election, the FDA said it would halt its movement in that direction while the new administration took office. Then in January, the FDA issued a discussion paper on LDTs, which it said did not represent the formal position of the agency and was not enforceable. "We hope to simply advance the public discussion by providing a possible approach to spur further dialogue," the FDA said.

What Comes Next For LDTs?

That seems to have set the stage for the emergence of the proposed Diagnostic Accuracy and Innovation Act. But every bill that surfaces in Congress is because some individual or group has raised the need for such a bill with sympathetic lawmakers.

Thus, to understand who would benefit from the language of this bill, it is necessary to know which lab industry companies and vendors brought this issue to the attention of Bucshon and DeGette. That is the more interesting story which has yet to be told. Some lab professionals familiar with the language of the DAIA say that it appears to reduce regulation of the test kits manufactured by the IVD companies while increasing the regulatory burden for labs performing LDTs. If true, then another lab industry fight may be about to commence. **TDR**

—Joseph Burns

More Hospitals Consider Options for Their Labs

More hospitals and health systems assess possibility of lab sale or lab management deals

CEO SUMMARY: Is it a new sign of the times? After decades of reluctance to sell their lab outreach businesses or enter into inpatient lab management agreements with commercial lab companies, a surprising number of hospitals and health systems are taking that step. Since the first of the year, sales of several major hospital lab outreach programs have been announced. Executives at commercial lab companies are bullish on their prospects to nail down more such deals.

SINCE JANUARY, SEVERAL HOSPITALS AND HEALTH systems moved aggressively to shore up their finances, restructure their lab operations and, in some cases, to jettison long-established lab outreach programs.

Just since the New Year, **Laboratory Corporation of America, Quest Diagnostics,** and **Sonic Healthcare USA** each announced deals to acquire lab operations from hospitals or to partner with health systems seeking expertise in the lab business, stated Noel Maring, Sonic's Vice President of Hospital Affiliations.

Strategic Decisions

"Hospitals and health systems are making strategic decisions about their clinical laboratories and, as they act on those decisions, the market for partnerships and outright sales of lab operations has become very active in recent years," commented Maring. "Consider the partnerships Sonic established, along with different announcements of hospital lab outreach sales and hospital lab management agreements from LabCorp and Quest Diagnostics. Collectively, these agreements demonstrate the bigger issues hospitals and health systems are facing."

Market pressures are motivating some hospitals and health systems to sell their lab outreach businesses or seek a joint venture or lab management arrangement with commercial lab companies.

"Take, for example, LabCorp's deal in January to acquire the assets of **Mount Sinai's Clinical Outreach Laboratories** in New York," Maring said. "In February, Quest Diagnostics announced a deal to buy the lab operations of **PeaceHealth** and manage 10 PeaceHealth labs in Alaska, Oregon, and Washington. And, more recently, LabCorp said it was acquiring an ownership interest in **Pathology Associates Medical Laboratories**, (PAML) of Spokane, Wash., and most of PAML's partnerships."

In February, Sonic announced agreements with **Western Connecticut Health Network** and with **Baptist Memorial Health Care**, in Memphis.

"This activity reflects a strong trend that we can attribute to three factors," Maring explained. "First, hospitals are asking themselves if they will remain in the outreach

business in the future. Can they run it profitably, particularly considering the potential for reimbursement reductions?

"Most hospitals have competent people running their inpatient lab operations," he continued. "But running a successful lab outreach business can be a struggle for them. Then there is the looming threat of the Medicare Part B lab test fee cuts that will happen in 2018. Hospital administrators are modeling the negative financial effect these cuts will have on labs.

"We know the Protecting Access to Medicare Act (PAMA) was an important issue in PeaceHealth's decision to sell its outreach lab business," he added. "Most hospital administrators recognize that, in the long run, the higher commercial lab reimbursements will go away, particularly as we move from fee-for-service to value- or risk-based reimbursement models.

Are Labs a Key Service?

"So, they ask themselves if their lab outreach business is a core competency, and, if it is, can they run it profitably in the future," he added. "Those are difficult questions for any hospital to answer.

"The second question they ask is whether the clinical lab—and outreach lab testing in particular—is a key service line for the health system," explained Maring. "Frequently, the answer is equivocal. They may determine that the outreach lab business is not a key service line. However, outreach lab testing typically does utilize unused capacity and generates economies in a hospital laboratory. So the associated outreach business certainly does help to keep inpatient laboratory costs down.

"That discussion then leads to this question: Do we sell it, maintain the status quo, or enlist a partner to help us run more efficiently?" he said.

"There seems to be a significant potential in monetizing outreach businesses right now simply because of the value that the two national labs are putting on that business," he said. "Some hospitals need to monetize their outreach operations to shore up their balance sheets. Other hospitals see the value in keeping the outreach business, leveraging the lab data, and main-

Two Deals Show Hospitals' Move Toward Partnerships

IN FEBRUARY, SONIC HEALTHCARE USA announced two new agreements that show how one lab company is seeking joint-venture partners. Sonic did not release details on the financial arrangements for either partnership, both of which will become final next month.

One agreement is with **Western Connecticut Health Network**, a three-hospital system serving Norwalk, New Milford, and Danbury, Conn. The other agreement is with **Baptist Memorial Health Care**, in Memphis, in which Sonic will operate a bacteriology center of excellence to 17 of Baptist's hospitals in Arkansas, Mississippi, and Tennessee, and Sonic's referring physicians in the southern states.

When it announced the Baptist deal, Sonic said the partnership would be called **BMHSI/AEL Microbiology Laboratory GP** in part because it would build on an existing relationship that Sonic's subsidiary, **American Esoteric Laboratories**, has with Baptist. In that relationship, AEL is Baptist's principal reference laboratory. Under the new arrangement, AEL will manage the bacteriology laboratory.

"We've been developing hospital partnerships and management agreements with health systems across the country and around the world," commented Noel K. Maring, Sonic's Vice President of Hospital Affiliations. "In fact, we're working with more than 100 hospitals around the world, including the lab partnership we completed in 2014 with **University College Park Hospital** in London. That one is similar in structure to our partnership in Connecticut. We also manage labs for university hospitals in Germany and Australia."

taining a profit line down the road, if they can maintain it as profitable.

"Each hospital, each lab outreach business, and each market is different. So, there are no simple answers," he commented.

"One large health system that decided to go all in with its lab business—including outreach—was **Northwell Health**, formerly the **North Shore Long Island Jewish Hospital System,"** he said. Northwell made a significant investment in its core lab. Two other health systems making similar decisions are **Aurora and Advocate Healthcare**, joint owners of **ACL** laboratories in Milwaukee and Chicago.

Inpatient Revenue Declining

"Consider what hospitals face today, such as declining revenue per inpatient," continued Maring. "They may want to stay in the lab outreach business. But if they do so, they need to shore up that business and cut their costs. Once they get to that point, they have more questions to answer. Can they do that on their own or do they need a partner? Or should they get out of the business?

"The national lab companies recognize these issues and have begun to provide answers where they can," Maring said. "From what we've seen of LabCorp's recent deals—such as the Mount Sinai deal—LabCorp may tend to want to buy hospitals' outreach businesses. They seem to have relatively little interest in managing inpatient laboratory operations. Nor do they seem to have interest in making partnership deals with health systems. They appear to just want to buy and run outreach lab operations.

"Quest Diagnostics also seems to be shaping up as a company that has an interest in acquiring lab outreach operations," he added. "But they are a bit different in that they also have made a concerted effort to manage inpatient lab operations. In addition, Quest has some partnerships, but going forward I predict they will have less interest in partnerships.

"Here at Sonic Healthcare, we positioned ourselves to acquire lab outreach businesses," he said. "We'll also look at inpatient management contracts, but that's not our primary focus. Depending on a health system's immediate financial needs, we are not convinced it is always in their best interests to sell their outreach lab business or outsource their labs.

"In addition, inpatient lab management agreements have historically been short-term solutions and hospitals have tended to take their labs back within five to seven years," he added.

"More importantly, health systems need to streamline their lab operations, reduce costs, and leverage lab data," Maring explained. "We believe this can be accomplished through a partnership with aligned incentives designed to maintain testing in the hospital while leveraging Sonic's global purchasing, technical expertise, and labor optimization abilities.

"Hospitals need onsite lab testing for their inpatients," he added. "Outreach lab testing is not going to go away, and it can help a hospital reduce inpatient testing costs. We think health systems simply need a partner to help reduce costs and insource the lab outreach business.

Pursuing Value-Based Care

"So, the first two issues for hospitals are: do they want help managing outreach or inpatient testing?" he said. "The third issue is how to prepare for value-based reimbursement.

"Although spending on clinical lab testing is only 3% to 4% of the typical health system's budget, some innovative hospital administrators now recognize that, by utilizing lab data more effectively, they can impact the other 96% of healthcare costs," Maring concluded. "They also recognize that they can use an outside lab partner who can help them identify these patients proactively." TDR

—Joseph Burns

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INTELLIGENCE

LATE & LATENT

Items too late to print, too early to report

Theranos, Inc., is again in the news. On April 17, the company disclosed a global settlement with the federal **Centers for Medicare & Medicaid Services** (CMS) to resolve "all outstanding legal and regulatory proceedings between CMS and Theranos." The company said, pursuant to terms of the settlement, CMS withdrew revocation of the company's CLIA operating certificates and reduced its civil monetary penalty against the company to $30,000. Theranos agreed that it "will not own or operate a clinical laboratory within the next two years." The following day, on April 18, Theranos disclosed an agreement with the Arizona Attorney General's office. Theranos will reimburse Arizona residents for all amounts they paid for Theranos blood testing services between 2013 and 2016, an amount which totals $4.65 million.

MORE ON: *Theranos*

In its settlement with the Arizona AG, Theranos "also affirmed that it will not own or operate a CLIA-licensed laboratory in Arizona for two years, commencing March 28, 2017, and will pay the attorney general's office $200,000 in civil penalties and $25,000 in attorneys' fees and other legal costs."

NANTOMICS ACQUIRES GENOS

Genos, a small gene sequencing company in San Francisco, was acquired by **NantOmics**, a subsidiary of **NantWorks** of Culver City, Calif. Nantworks is owned by Patrick Soon-Shiong, MD. Nantworks offers a diagnostic test called GPS Cancer. Soon-Shiong is a high-profile physician and entrepreneur who is regularly in the headlines. Sales reps from his company have been calling on academic center labs and hospital labs across the nation to solicit case referrals for the GPS Cancer test, which news reports say costs about $11,000.

TRANSITIONS

• Bill Bonello is the new Vice President, Treasurer, and Director of Corporation Development for **Neogenomics** of Fort Myers, Fla. He has held positions with **Piper Jaffray**, **Wachovia**, **RBC Capital Markets,** and **Laboratory Corporation of America**.

• Alister W. (Al) Reynolds was appointed CEO of **SomaLogic** of Boulder, Colo. Reynolds has been on SomaLogic's board since 2003 and previously held executive positions at **Quest Diagnostics Incorporated** and **Corning Inc.**

That's all the insider intelligence for this report. Look for the next briefing on Monday, May 15, 2017.