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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

Restricted information, see page 3

COMMENTARY & OPINION by...

R. Lewis Dark
Founder & Publisher

Getting Vitamin D Right for the Doctor and Patient

MOST OF YOU ARE FAMILIAR with how W. Edwards Deming and Japanese manufacturers demonstrated the power of understanding customer expectations and organizing one's business to deliver products and services which meet and exceed those expectations.

For the past four decades, one thing that many of the world's most successful organizations have in common is an exceptional ability to meet and exceed the expectations of their customers. It is not a coincidence that, about the time that **The Joint Commission** joined the **Leapfrog Group** earlier in this decade, it raised the profile of patient satisfaction surveys as a component of the hospital accreditation process. *(See TDR, January 28, 2002.)*

In recent years, as laboratories and hospitals in this country adopted Deming-based quality management methods, pathologists and lab managers in those organizations have begun to regularly consider patient expectations and satisfaction. Another aspect of Deming-based quality management methods, such as Lean and Six Sigma, is the use of errors-per-million-events as a way to measure performance and as a guide to eliminating the source of waste, defects, and errors.

Working in a complementary fashion, these quality management methods are going to cause the analytical science of laboratory medicine to more directly intersect with the expectations of patients and physicians. As this occurs, it will demand additional rigor from the analytical phase of lab medicine.

Our editor provides an example of why this will happen on pages 10-16 of this issue of THE DARK REPORT. One day this spring, he had blood collected, properly processed, and sent 24 times to nine different laboratories to be tested for Vitamin 25(OH) D. Of course, our expectation as laboratory professionals—as are the expectations of doctors and patients—is that the same blood should produce essentially the same result when tested by an accepted methodology. This should be true within the same lab, as well as across all labs testing the same patient's blood.

However, that is not what happened to our editor's blood. One methodology—the FDA-cleared immunoassay—did deliver a tight spread of results. By contrast, the home brew tandem mass spec method produced a much wider spread of results. My view is that our editor's unique real-world experiment demonstrates why the lab testing profession must strive to improve in ways that fully meet the expectations of physicians and patients. TDR

Plain Talk about Current "Health Reform" Effort

Media coverage and public discourse fail to evaluate various options to improve healthcare

CEO SUMMARY: It appears that a determined effort to reshape and restructure the entire American healthcare system is unfolding in Congress. Missing in public discourse about this vital topic is informed, intelligent discussion about the types of alternative healthcare delivery models and options that might successfully address problems in the current U.S. healthcare system, without a total makeover of healthcare as it exists today. This is a big stakes issue for the entire laboratory testing industry.

By Robert L. Michel

IT IS LIKELY THAT MOST AMERICANS will look back on 2009 as a momentous year in our nation's history. We are in the midst of the deepest recession since 1981-82. There has been an unprecedented meltdown in the banking, mortgage, and auto industries. And... to top off all of that: a major restructuring of healthcare in the United States is widely predicted to happen.

Now that both houses of Congress are in their August recess, there will be a month of highly-polarized debate by both sides of the political spectrum as they speak to their constituencies about different aspects of healthcare restructuring. It may be a nasty time in our nation's public discourse, since changing the American healthcare system touches deep emotions for many Americans.

I know this is a topic of keen interest for pathologists, executives, and lab managers. That's because, at the offices of THE DARK REPORT and in my travels, I am regularly asked for my opinions and predictions about the shape and form of healthcare restructuring that is likely to emerge from the wrangling in Congress.

My honest answer to these questions is "how can anyone accurately predict what will emerge from all the back room politics, shaped by the intense lobbying of a myriad of powerful interests?" On the other hand, THE DARK REPORT would be derelict in its responsibility to provide informed strategic assessments of the situation as it relates to the clinical laboratory and anatomic pathology profession.

With that preface, I will wade into this most difficult of topics. The goal of this

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SUBSCRIPTION TO THE DARK REPORT INTELLIGENCE SERVICE, which includes *THE DARK REPORT* plus timely briefings and private teleconferences, is $13.10 per week in the US, $13.70 per week in Canada, $14.85 per week elsewhere (billed semi-annually).

commentary is to provide objective observations and insights about what has been made public about healthcare restructuring proposals.

Reform Versus Restructure

My first point is to address the issue of healthcare reform versus healthcare restructuring. In this commentary, the use of "healthcare restructuring" is intentional. My interpretation of what is known publicly about the house and senate bills moving through committees is that these are comprehensive make-overs of the entire U.S. health system—not sincere attempts to reform core problems without overturning the entire existing scheme of care in this nation.

Thus, I recommend that pathologists and lab directors assess the implications of proposed legislation through the strategic lens of "total makeover." Congress appears to be moving down the path of a massive, one-shot redo of healthcare. What parts they get wrong are likely to be irreversible a few years down the road.

The second point is to address the private choice versus single-payer issue. At this time, the privately-insured middle class (about 185 million Americans) and Medicare beneficiaries (about 45 million Americans) have a fair amount of freedom to choose both their health insurance plans and their providers.

Remember HMOs of 1990s?

Media sources seldom address how the proposed legislation is likely to restrict patient choice. Were a single-payer system to evolve and result from this current round of healthcare restructuring, these 230 million Americans will find themselves confronting a familiar nightmare. Remember the closed panel, gatekeeper model HMOs of the 1990s, so emphatically rejected by middle class Americans? A single-payer system administered by government bureaucrats will be even more daunting for patients to challenge than the irascible HMOs run by **Aetna/U.S.Healthcare**, **Pacificare**, and others in the mid-1990s.

Clinical laboratories and pathology groups can expect that the same HMO exclusionary network contracting practices will be employed by a single-payer, government-run system. After all, squeezing down price with little consideration of quality has been a characteristic regularly displayed by Medicare and Medicaid program administrators.

Point number three involves the remarkable lack of public discussion, evaluation, and debate about different options and approaches to true reforms of existing flaws in our healthcare system. I'll bet not one of you readers has seen a side-by-side analysis of how the proposed changes in pending bills compares with credible reform ideas of recognized experts. By itself this is a remarkable fact. Congress is about to restructure almost 20% of the U.S. economy and rank and file Americans have precious little information about which options might best meet their needs while solving recognized problems in today's healthcare system.

Health Vouchers Not Offered

For example, what about healthcare vouchers? Were a system of health insurance vouchers to be developed, might this be successful? In one approach, uninsured people just over the poverty level could get a government health insurance voucher that allows them to buy basic coverage from any qualified insurance plan.

In another approach, maybe vouchers for Medicare beneficiaries is a way to control year-to-year increases in Medicare program costs. The voucher would be enough to purchase the accepted level of health insurance coverage. Medicare beneficaries who want additional or premium care would be free to purchase such additional coverage on their own.

The central idea here is none of us have seen an informed public comparison of the health voucher concept against what Congress is actively working to pass. Nor

have we seen a public comparison of any other reform approach to fixing problems in the current health system versus what Congressional nabobs are working to pass.

Point number four is the search for ideas, inspiration, and relevant experience from health systems in other developed countries. It would seem common sense that policymakers in Congress would want to mine the experience of other countries for the best ideas to apply here in the United States.

Other Countries' Successes

Yet few in the American public have seen a credible, well-researched study that identifies the best successes of other healthcare systems. For example, Australia has a universal coverage requirement, funded by income tax collections. Australian citizens who want to obtain more extensive health benefits can purchase this coverage from private plans. In Singapore, health savings accounts (HSAs) have played an important role in their health system since the 1980s.

It is likely some of these approaches could solve problems in this country. It is a "best practices" study that can allow the United States to avoid "reinventing the wheel." But at this point, Congress seems to have shut the door to this source of proven innovation.

Point number five focuses on the cornerstone of science: multiple experiments. No political leader is suggesting that one way to improve the flaws in the American health system is to enable different states to experiment with various approaches to healthcare coverage. Yet, in science, it is the ability to perform experiments which guides the researchers to a more accurate understanding of the natural world.

We have the capability to run these experiments. Examples are the Oregon Health Plan of the 1990s, Tennessee's TennCare Medicaid plan of the 1990s, and, most recently, the Massachussetts plan for universal coverage which launched in 2006.

In the private sector, **Kaiser Permanente**, **Mayo Clinic**, and **Geisinger Health** are regularly hailed by policymakers as examples of the type of healthcare delivery models that are patient-friendly and are not plagued by many of the problems seen in the general fee-for-service health system that predominates in this country. Will Congress cast aside these greatly-admired health organizations in the final bill it passes? Alternatively, why does Congress seem unwilling, as of this moment, to incorporate these types of care delivery alternatives into the proposed bills so as to encourage wider use of these successful healthcare delivery models?

These five points represent objective observations about the current direction of healthcare restructuring as I see it as of this moment. Of course, as events unfold in coming weeks, lots of things are likely to change with the specifics of the senate and house bills currently under consideration.

A Major Overhaul Bill

Something big is likely to emerge from this effort to restructure healthcare in the United States. That's because a single party controls both houses of Congress and the presidency—a situation which doesn't happen regularly in American politics.

My theme in this analysis is that the public discourse about how healthcare in this country should be restructured fails to identify valid and reasonable alternatives that could help solve existing problems. That means both elected officials and the electorate at large are not informed about the full menu of options and alternative ways to improve the delivery and cost of care.

This does not bode well for the final bill that may eventually wind through Congress and reach the desk of the president for his signature. It would be a tragedy if the best aspects of this nation's healthcare were undermined because the nation at large was not able to consider and debate all the best ideas for improving healthcare. TDR

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Using Lean at Henry Ford Transforms Pathology TAT

Henry Ford Production System and Lean methods used to unlock major improvements in pathology

CEO SUMMARY: Long-standing work flow traditions in anatomic pathology provide fertile ground for improvement with Lean and similar process improvement methods. That was the case at Henry Ford Health System, where empowered teams in the pathology laboratory employed the principles of single-piece/small batch work flow, "pull", and standard work. The outcomes were reduced defects, improved productivity, and a reduction in average turnaround time in specimen processing of up to 50%!

INNOVATIVE LABORATORIES are using Lean methods and new automated systems to transform workflow. The goal is to dramatically reduce defects and inefficiencies, while improving quality and saving considerable amounts of money.

Henry Ford Health System in Detroit, Michigan, operates one of the nation's largest health system laboratories. It is using Lean and similar process improvement methods in pathology to unlock remarkable gains in productivity and quality, including a 50% reduction in average turnaround time.

"It was 2005 when laboratory managers introduced The Henry Ford Production System," stated Rita D'Angelo, the Pathology Department's Quality Improvement Specialist. "This quality improvement process is modeled on the Toyota Production System, which inspired the Lean methods that are widely used today.

"As a result of this system, we now perform hundreds of process improvement efforts every year," D'Angelo said. "Our strategy is for pathology lab staff to work in integrated teams and to encourage multiple teams to work together to achieve mutual goals."

Since 2005, the pathology department has applied process improvement to a wide variety of routine processes. These cover every aspect of specimen processing, including workload smoothing, accessioning, and sample identification. "At the time this effort was launched, Henry Ford Health System did not invest in outside consulting services," noted D'Angelo. "Instead, laboratory administration asked our laboratory staff to develop ideas for process improvement and take the lead in implementing these ideas.

Implement Process Redesign

"However, before we could implement process redesign, we needed to change the existing culture in our laboratory," explained D'Angelo. "Micro-management was common, as was an atmosphere of persistent blame. People were afraid to talk and team members were reluctant to share their ideas. Micro-management had to stop and staff needed to feel empowered to contribute ideas and to implement improvements to the system.

"A major first step in our redesign of work flow was to identify and implement standard ways of performing our work," she said. "As Lean practitioners know, it is essential that employees who perform this work are the ones who evaluate and develop the standardized work. This needs to be a 'bottom up' effort, not a 'top down' directive.

"The cornerstone of our histology lab's efficiency is continuous flow, designed to pull specimens through the lab using the single piece/small batch method," she stated. "With this system, we pull small batches through the system rather than doing work in large boluses that can overwhelm a work station and add delays.

Creating Continuous Flow

"Before Lean, our anatomic pathology processing laboratory was like many others," she noted. "Most specimens arrived in the morning and that is when the majority of staff worked. Now, specimens flow in throughout the day and our staffing stretches out to accommodate that work.

"In the beginning, we quickly learned how much we didn't know about our histology lab," added D'Angelo. "For example, we had no clue about how many specimens came through the system at any given time during the day. We did not know how many specimens were in the gross station or how many specimens were in each processor.

"It was the same for the activities of our histotechnologists," continued D'Angelo. "Without knowing how many blocks and slides each histotech handled, we lacked the criteria for evaluating workload. Lean changed all of that. We now constantly collect data on all of these activities and make improvements as we go. The improvements and benefits are often quite impressive.

"For example, one of our most significant improvements involves how we process prostate specimens," D'Angelo said. "Standard work was the tool we used to eliminate variation. We determined that our existing method for handling prostate specimens required that about a third of them be resubmitted for processing because they were improperly fixed.

Implementing A New Protocol

"To prepare a prostate sample for analysis, our new protocol is to inject every prostate sample that comes in with formalin to improve fixation time," she said. "Prior to this process improvement project, it was common for our lab to reject about 31% of samples due to unfixed tissue blocks and poorly-cut slides. Each rejected sample had to be resubmitted because it couldn't be processed as is.

"Following our improvement process, the reject rate was lowered by one-third, to 21%. This was an important benefit. The reduction of 10 percentage points allowed us to shorten an average four-day processing time to three days! The key improvement was a simple revision to the prostate injection process, along with standardizing workflow.

"Another significant improvement involved batch size reduction," she said. "In 2005, we would accession specimens in one large batch. Specimens would be crammed into huge pink buckets—in no order whatsoever.

Handling Specimens

"Also, in anatomic pathology we handled each specimen at least five times involving about six steps. Accept it in the lab, take it out of the baggy, identify it, record it, put it back into the baggy, and replace it in the bucket," recalled D'Angelo. "Post-Lean, our histotechs take a specimen out once and put it into a workcell tray that includes specimen container, the requisition, and the cassette. This is accomplished in four steps.

"As a result, accessioning time was cut by 50%!" she stated. "It was a simple solution, reducing the number of steps from six to four. As part of this project, we insti-

tuted a different color tray for each type of tissue work stream or priority."

Batch Size Reduction

Henry Ford Health's anatomic pathology laboratory applied the single piece/small batch method to other areas of work flow, with similarly impressive results. One big opportunity was to apply Lean to the common practice of batching and processing all of the day's specimens overnight.

"This is a situation common to most hospital-based histology laboratories," noted D'Angelo. "Typically, all the day's specimens are in the lab by 8:00 p.m., but there is no staff in the laboratory in the evening to handle that work.

"To handle that large volume of specimens at Henry Ford, we started our accessioning staff at 5:00 a.m.," she explained. "Not only did that mean our histology specimens sat for nine hours untouched in the lab overnight, but it also required us to staff a sizeable number of people in the early morning to process that large volume of specimens.

"By implementing a work flow based on single piece/small batch in a continuous flow, we could schedule techs throughout the day to avoid that 'big batch rush' at 5 a.m. each morning. Staffing is now balanced across all working hours. We implemented a second shift to support single piece/small batch work flow throughout the day.

Level Workload

"We identified another opportunity to level the workload and support 'pull' in the work flow," explained D'Angelo. "We instituted a standard of 20 slides per pathologist per tray.

"This simple solution supports 'pull' because each histotech only produces what is needed to pass work forward to the next step in production," she said. "The standard of 20 slides per pathologist per tray eliminated a source of individual bottlenecks because we removed inventory stores between each work cell."

Deployment of the Henry Ford Production System and use of its Lean methods has paid big dividends for the anatomic pathology laboratory. These encompass multiple benefits.

"Collectively, these process improvement projects have slashed average turnaround time from one day to 12 hours in anatomic pathology," said D'Angelo. "That's a 50% improvement and directly contributes to improved patient care."

Successes From Use of Lean

Use of Lean and the Henry Ford Production System by this pathology laboratory demonstrates the power of these quality management methods to unlock major gains, often in improvement projects that deliver results in just a few weeks. Wider adoption of Lean and similar quality management approaches will trigger fundamental changes in basic operational practices in histology and pathology labs across the country.

The Department of Pathology at Henry Ford Health System has been recognized for its effective use Lean methods. At both the 2007 and 2008 *Lab Quality Confab* conferences, Lean Six Sigma poster presentations given by D'Angelo and her colleagues won national awards, accompanied by cash prizes.

THE DARK REPORT observes that the experience of the pathology department at Henry Ford Health provides an example of how long-standing operational practices and work flow arrangements in the profession are giving way in the face of new management approaches and new automation solutions. Often, pathologists overlook the fact that when Lean management methods are combined with automated histology systems, a totally unorthodox work flow often results.

However, this unorthodox work flow generally produces higher quality pathology

Lab Staff Finds a Way to Mistake-Proof Handling of Anatomic Pathology Specimens at Accessioning

ONE FERTILE OPPORTUNITY for mistake-proofing involves selecting an accurate body part type at accessioning. Existing work practices at many histology laboratories allow an unacceptable rate of defects to occur at this step in specimen processing.

At Henry Ford Health System, Quality Improvement Specialist Rita D'Angelo shared how the pathology department used the methods of the Henry Ford Production System to attack and fix this problem. "When a biopsy is collected in a doctor's office, office staff put the biopsy and the requisition into a bag and send it to the laboratory," she said.

"But, often, that specimen arrives in pathology without a correct body-part type,' explained D'Angelo. "This presents a problem for accessioners, who must identify the body-part type. Accessioners will add the information they have into the database and then estimate the body-part type from a drop-down menu box provided by the computer system.

"Many times, accessioners pick the incorrect part type," D'Angelo said. "Our process improvement team identified this as a high-payoff opportunity.

"A first step was to collect data to determine the rate of body-part type identification errors," she continued. "To accomplish this, a white poster board was hung in the histology gross room and other poster boards were placed in the pathologists' work areas. Each time a body-part type error was identified, that individual was asked to record the event on the poster board.

"This data collection effort generated interesting numbers," observed D'Angelo. "We tallied 123 problems from a population of 1,690 specimens. That's an error rate of about 7.3 %, which is significant. Further, each mistake is frustrating for the pathologists at the end of the line. When a pathologist working with such a specimen detects an error, he or she must take additional time to correct all the information required to produce an accurate report.

"Informed by this data, we recognized that this problem encompassed several departments," she said. "We next evaluated the 2,000 body-part types listed in our laboratory information system (LIS). Pathologists reviewed the list to make sure each item was accurate and up-to-date.

"This corrected list was used within the lab for training," continued D'Angelo. "We now also inservice the clinicians and their staffs who originate and label these specimens. This entire improvement project took about eight months, from validating the database list to staff training and clinician education.

"It was well worth the effort," noted D'Angelo. "Our lab saw the number of errors tied to body-part type fall from 123 to just one! By any measure, that is a significant success in mistake-proofing."

services, at a lower cost and with fewer errors. These are all important benefits at a time when the pathology profession is undergoing transformation by molecular technologies and digital pathology systems.

Recognition of these trends is one reason why growing numbers of histology laboratories and pathology groups are introducing Lean methods into their organizations. It also shows why the competitive bar is being raised in the anotomic pathology marketplace. **TDR**

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Do different Vitamin D methods confuse doctors?

Our Editor Gets His Vitamin D Test Results From 9 Different Labs

➤➤CEO Summary: ***Editor-In-Chief Robert L. Michel gave blood for the cause and it's another laboratory industry first! To understand what doctors and patients see as national labs use different methodologies and reference ranges to report Vitamin 25(OH) D results, his blood was tested 24 times by nine laboratories. The results were unveiled at the*** **Executive War College** ***last May in New Orleans. These results are published here, along with comments from the All-Star Vitamin D Panel experts who discussed reasons why doctors might be confused and might misinterpret Vitamin D lab test results.***

UNTIL RECENT YEARS, THE VITAMIN D TESTING MARKET was a rather quiet, uncontroversial corner of the lab testing marketplace. This was true because of the widespread acceptance and use of a long-established, FDA-cleared immunoassay test for Vitamin 25(OH) D.

However, this status quo in Vitamin D was disrupted when some national laboratories began performing Vitamin 25(OH) D testing using tandem mass spectrometry (LC-MS). For a variety of reasons, this different methodology introduced a new element of complexity for physicians and their patients.

In recent years, laboratory scientists and pathologists have begun to publicly discuss and debate the pros and cons of testing for Vitamin 25(OH) D by each of the available methodologies. Much of this discussion centers on analytical precision.

However, this scientific debate about analytical precision of different methodologies among laboratory testing professionals often fails to recognize the needs of physicians and their patients. Clinical laboratory testing is done at the specific request of a physician who is evaluating and treating a patient. These physicians and patients are the true customers of the clinical laboratory. Thus, their needs and expectations for Vitamin 25(OH) D testing should be addressed in the public discussions of laboratory scientists.

During the All-Star Vitamin D Panel at the *Executive War College* in New Orleans last May, the perspective of the patient was introduced in a novel and unique way. Robert L. Michel, moderator of the panel and Editor-In-Chief of THE DARK REPORT, shared the results of 24 Vitamin D tests performed on his blood by nine different laboratories in the United States.

It was a revealing moment, both for the five experts on the panel and for the entire audience. Twelve of Michel's Vitamin 25(OH) D results were reported by immunoassay methods and 12 Vitamin D results were reported by home brew tandem mass spectrometry methods.

A sidebar on page 13 presents the Vitamin D results as reported to each of the two laboratories which received blood drawn from Michel at the same time. These two labs aliquotted Michel's samples and sent two aliquots—about 21 days apart—to each send-out laboratory.

To illustrate why a physician and a patient could be confused, the sidebar on page 15 presents all the individual Vitamin D results reported on Michel's blood so as to show the low-to-high range of numbers.

When viewed from the perspective of a physician and a patient, the potential for confusion—as well as misdiagnosis and/or mistreatment—was obvious. That's because, although Michel's Vitamin D level is clearly in the sufficient range (above 30 ng/mL), individual Vitamin D results reported his level to be as low as 36 ng/mL and as high as 66 ng/mL!

➤Are Physicians Confused?

This illustrates a problem that generally goes unaddressed when laboratory scientists discuss and debate the analytical accuracy and performance of different methodologies and reference ranges used in testing for Vitamin 25(OH) D. That problem is the potential for physicians and patients to be confused as they attempt to interpret results generated by different methodologies, in the context of reference ranges that themselves reflect no scientific consensus.

There are two dimensions to this problem of potential confusion. First, different Vitamin 25(OH) testing methodologies have a recognized bias relative to each other. That bias can be quite significant between individual laboratories, based on how they have set up the particular Vitamin D methodology they use in their laboratory. Clinicians are frequently ignorant of the bias factor when they evaluate Vitamin D results

reported on their patients by different laboratories using different Vitamin D methodologies.

Second, the reference ranges used by various laboratories in the United States to report their Vitamin D results do not reflect a single standard supported by the general consensus of the scientific community.

However, there is a *de facto* standard! It is familiar to any clinician who has practiced medicine since 1993 and has worked regularly with Vitamin 25(OH) D testing since that date. It is the first FDA-cleared predicate "device" or kit, the RIA assay manufactured by **Diasorin**.

Since 1993, the broader medical profession has become familiar with the reference ranges associated with use of the FDA-cleared immunoassay. That means physicians who actively measure and manage the Vitamin D levels of their patients are quite familiar with the meaning of these reference ranges. They understand how immunoassay results reported on their patients should be interpreted relative to these broadly-accepted reference ranges.

Separately, over the past 20 years, a significant number of published clinical studies involving Vitamin 25(OH) D gathered data using the immunoassay methodology. Physicians aware of the findings of these studies have used the recommended Vitamin D levels and reference ranges suggested by these studies and based on use of the FDA-cleared predicate device/kit in the studies.

➤*De Facto* Vitamin D Standard

This *de facto* standard exists today in the clinical marketplace. It often goes unremarked and undiscussed when laboratory scientists debate the analytical accuracy of their preferred Vitamin D methodology.

But this *de facto* standard is the source of another practical problem for clinicians and patients. Assume a laboratory introduces a home brew test for Vitamin 25(OH) D into clinical use that has a significant bias relative to the FDA predicate device (which is the RIA manufactured by **Diasorin**). Scientifically and ethically, how should the laboratory communicate the fact of this bias in the patient's result to the physician—particularly if the physician has almost 20 years of clinical experience in use of the FDA-cleared methodology for testing Vitamin 25(OH) D?

Further, if the reporting laboratory uses essentially the same reference range that accompanies the FDA-cleared Vitamin 25(OH) D immunoassay, scientifically and ethically, how should the reporting laboratory alert the physician to the bias of the reported result and how that bias might affect the physician's interpretation of the patient's result against that lab's reference range, which may be almost identical to the FDA-cleared predicate methodology?

➤Real-World Consideration

These are not theoretical questions. In the laboratory marketplace, competing laboratories are getting complaints about the "inaccuracy" of their Vitamin D results. Some doctors even accuse the laboratory they use of reporting flawed results. The laboratory accused of such misdeeds quickly recognizes that the complaining doctor is often confused because another laboratory providing testing to his medical practice may be using a different Vitamin D methodology, with a bias that has gone unrecognized by the doctor—and undisclosed or unremarked by the reporting laboratory to that doctor.

Certainly laboratory scientists recognize the problem created for clinicians by the lack of a standardized reference range for Vitamin 25(OH) D levels. But seldom does a pathologist or clinical chemist publically address how and why the current situation could be troublesome for physicians, and how it might possibly contribute to less-than-ideal care for patients.

That was not the case with the All-Star Vitamin D Panel at the *Executive War College*. Using Editor Michel's 24 Vitamin

Gauging How Different Laboratories Produce and Report Vitamin D Results and Reference Ranges

ARE PHYSICIANS AND THEIR PATIENTS CONFUSED by the results and the reference ranges used on lab test reports issued by laboratories which perform Vitamin 25(OH) D testing using different methodologies? The table below demonstrates why the potential for confusion exists in today's lab testing marketplace. The table shows how Editor Robert Michel's blood—tested 24 times by nine different laboratories—produced a wide range of Vitamin D measurements, reported against an array of slightly different reference ranges.

Laboratory A Send-outs

Performing Site	Methodology	Early March, 2009			Late March, 2009			
		D2	*D3*	*Total*	*D2*	*D3*	*Total*	*Reference range*
UMass	Liaison CIA	-	-	**45.2**	-	-	**45.4**	30-100 ng/mL
ARUP	Liaison CIA	-	-	**46**	-	-	**49**	30-80 ng/mL
ARUP	Diasorin RIA	-	-	**46**	-	-	**42**	30-80 ng/ml
Mayo	LCMS	<4	61	**61**	<4	51	**51**	25-80 ng/mL
Quest-Nichols	LCMS	<4	66	**66**	<4	51	**51**	20-100 ng/mL

Laboratory B Send-outs

Performing Site	Methodology	Early March, 2009			Late March, 2009			
		D2	*D3*	*Total*	*D2*	*D3*	*Total*	*Reference range*
CPL-Austin	IA	-	-	**45**	-	-	**42**	30-60 ng/mL
LabCorp	IA	-	-	**39.6**	-	-	**47.1**	32-100 ng/mL
ARUP	Chemi	-	-	**48**	-	-	**47**	30-80 ng/mL
Quest-Irving	LCMS	<4	42	**42**	<4	55	**55**	20-200 ng/mL
Quest-Nichols	LCMS	<4	54	**54**	<4	36	**36**	20-200 ng/mL
Mayo	LCMS	<4	48	**48**	<4	48	**48**	25-80 ng/mL
Esoterix	LCMS	<1	42	**42**	<1	47	**47**	32-100 ng/mL

How this Vitamin D evaluation was conducted:

1) In early March, Editor Robert Michel had blood drawn. Seven SST gel-topped tubes and four red-topped tubes were collected.

2) These specimens were carefully processed, packed, and transported with extra care and attention. Half of those specimens were sent to laboratory A. The other half of those specimens went to laboratory B.

3) Both laboratories aliquotted Michel's blood into split specimens. On his behalf, the first aliquot was sent to multiple laboratories. Three weeks later, a second aliquot of Michel's blood was sent to those same laboratories.

4) In some cases, the same laboratory got a total of four specimens of Michel's blood, sent by two referring laboratories on different dates. All nine labs received at least two samples of Michel's blood.

5) The following table shows each laboratory which performed testing on Michel's blood, the methodology, the Vitamin 25(OH) D results, and the reference range provided on the lab test report.

D results from nine laboratories, the experts were willing to acknowledge the two practical problems—from the perspective of physician and patient—created by: 1) bias in different methodologies that goes unrecognized by clinicians; and, 2) how laboratories establish their reference ranges for reporting Vitamin D results.

Coefficient Of Variation

"In looking at these 24 Vitamin D test results, what jumps out for me is the very tight coefficient of variation, 40 to 48, among the laboratories which performed the test by immunoassay," observed L.V. Rao, Ph.D., who is Director of the Core Laboratory and Immunology at the **UMass Laboratory** in Worcester, Massachusetts. "By contrast, labs performing the test by LC-MS have a larger coefficient of variation, 36 to 66."

Rao had earlier shared with the audience the findings of his laboratory as it developed a home brew LC-MS assay to meet the requests of outreach physicians for this methodology. In THE DARK REPORT issue of July 20, 2009, the data presented by Rao was published, along with Rao's analysis and comments. In evaluating results of the home brew LC-MS against the immunoassay, Rao stated that "The data showed a fairly acceptable correlation (r=0.80), but with significant bias (approximately 40%)."

Similar points caught the attention of the other Vitamin D panelists as they viewed Michel's 24 Vitamin D test results. "Three things stand out as I view these results," stated Julian Barth, Ph.D., Consultant in Chemical Pathology & Metabolic Medicine, **The General Infirmary at Leeds**, Leeds, West Yorkshire, United Kingdom. "First—and a point which I think is quite important for your clinicians—is that all these labs use different reference ranges. It's the same data. What are the reasons why they report these data framed by such different numbers for their reference ranges?

"Second, for laboratories using the immunoassay methodology, this data is a testament to Diasorin's manufacturing ability. The uniformity in the performance of the Diasorin kits is stunning," he noted.

"Third, I'd like to build on earlier comments about analytical accuracy and standardization," Barth explained. "Going forward, Michel's Vitamin D results demonstrate why a key need for mass spectrometry is to provide the same answer everywhere, in the same way that labs using the immunoassay kits are demonstrating standardization."

Andre Valcour, Ph.D., spoke directly to the consequences of a physician attempting to understand the clinical significance of such a wide range of Vitamin D results and reference ranges. "If Michel's physician called me, I can tell him/her that Michel's Vitamin D levels are good. Most patients we see don't have Vitamin D levels in the 40s, like Michel," stated Valcour, who is Vice President and Laboratory Director at **Laboratory Corporation of America** in Burlington, North Carolina.

Confusing To Physicians

"But what would this range of results tell a physician if they were much lower?" questioned Valcour. "Let us say that Michel's Vitamin D value by the Diasorin method was 20, and his doctor sent me some of these labs. I would tell him that his patient is low and needs to be at a minimum of 32.

"Assume this doctor sends Michel's sample to another lab and that lab reports it as a 20 with a reference range that says 20 is 'sufficient.' That confuses both Michel and his physician.

"Not surprisingly, the physician will say, 'I don't trust this test. This whole vitamin D stuff is hokum. I can't trust the results because two laboratories tell me different things based on the same value. One tells me my patient is deficient. Another lab tells me my patient is completely replete'," observed Valcour.

"This is too confusing," he added. "It may discourage the physician from order-

Illustrating Variability in Vitamin D Results and Bias of Mass Spec Relative to Immunoassay Method

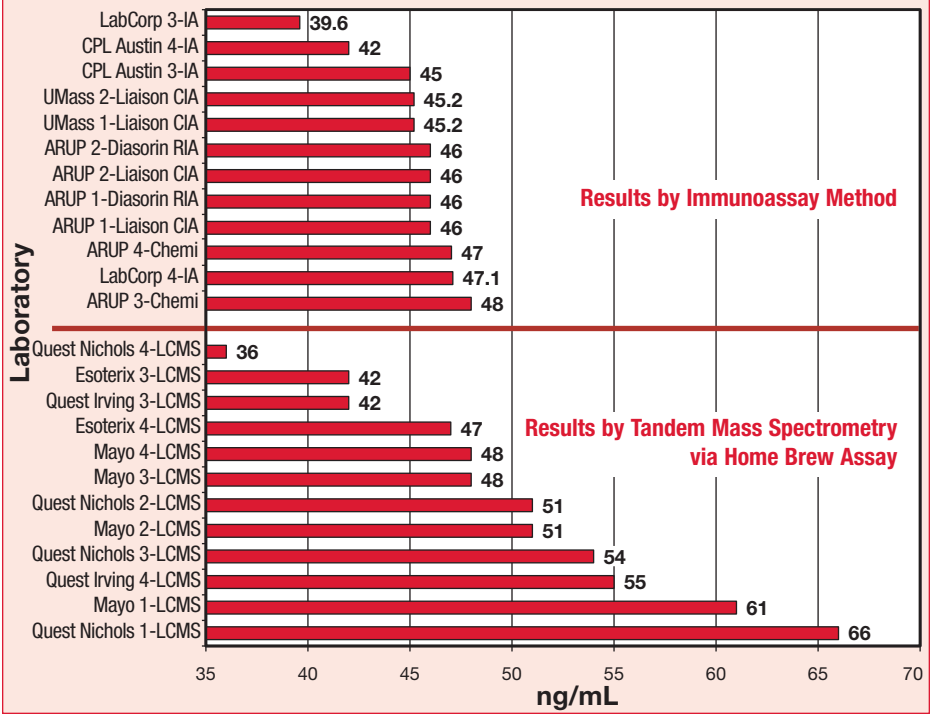
ONE FUNDAMENTAL GOAL OF LABORATORY MEDICINE is that every laboratory should produce the same result on a single patient's blood, drawn at one moment in time. Ideally, the following bar chart should demonstrate how nine of the nation's leading laboratories reported essentially the same result—within an acceptably narrow band. Specimens labeled 1,2,3,4 for the same laboratory would be expected to generate the same result.

Below is a bar chart which presents the results of Editor Robert Michel's 24 Vitamin 25(OH) D tests, as performed by nine different laboratories. The top half of the bar chart contains the 12 test results performed by immunoassay method. The bottom half of the bar chart contains the 12 tests results performed by tandem mass spectrometry.

During the All-Star Vitamin D Panel at the *Executive War College* last May, the panel's experts recognized the consistent performance of the immunoassay method. Ten of the 12 results were clustered within three ng/mL, from 45 to 48. By contrast, of the 12 LC-MS results, only four LC-MS results clustered within three ng/mL, from 48 to 51.

This study, not conducted in a statistically-valid manner, does demonstrate the practical challenges confronting physicians and patients. It is left to physicians to accurately understand the meaning of the Vitamin D result and reference range, even as the laboratory community understands why differences exist in the results generated by different methodologies.

Vitamin D Test Results for Editor Robert L. Michel



ing the test. But the worst thing is it may also discourage both the physician and this patient from monitoring his Vitamin D levels. That's not a good outcome, because so many new clinical studies indicate that maintaining higher levels of Vitamin D can contribute to better health and extend life expectancy."

Valcour sees this confusion among physicians almost daily. "It is real world that different laboratories are reporting different numbers and using reference ranges that doctors find bewildering," he said. "I deal with this situation every day. I inevitably get the call from the doctor who inadvertently sent a sample to another lab and has also sent to me, and our two labs report different results on the same patient. Quite frankly, it's time for laboratories to solve this Vitamin D testing issue and I'm really glad we are here today to talk about it."

Tackling The Problem Of Bias

One panelist wanted to tackle the issue of bias between methodologies head on, picking up on Valcour's theme. "For a clinician, bias in the results generated by one Vitamin D methodology versus another has consequences in his medical practice," offered Bruce Hollis, Ph.D., Professor of Pediatrics and Neonatology at the **Medical University of South Carolina** in Charleston, South Carolina.

"Say a lab runs a mass spec Vitamin D assay that consistently produces a result number that is 40% above the RIA, which is the FDA-cleared predicate device/kit," he continued. "There are some outside assessments that indicate such a 40% higher result was true of the mass spec assay at **Quest Diagnostics Incorporated** at the time they introduced their internally-developed lab test into general clinical use. In my example, assume this lab uses 20 as the cut-off for sufficient and reports the patient at 20.

"However, based on the RIA, the patient would test at 12 or 15, which is half of the target 30 used by most labs—and this patient is clearly insufficient!" postulated Hollis. "In this scenario, the doctor will tell the patient he or she is okay and doesn't need treatment for Vitamin D insufficiency. To me, this is not good medicine. It's potentially harmful across many disease spectrums for the patient. And the source of the confusion is bias between two Vitamin D methodologies, which is not explained to the physician by the lab using the mass spec assay with that higher bias.

How Patients Are Affected

"Moreover, this problem is not a concern for the upper level of results," noted Hollis. "Doctors seldom see patients with 70 or 80. Rather, the concern is at the low levels of Vitamin D which are seen constantly, all the time. Thus, how the laboratory defines that low range is the real key to helping the physician develop the right treatment plan. It's my view that setting a low-end level of 20 as sufficient, and then reporting results with a bias of 1.4 over the RIA is not good lab medicine."

Recognizing the role of standardization, panelist Russell Grant, Ph.D., Strategic Director, National Office of Quality & Science at **Esoterix, Inc.**, in Burlington, North Carolina, stated "The need is clear. The first pass for the laboratory profession is standardization to address these issues. The second pass is harmonization—or at least a gold standard underneath that, since calibration is one element of harmonization."

Progress In Vitamin D Testing

As the comments by the experts participating in this All-Star Vitamin D Panel demonstrate, there is plenty of evidence that physicians and patients can be confused when they interact with multiple laboratories, each using different Vitamin 25(OH) D testing methodologies. Additional intelligence briefings on the Vitamin D testing marketplace will be forthcoming. TDR

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New Lab Player Launches In Breast Cancer Market

Its proprietary assay evaluates 70 genes to predict odds of breast cancer recurrence

CEO SUMMARY: Having opened its CLIA-licensed laboratory in Huntington Beach, California, Agendia, Inc., becomes the newest competitor to enter the market for breast cancer testing. Its proprietary assay looks at 70 genes to assess the risk of recurrence. The company expects to collaborate with local pathologists, as its test requires fresh tissue and can provide a diagnostic answer for untreated patients, including both ER-positive and ER-negative patients. Agendia executives are pursuing Medicare coverage for the assay.

THERE ARE TWO ONGOING TRENDS in the highly-competitive market for breast cancer testing. First, new laboratory testing companies continue crowding into the market to compete for cases. Second, there's a biomarker explosion underway, as a number of new assays for breast cancer utilize multiple biomarkers or genes to accomplish the analysis.

Both trends are illustrated by **Agendia Inc.**, of Huntington Beach, California. In May, Agendia opened its CLIA-approved clinical genomics laboratory and began selling its services to pathologists nationally. Its primary new assay is MammaPrint. As a tumor gene expression profile test, it evaluates 70 genes that the company says helps physicians design tailored cancer therapy programs for the individual breast cancer patient.

Involve Local Pathologists

For pathologists, one notable aspect of Agendia's business plan is that it wants to collaborate with local pathologists. "Agendia does not do ER/PR (estrogen receptor/progesterone receptor) or HER/2 testing. That's the role pathologists play," stated Daniel Forche, Vice President of Sales and Marketing at Agendia. "Rather, the molecular information provided by our MammaPrint assay supplements diagnostic data that pathologists already have. Given this scenario, we believe pathologists will be at the center of this work because molecular pathology is becoming more and more prevalent in healthcare.

"MammaPrint is a 70-gene test that identifies each patient's chance for recurrence" Forche said. "The FDA cleared MammaPrint, an *in vitro* diagnostic multivariate index assay (IVDMIA), in February 2007. The results of this test place women in either a high-risk or a low-risk group for breast cancer to recur within 10 years. When the information from our test is combined with the information coming from the pathologist, it improves the ability of the oncologist to select the best therapy for their patients.

"Our assays work in a way that enhances the role of local pathologists," explained Forche. "Our research deter-

mined that at least 231 genes seem to be prognostic in nature for breast cancer. We use 70 of the most critical genes to get a high- and low-risk result for breast cancer. One feature of our test is that it can be used on both ER-positive and ER-negative patients. Other assays can only be used with ER-positive patients. That's important, for the following reason.

No Intermediate Group

"Other breast cancer tests have a large intermediate result," he continued. "About 40% to 50% of patients fall into this intermediate group. International guidelines released recently basically state that there is no clinical utility from intermediate results. When a patient gets our test and is reported to be in the low-risk group, that person has a 10% chance of recurrence of breast cancer for 10 years. If physicians give those patients hormonal treatment, that risk drops to 5%.

"Another fact that sets our MammaPrint assay apart from others in the market is that it was developed for use with untreated breast cancer patients," stated Forche. "That's one main differentiator between our product and others."

Attractive Market Segment

The recent entry of Agendia into an already crowded market for breast cancer testing demonstrates that breast cancer testing continues to be an attractive market segment for researchers and investors alike. Moreover, the development pipeline is full of additional new biomarkers and lab tests for breast cancer. As these new tests are launched, they will create new capabilities for pathologists and the clinicians they serve.

The Agendia business model also illustrates how new opportunities will open up for pathologists. Once a local pathology group has done ER/PR testing on the patient, if it is clinically relevant for an individual patient, the pathologists can refer fresh tissue (fixed with a molecular fixative) to Agendia. Agendia will perform the MammaPrint assay and deliver back the diagnostic answer that can help the oncologist and patient make more precise decisions about therapeutic options.

Further, the regular introduction of new, multi-marker genetic and molecular assays for breast cancer demonstrates how rapidly clinical practice is changing in this field. Diagnostic assays like these are the essential steps on the path to personalized medicine and companion diagnostics. They are a reminder that the profession of anatomic pathology is transforming at a steady pace. TDR

Contact Dan Forche at 714-849-7515 ext. 228; or dan.forche@agendia.com.

Seeking Medicare Coverage for the MammaPrint Test

"AS PATHOLOGISTS KNOW, the key to success when offering genomic tests is getting Medicare reimbursement for these tests," observed Daniel Forche, Vice President of Sales and Marketing at Agendia, Inc. "We are currently in talks with the **Centers for Medicare and Medicaid Services** (CMS).

"The Medicare program has been supportive of personalized medicine testing," he added. "In the 1990s, **Myriad Genetics, Inc.** paved the way when it won Medicare approval for coverage of its BRACAnalysis test, which assesses a woman's risk of developing breast or ovarian cancer based on an evaluation of the BRCA1 and BRCA2 genes.

"Next came **Genomic Health, Inc.**, with its Oncotype DX assay for breast cancer," stated Forche. "This was a different assay because it looked at tumor genomics. Again, the Medicare program agreed to cover this assay.

"Currently, we use the same codes that Genomic Health uses to bill third-party payers for the MammaPrint test," he noted. "Our early talks with CMS have been promising. There is growing recognition that personalized medicine is advanced by genetic diagnostic assays like these."

INTELLIGENCE

LATE & LATENT

Items too late to print, too early to report

Last week, the pathology profession got a new professional group. It is the **Digital Pathology Association** (DPA) and it was formed by several companies offering digital pathology systems and services. DPA's founders say it will support digital pathology education initiatives, define best practices, and will seek to influence standards and interfaces in digital pathology systems. The first president of DBA is Dirk Soenksen, who is also CEO of **Aperio Technologies, Inc.**, a digital pathology systems provider based in Vista, California. Timing of the formation of this new association is one sign that growing numbers of pathology groups are taking steps to implement a digital scanning solution or a complete digital pathology system.

MORE ON: Digital Path

Creation of the Digital Pathology Association is evidence that adoption of digital scanning and digital pathology systems continues to widen. According to Soenksen, during the past 18 months, digital pathology companies have attracted more than $100 million in investment capital. Along with Aperio, other digital pathology companies involved in the new association are **BioImagene** of Cupertino, California, and **Omnyx, LLC**, the joint venture of **GE Healthcare** and the **University of Pittsburgh Medical Center**.

RAPID A/NOVEL H1N1 FLU TESTS HAVE LOW DETECTION RATES

A report released last week on rapid tests for influenza A/Novel H1N1 by the federal **Centers for Disease Control and Prevention** (CDC) finds that three rapid tests designed to detect A/Novel H1N1 detected the novel strain only 40% to 69% of the time. *Genome Web Daily News*, writing about the findings in the CDC report, wrote that "The sensitivity of rapid influenza diagnostic tests for detecting the new H1N1 influenza A ('swine flu') and other flu viruses drops off in patient samples containing lower viral titer, according to this week's issue of the U.S. Centers of Disease Control and Prevention publication." If physicians are using rapid flu tests with sensitivity comparable to the odds of a coin toss, then the upcoming flu season may bring interesting new challenges for labs in this country.

That's all the insider intelligence for this report. Look for the next briefing on Monday, August 31, 2009.

Now in its third year!

PREVIEW #3

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